

Influence of a positive family history and associated allergic diseases on the natural course of asthma

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Summary

The outcome of childhood asthma was studied in a cohort of 406 asthmatic children, with emphasis on the influence of family history for allergic disease, as well as the influence of associated allergic diseases on prognosis. Sixty-two per cent had a positive family history for atopy. In young adulthood no differences, either in symptoms or lung function were demonstrated in comparison to subjects with a negative family history. Fifty-two per cent of the children had no other allergic disease, 48% had either eczema or hay fever or both. When subjects were stratified based on associated allergic disease, no differences in outcome in adulthood were revealed either. It is concluded that neither a positive family history, nor concurrent associated allergic diseases in the child contribute to the prognosis of asthma from childhood to young adulthood. Therefore, environmental factors as well as patient characteristics (including lung function level, level of bronchial responsiveness) are likely to be more important for the prognosis.

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Introduction

Allergic manifestations are prominent features of children with asthma, as the majority of asthmatic children have an inherited tendency towards allergy, and many also have other allergic diseases. Among asthmatic patients the prevalence of allergic rhinitis (hay fever) varies between 28% and 61% [1,2]. The prevalence of allergic dermatitis (eczema) in asthmatic children ranges from 30% to 60% [3,4]. The pattern of manifestations of allergic diseases, such as hay fever and dermatitis (eczema) as well as asthma, may, however, vary with age. Both allergic eczema and hay fever frequently precede the development of asthma in children, as 60% of children with allergic eczema, and at least 10% of children with hay fever may develop asthma. In several studies it was suggested that associated allergic diseases may worsen the asthmatic symptoms and increase the likelihood of the development of chronic asthma [5–8].

The association with family history of allergic disease is well known. However, it is likely that besides genetic

factors, environmental factors also influence the development of allergy, and may even be more important [9–11]. As many as 40–80% of asthmatic patients and patients with hay fever have a positive family history of atopy, compared to 20% or less individuals without allergic disease [12]. The influence of this positive family history on the natural course of asthma severity is relatively unknown. In the literature it has been suggested that a positive family history of allergy may be related to more severe asthmatic symptoms and risk of ongoing respiratory symptoms from childhood to adulthood [6,7,12,13]. It seems that there is a familial preference for the pattern and severity of allergic disease. To date little is known about the genetic basis of the inheritance of allergic diseases, although in recent studies progress has been made in defining the type of inheritance and gene locus of asthma [14].

Aims of the study

We studied the outcome of asthma from childhood to young adulthood in a cohort of 406 asthmatic children; 97% were allergic on entering the study. To assess the influence of family history of allergic disease on the outcome, the family history of first degree relatives for allergic diseases was analysed in relation to manifestation

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and severity of symptoms and functional parameters in childhood and adulthood. Second, the prevalence of concurrent associated atopic diseases, such as allergic eczema and hay fever, in the participants and the influence of these associated atopic disease in childhood on the outcome of asthma in young adulthood were studied.

Patients and methods

Patients

The original study group consisted of 406 children, aged 8–12 years, referred to the outpatient clinic of the Department of Pediatric Pulmonology of the University Hospital of Groningen between January 1972 and December 1976, in whom the diagnosis of asthma was made, based on symptoms, lung function parameters and skin tests. They were all referred by their general practitioners. The sex ratio was 1 to 2, 133 girls (33%) and 273 boys (67%). The children were included if a sufficient set of childhood data on symptoms, physical examination, lung function tests, bronchial responsiveness and allergy (skin test reactivity and eosinophil count) was available. No important differences were found between this cohort and the other 80 patients of the same age group, referred during the same five-year period, who were not included because of missing data. Therefore, the children included appear to be a representative sample from our outpatient population.

Family history for atopy in first degree relatives (parents and siblings) was considered as a binomial variable, either positive or negative. Therefore, at the first survey subjects were stratified in a group with a positive family history of atopy ($n=273$) and another group with a negative family history of atopy ($n=122$). Of the remaining 11 children no data on family history of atopy were available.

In the second survey in adulthood, performed between June 1987 and December 1990, 34 persons (8.4%) could not be traced; six subjects (1.5%) lived abroad. Two persons (0.5%) were hospitalized because of psychiatric illness. Sixteen subjects (3.9%) were not co-operative. A total of 58 subjects (14.3%) were lost to follow-up.

The remaining 348 persons (85.7%) participated in the follow-up study. In the outpatient clinic 285 adults (70.2% of the original patients of childhood), aged 21–29 years, were re-investigated, using the same methods as in childhood. Sixty-three adults (15.5%) replied to the questionnaire, but were not able or willing to perform the tests.

In adulthood, subjects were seen as much as possible in the same season of the year as in the first survey, to avoid seasonal influences. Informed consent from all partici-

pants was obtained. The study was approved by the Medical Ethics Committee of the University Hospital of Groningen. Both in childhood and adulthood, inhaled bronchodilators were withheld for at least 12 hr before the tests, and xanthine derivatives for a minimum of 48 hr. If required, maintenance treatment with cromoglycate or inhaled corticosteroids was continued.

Methods

Questionnaire The Dutch version of the standardized questionnaire of the British Medical Research Council (MRC—European Community for Coal and Steel questionnaire) was used in childhood as well as in adulthood [15]. In childhood, the questions were mostly answered by the parents, in adulthood the answers were obtained from the participants themselves. The questionnaire was extended to include questions about the occurrence of current or past symptoms of hay fever, eczema or other allergic features in the patients or their first degree relatives.

The atopic disorders represent a subgroup of allergic diseases with a familial tendency, often coexisting in the same individual. Although atopy refers to a hereditary predisposition for the production of IgE antibodies, unfortunately this could not be tested in the relatives of the participants. Therefore, in the study a first degree relative was considered atopic, if symptoms of either eczema, hay fever or asthma were reported in the questionnaire, corresponding to the following definitions: Hay fever has been defined as transient episodes of upper respiratory tract itching or sneezing and increased nasal mucous production, mostly in spring and/or summer [8]. Eczema consisted of scaly, red itching skin lesions, particularly occurring in flexural areas, face or trunk, that persisted for 4 weeks or more [16]. Asthma was scored positive if periods or attacks of breathlessness with wheezing and/or coughing were reported, or a doctor's diagnosis of asthma had previously been made.

Family history of atopy was considered positive if at least one of the parent(s) and/or sibling(s) were known to have had asthma, hay fever or eczema or a combination. Persons were considered as having asthmatic symptoms if they had at least one of four major symptoms; a symptom score was used to quantify these symptoms. The symptom score is a cumulative score, ranging from 0–4, being the sum of four categories of binomial symptoms: cough, wheeze, exercise-induced asthma and asthma attacks. Each of the symptoms is of equal value in this score. Symptoms were scored according to the guide-lines of the MRC-ECCS questionnaire:

Cough was considered to be present if subjects coughed for at least 3 months in a year.

Wheezing was considered present if wheezing or whistling chest sounds were heard more or less frequently.

Dyspnoea was subdivided in two categories: exercise induced dyspnoea and asthma attacks. Exercise-induced asthma was scored if the subject reported shortness of breath at physical exertion or sports.

Attacks of breathlessness with wheezing in the last 3 years were noted as asthma attacks.

Pulmonary function Spirometry was performed with a water-sealed spirometer (Lode spiograph D75, Groningen, The Netherlands). Inspiratory vital capacity (IVC) and forced expiratory volume in one second (FEV₁) were measured until three technically satisfactory recordings were produced. The best of these three efforts of baseline lung function measurement was used as pre-challenge value for the histamine provocation test, as well as for statistical analysis. Reference values of Tammeling were used [17]. FEV₁ data are expressed as FEV₁% predicted = (FEV₁/FEV₁ predicted) × 100%.

Histamine inhalation test Histamine provocation was carried out according to the modified method of Tiffeneau, described by De Vries and Knol [18,19]. A 30 sec tidal breathing method was used with a Wiesbadener Doppel inhalation device, filled with 4 ml of test solution, with a gauged airflow of approximately 5 l/min. Under these conditions nebulizer output was 0.06 ml/min.

After baseline lung function measurement, an aerosol of control solution was inhaled. Then doubling concentrations of histamine biphosphate, ranging from 0.5 mg/ml to 64 mg/ml, were inhaled. The concentration steps were 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0 and 64.0 mg/ml. The 64.0 mg/ml concentration was used in adulthood only. FEV₁ values were measured 30 and 90 sec after the end of each inhalation step. As soon as a decrease of at least 10% of baseline FEV₁ was reached in all recordings after a certain step, or the maximum histamine concentration had been given, the provocation was stopped. The histamine concentration at which there was a decrease in FEV₁ of at least 10% of baseline value was taken as the threshold value (PC₁₀-histamine). The exact PC₁₀-histamine was calculated from the log-dose response curve [20]. Determination of PC₁₀ had been the standard method used to define bronchial responsiveness in the first survey and was, therefore, used again in the present survey to make a comparison possible.

Skin tests A panel of seven (eight) antigens (Diephuis Laboratory, Groningen, The Netherlands), a Coca-solution (negative control) and a histamine control solution (positive control) were tested on the volar surface of the forearm. The antigens tested were house dust,

house-dust mite (in adulthood only), grass pollen, weeds, spring pollen, tree pollen, moulds, animal dander and feather mixture. Of each allergen, as well as histamine and control solution, 0.1 ml was injected intradermally.

After 15 min the weal diameter was scored bi-directionally using the following criteria: mean diameter < 5 mm, score 0; 5–10 mm, score 1; 10–15 mm, score 2; > 15 mm, score 3. It has been previously shown that a combination of house-dust mite, grass pollen and cat dander identifies > 98% of atopic children in the U.K. [21]. Therefore, in our study, to compute a cumulative, 'total' skin test score, the scores for the three most prominent allergens (house dust, grass pollen, and animal dander and feather mixture), ranging from 0 to 3 for each allergen tested, were added. Total skin test score was then considered as a categorical variable: class 1, score 0–3; class 2, score 4–6; class 3, score 7–9.

Eosinophil count Eosinophil granulocytes in peripheral blood were counted in a Bürker counting chamber. Reference values for the age-dependent criterion of eosinophilia were published by Veening [22].

Statistical analysis Statistical analysis was performed with the SPSS—PC (Statistical Package for Social Sciences for personal computers) software program. As no relevant statistically significant differences were found between the data of the 285 subjects, participating in the detailed study in adulthood, and the data of the 63 subjects who responded to the questionnaire only in adulthood, using either unpaired Student's *t*-test or Chi-squared test, in adulthood these two groups were not separately analysed.

Within each group childhood and adulthood data were analysed with a paired Student's *t*-test and McNemar's Chi-squared test. The data of the various subgroups were tested for statistically significant differences by means of either a Chi-squared test, when absolute numbers or proportion were compared, or analysis of variance techniques for continuous variables. A *P*-value < 0.05 was considered statistically significant.

Results

Family history of asthma and allergic disease

Data on family history of atopy were available for 320 subjects, participating in both surveys. Childhood and adulthood data for subjects with a positive and those with a negative family history were compared. Results are given in Table 1.

No striking differences in age at entry of the study, gender distribution and interval of follow-up were noted. The prevalence of associated allergic diseases, other than

Table 1. Influence of family history of atopy

	Family history of atopy		<i>P</i>
	Positive (<i>n</i> = 198)	Negative (<i>n</i> = 122)	
Age at first survey (years)	9.8 (1.5)	10.0 (1.5)	0.29*
Interval of follow-up (years)	15.0 (1.6)	14.8 (1.7)	0.28*
Sex ratio ♂:♀	131:67	88:34	0.32†
Associated allergic diseases, <i>n</i> = (%)	98 (49)	56 (47)	0.61†
<i>Childhood</i>			
Age of onset of respiratory symptoms (years) mean (s.d.)	3.1 (2.9)	2.7 (2.7)	0.20*
Respiratory symptom score, mean (s.d.)	3.0 (1.0)	2.9 (1.0)	0.21*
IVC% predicted, mean (s.d.)	97 (13)	97 (13)	0.90*
FEV ₁ % predicted, mean (s.d.)	91 (17)	91 (16)	0.84*
PC ₁₀ histamine, geom. mean (% s.d.) (mg/ml)	7.3 (5.3)	7.9 (5.3)	0.03*
<i>Adulthood</i>			
Current respiratory symptoms, <i>n</i> = (%)	140 (71)	81 (66)	0.49†
Respiratory symptom score, mean (s.d.)	1.4 (1.2)	1.3 (1.2)	0.64*
IVC% predicted, mean (s.d.)	104 (13)	104 (11)	0.74*
FEV ₁ % predicted, mean (s.d.)	96 (18)	95 (17)	0.68*
PC ₁₀ histamine, geom. mean (% s.d.) (mg/ml)	7.9 (5.9)	8.3 (5.9)	0.53*

* Paired Student's *t*-test.

† McNemar's Chi-squared test.

asthma, was practically equal in both groups. Age of onset and severity of respiratory symptoms were comparable. Lung function data (IVC% predicted and FEV₁% predicted) as well as data on bronchial responsiveness in childhood showed no important differences. No correlation to the risk of current respiratory symptoms in adulthood was found, nor were statistically significant differences revealed in symptom scores in adulthood.

In the second survey, parameters of lung function were still in the same range in both groups, as was the mean level of bronchial responsiveness.

Associated allergic disease

The prevalences of associated eczema and hay fever in children with asthma in the study were 41% and 13%, respectively, including 5.6% of subjects who had associated eczema as well as hay fever.

We correlated the existence of these allergic diseases to mean skin test score and eosinophil count for each group in both surveys (Table 2). Skin test scores were significantly lower in subjects without associated allergic diseases than in the remaining groups, both in children and adults. Mean eosinophil count was highest in subjects

with the triad of asthma, eczema and hay fever, both in childhood and adulthood, but was also significantly higher in children with asthma and eczema.

For each subgroup the mean symptom score in both surveys and the proportion of ongoing respiratory symptoms in adulthood was assessed. Figures did not differ significantly. Functional data of lung function tests and measurements of bronchial responsiveness were comparable.

Discussion

In this study the influence of a positive family history of atopy, as well as associated allergic diseases in the child, were studied in relation to the outcome of childhood asthma. No influences of either a positive family history of asthma or atopy on disease severity, neither in childhood nor in adulthood, could be demonstrated. No relation between positive family history for atopy and the risk of having current respiratory symptoms in young adulthood was found.

The prevalence of hay fever was relatively low in this study, compared to data on the coexistence of asthma and hay fever in the literature [1,2,16]. The prevalence of

Table 2. Influence of concurrent allergic diseases in childhood

	Associated allergic disease				
	None	Eczema	Hay fever	Eczema and hay fever	<i>P</i>
<i>Childhood (n = 395)</i>					
<i>n</i> =	204	140	29	22	
% =	52	35	7	6	
Skin test score					
mean	4.2	5.8	5.8	5.7	<0.01*
s.d.	2.7	2.4	2.6	2.1	
Eosinophil count (<i>n</i> × 10 ⁶ /l)					
mean	407	536	376	617	<0.01*
s.d.	323	364	363	280	
Respiratory symptom score					
mean	2.8	3.0	2.9	3.1	0.23*
s.d.	1.2	0.9	1.3	1.0	
IVC% predicted					
mean	96	99	97	99	0.57*
s.d.	15	14	15	9	
FEV ₁ % predicted					
mean	91	90	93	94	0.70*
s.d.	16	17	19	15	
PC ₁₀ histamine (mg/ml)					
geometric mean	7.8	7.2	6.9	6.4	0.11*
% s.d.	5.2	5.2	5.1	5.0	
<i>Adulthood (n = 285)</i>					
<i>n</i> =	141	106	23	15	
% =	50	37	8	5	
Skin test score					
mean	4.4	5.5	6.1	5.2	0.01*
s.d.	3.4	3.5	3.5	3.9	
Eosinophil count (<i>n</i> × 10 ⁶ /l)					
mean	251	290	274	339	0.47*
s.d.	222	262	187	358	
Current respiratory symptoms					
<i>n</i> =	106	88	18	11	0.49†
% =	75	83	78	73	
Respiratory symptom score					
mean	1.2	1.5	1.4	1.3	0.39*
s.d.	1.2	1.1	1.2	1.5	
IVC% predicted					
mean	105	102	105	105	0.45*
s.d.	13	13	14	7	
FEV ₁ % predicted					
mean	98	94	96	95	0.26*
s.d.	17	19	19	14	
PC ₁₀ histamine (mg/ml)					
geometric mean	8.5	7.4	7.6	7.4	0.26*
% s.d.	5.6	5.9	5.3	6.3	

* Anova.

† Chi-squared test.

allergic dermatitis (eczema) in subjects with allergic asthma is comparable to the figures in the literature [3,4,16]. It is known that the prevalence of hay fever increases with age, whereas that of eczema declines [16]. The low prevalence of hay fever may probably be explained by the relatively young age of the children.

Concurrent associated allergic diseases such as eczema or hay fever did not aggravate symptoms in either survey. No relation between concurrent associated allergic diseases and the proportion of subjects with current respiratory symptoms in adulthood was found.

No differences were seen in lung function data or bronchial responsiveness that might have been related to either family history of atopy or associated allergic diseases. A significant relationship was found between the presence of associated allergic diseases in the patient, and skin reactivity in childhood, as well as adulthood. The coexistence of allergic eczema was related to a significantly higher eosinophil count in childhood; this difference had disappeared in adults. However, none of these allergic parameters had an effect on prognosis of symptoms or lung function.

Therefore the outcome of childhood asthma, as defined by the presence and severity of respiratory symptoms, was not predicted either by a positive family history for atopy, or associated allergic diseases. This finding is in agreement with a recent study in another group of allergic asthmatic subjects from our outpatient department [3]. These two studies were both done in a well-defined study group of young, mostly allergic, asthmatic children. However, in a group of non-asthmatic subjects, a positive family history and associated allergic diseases in the subject might have a greater impact on the outcome of respiratory symptoms. This, of course, especially applies to epidemiological studies. The majority of clinical studies, however, fail to define properly the population under study, and give no or only limited data about the prevalence of allergy in the study group. Therefore, comparison of figures is difficult.

We do realise that, although data assessment was carefully done, the use of a questionnaire may lead to some recall bias. It has been shown that parental recall of respiratory symptoms in infancy was increased if later respiratory problems occurred [23]. A comparable recall bias may have played a role in answering the questions on atopic diseases in relatives. The design of our study, however, did not enable us to measure the extent to which false reporting of symptoms may have been occurring.

Relatively few data are presented on the influence of family predisposition in relation to the outcome. In a questionnaire based study by Clifford *et al.* [24] in 2503 children aged 7 and 11, the prevalence of wheeze and asthma were strongly related to parental asthma. More-

over, in a sample of 397 children from the cohort, a strong relationship has been shown between wheeze, reported in the questionnaire, and bronchial responsiveness and atopy [25]. In this study, however, the influence of family history of atopy in relation to prognosis towards adulthood was not studied. Ryssing and Flensburg [26] and Blair [1] stated that a positive family history for atopy was associated with an unfavourable outcome. A positive family history did not worsen the prognosis in the study of Mukoyama *et al.* [27]. Another Japanese study did not find a relationship between family history and prognosis of asthmatic children either [28].

Family history of atopy may affect prognosis of asthmatic children in at least two ways: the severity of asthma may either be genetically determined, or may be mainly influenced by the common family environment. In our study, most of the adult participants had left their parental home for a considerable period of time. Nowadays, a genetic predisposition by a dominant inheritance of atopy is suggested from family studies of IgE responses to common inhaled allergens [29]. Recently the gene locus for asthma and hay fever has been assigned to chromosome 11 [12]. Cookson and co-workers have found that the children with two affected parents had the more severe respiratory symptoms and thus may be homozygous for the atopy gene. However, apart from genetic predisposition, other factors, including environmental factors, must influence the clinical expression and prognosis of asthma. Studying the concordance rates of asthma, hay fever and allergic eczema in monozygotic twins, it was concluded that, although the data supported a significant genetic component, the effect of the genetic component was small, since approximately 80% of monozygotic twins were discordant for these three allergic diseases [30].

In the same study it has been found that family history of atopy was somewhat disease specific, suggesting that probably family history of asthma may be more important for the prognosis of an individual with asthma, than the family history of other atopic diseases. In our group of 198 children with a positive family history of atopy, the great majority (93%) had at least one first degree relative with asthma.

Since no differences were noted in the outcome in adulthood between subjects with and without a positive family history of atopy, in our study it is suggested that these other factors are more likely to be responsible for the persistence of asthma from childhood to adulthood than genetic influences. Atopy is an inherited trait, but clinical symptoms may be mainly dependent on prolonged allergen exposure [11].

Various authors have studied the influence of associated atopic diseases on the outcome of childhood asthma [1,5-8,31-34]. Blair [1] has found that the pres-

ence of infantile eczema did not affect the severity of the asthma, but associated persistent adult eczema was highly significant indicating a severe and persistent asthma in adulthood. In his study, the prevalence of allergy varied between 41 and 79% of subjects, depending on asthma severity. Kuzemko also suggested that allergic dermatitis per se did not influence prognosis; however, when this skin condition persists throughout adulthood, it does not affect the outcome [4].

Von Harnack and Panten stated that prognosis in adolescence and young adulthood was unfavourable in children with associated infantile eczema [31], as did Buffum and Settupane [32] and Baum [33]. In none of these studies are precise data on allergic status presented. In a follow-up survey of the subjects originally studied by McNicol and Williams [34], Martin *et al.* have found an association between the occurrence of hay fever and severe asthma at age 21 [35]. In this study, subjects were classified according to asthma severity; allergy was present in 20–80% of subjects. Eczema was significantly present only in subjects with the most severe asthma. However, although eczema occurred more commonly in the subjects with severe asthma, this finding should not be taken to indicate that children who develop eczema have a less favourable prognosis for asthma [35]. At age 28, the occurrence of hay fever was again strongly related to the severity of asthma, as its prevalence increased with the severity of asthma and was highest in the group of subjects with the most severe asthma [8]. Most subjects complaining of hay fever had had an asthma attack in the previous three years. Eczema was uncommon at this age in all groups. Therefore, although in their study the higher prevalence of concurrent hay fever in severe adult asthmatics might suggest an unfavourable effect of hay fever on prognosis, in fact the predictive value of hay fever in childhood on prognosis in adulthood was not directly studied. Moreover, there is no indication that eczema in childhood might worsen the outcome in adulthood. This result is in agreement with our findings.

In an epidemiological study, Broder [36] found a relation between prevalence of asthma and associated allergic diseases, demonstrating an unfavourable course of respiratory symptoms in children with associated hay fever or eczema. These conflicting results are likely to be due to the different populations that were studied.

The conclusions in most studies are based on associated findings in questionnaires; in none of the studies mentioned were subjects stratified in, for instance, either a positive or negative family history group at study entry. We feel that a comparison of objective measurements of functional data is even more relevant for an assessment of the influence on prognosis. However, as asthma is a

multifactorial disease, it is almost impossible to define the influence of a single item on the prognosis.

In conclusion, in our study we found that a positive family history of asthma or atopy, as well as associated allergic diseases in the child do not predict the prognosis of childhood asthma throughout life.

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References

- 1 Blair H. Natural history of childhood asthma. *Arch Dis Child* 1977; 52:613–19.
- 2 Reinberg A, Gervais P, Levi F, Smolensky M, DelCerro L, Ugolini C. Circadian and circannual rhythms of allergic rhinitis: an epidemiologic study involving chronobiologic methods. *J Allergy Clin Immunol* 1988; 81:51–62.
- 3 Gerritsen J, Koëter GH, Monchy de JGR, Knol K. Change in airway responsiveness to inhaled house dust from childhood to adulthood. *J Allergy Clin Immunol* 1990; 85:1083–9.
- 4 Godfrey S. Asthma in children. In: Clark TJH, Godfrey S, eds. *Asthma*. 2nd edn. London: Chapman and Hall, 1983.
- 5 Kuzemko JA. Natural history of childhood asthma. *J Pediatrics* 1980; 97:886–92.
- 6 Sibbald B. Extrinsic and intrinsic asthma: influence of classification on family history of asthma and allergic disease. *Clin Allergy* 1980; 10:313–18.
- 7 Sibbald B, Horn MEC, Gregg I. A family study of the genetic basis of asthma and wheezy bronchitis. *Arch Dis Childh* 1980; 55:354–7.
- 8 Kelly WJW, Hudson I, Phelan PD, Pain MCF, Olinsky A. Atopy in subjects with asthma followed to the age of 28 years. *J Allergy Clin Immunol* 1990; 85:548–57.
- 9 Johnstone DE. Some aspects of the natural history of asthma. *Annals of Allergy* 1982; 49:257–64.
- 10 Ownby DR. Environmental factors versus genetic determinants of childhood inhalant allergies. *J Allergy Clin Immunol* 1990; 86:279–87.
- 11 Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. House dust mite allergen (Der p I) exposure and the development of sensitization and asthma in childhood. *N Engl J Med* 1990; 323:502–7.
- 12 Martin AJ, Landau LI, Phelan PD. Predicting the course of asthma in children. *Aust Pediatr J* 1982; 18:84–7.
- 13 Benedictis FM de, Canny GJ, Levison H. The progressive nature of childhood asthma. *Lung* 1990; 168 Suppl:278–85.
- 14 Cookson WOCM, Sharp PAA, Faux JA, Hopkin JM. Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11 q. *Lancet* 1989; i:1292–5.
- 15 Lende van der R, Orie NGM. The MRC-ECCS question-

- naire on respiratory symptoms (use in epidemiology). *Scand J Respir Dis* 1972; 53:218-26.
- 16 Sporik R, Holgate ST, Cogswell JJ. Natural history of asthma in childhood—a birth cohort study. *Arch Dis Child* 1991; 66:1050-3.
 - 17 Tammeling GJ. Standard values for lung volumes and ventilatory capacity of sanatorium patients. *Selected Papers* 1969; 1:65-89.
 - 18 Vries de K, Goei T, Booy-Noord H, Orie NGM. Changes during 24 hours in the lung function and histamine hyperactivity of the bronchial tree in asthmatic and bronchitic patients. *Int Arch Allergy* 1962; 20:93-101.
 - 19 Knol K. A Clinical and epidemiological study of the significance of bronchial hyperreactivity in children with chronic non specific lung disease (CNSLD). Thesis, Groningen, 1965.
 - 20 Cockcroft DW, Kilian DN, Mellon JJA, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clin Allergy* 1977; 72:35-43.
 - 21 Clifford RD, Radford M, Howell JB, Holgate ST. Prevalence of atopy and range of bronchial response to methacholine in 7 and 11 year old schoolchildren. *Arch Dis Child* 1989; 64:1126-32.
 - 22 Veening GKK. Waarnemingen over het aantal eosinophile granulocyten in het bloed bij asthmatici en normalen. Thesis, Groningen, 1965.
 - 23 Strachan DP. The prevalence and natural history of wheezing in early childhood. *J R Coll Gen Pract* 1985; 35:182-4.
 - 24 Clifford RD, Radford M, Howell JB, Holgate ST. Prevalence of respiratory symptoms among 7 and 11 year old schoolchildren and association with asthma. *Arch Dis Child* 1989; 64:1118-25.
 - 25 Clifford RD, Radford M, Howell JB, Holgate ST. Associations between respiratory symptoms, bronchial response to methacholine, and atopy in two age groups of schoolchildren. *Arch Dis Child* 1989; 64:1133-9.
 - 26 Ryssing E, Flensburg EW. Prognosis after puberty for 442 asthmatic children examined and treated on specific allergologic principles. *Acta Paediatr (Stockh)* 1963; 52:97-105.
 - 27 Mukoyama T, Baba M, Kitajima Y, Iwatake K, Watanabe A, Kabasawa Y, Matsui T, Ebihara S, Mitsukawa M. The prognosis of asthma in children. *Acta Paediatr Jpn* 1975; 17:23-9.
 - 28 Nishima S, Inamitsu T, Shibata R, Kanegae N. Clinical manifestations, pulmonary function, and prognosis in asthmatic children: a comparison between groups with a high and a low serum IgE level. *Acta Paediatr Jpn* 1987; 29:639-44.
 - 29 Cookson WOCM, Hopkin JM. Dominant inheritance of atopic immunoglobulin-E responsiveness. *Lancet* 1988; i:86-8.
 - 30 Lubs M-LE. Empiric risks for genetic counselling in families with allergy. *J Pediatr* 1972; 80:26-31.
 - 31 Von Harnack GA, Panten H. Asthma bronchiale im Kindesalter. *M Schr Kinderheilk* 1957; 105:255-8.
 - 32 Buffum WP, Settipane GA. Prognosis of asthma in childhood. *Am J Dis Child* 1966; 112:214-17.
 - 33 Baum WF. Katamnestische Untersuchungen über Beginn und Verlauf des Asthma bronchiale im Kindesalter. *Kinderärztliche Praxis* 1975; 43:510-16.
 - 34 Williams H, McNicol KN. Prevalence, natural history and relationship of wheezy bronchitis and asthma in children. An epidemiological study. *Br Med J* 1969; 4:321-5.
 - 35 Martin AJ, Landau LI, Phelan PD. Natural history of allergy in asthmatic children followed to adult life. *Med J Aust* 1981; 2:470-4.
 - 36 Broder I, Barlow PP, Horton RJM. The epidemiology of asthma and hay fever in a total community. Tecumseh Michigan. II. The relation between asthma and hay fever. *J Allergy* 1962; 44:524-31.

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