

The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years

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Summary

The effect of genetic and environmental factors on the prevalence of allergic disorders in early childhood was determined in a prospective follow-up study. Information was available on 1174 children at the age of 2 years. Two-hundred and seventy-five were considered to have an allergic disorder. The prevalence varied from 3.2% for rhinitis to 10.9% for asthma. At 2 years 60 children reacted positively on skin-prick test (SPT). Multivariate logistic regression analysis was used to obtain adjusted odds ratios (95% confidence interval) for each factor. For asthma, positive family history, male sex, low birth-weight, maternal smoking and season of birth were significant risk factors. For eczema, positive family history was the only significant risk factor. For rhinitis, lower socio-economic group and autumn birth were significant. Male sex and low birth-weight were significant for skin test positivity. Positive family history and low birth-weight were significant risk factors for any allergy. Low birth-weight was also a significant risk for skin test reactivity to house dust mite. Genetic and environmental factors have a profound effect on the development of allergic disorders in the first two years of life.

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Introduction

Genetic factors are important in the development of allergic disorders [1]. Positive family history predisposes to allergic disorders [2]. There is also a male preponderance in allergic disorders particularly asthma [3–5]. During the last decade several studies have concluded that cord IgE is a good predictor of allergic disease [6–10].

Although it is important to study genetic factors so that infants at risk can be identified, there is little that can be done to influence the genetic aspects of allergic disease. Therefore attention must be turned to influencing the environmental factors. Some of these factors have been studied previously including method of feeding [9, 11–15], passive smoking [16–17] and month of birth [18–20].

An epidemiological, observational study was carried out to estimate the prevalence of allergic disorders and to identify genetic and environmental risk factors important in their development. The results of the first year of follow-up have been reported elsewhere [21–23]. In this communication the effect of various risk factors on the prevalence of allergic disorders at 2 years is reported.

Material and methods

The parents of 1215 infants born in the Isle of Wight between January 1989 and February 1990 were contacted soon after the birth of their child. Approval for the study was given by the ethical committee of the Isle of Wight Health Authority. Mothers (and fathers if available) were interviewed soon after the birth of their child. The study was fully explained and informed consent obtained. Information was obtained on the history of atopic disorders in the immediate family. A diagnosis of asthma, eczema, allergic rhinitis and food allergy was accepted when it had been diagnosed by a doctor. The infant was regarded as having a positive family history when either parent or sibling suffered from one or more atopic disorder. Allergy in distant relatives was not considered. Information was obtained on the parental smoking habits separately for mother and father. Those who smoked regularly (one or more cigarettes a day) were regarded as smokers. Information was also obtained on the presence of pets in the house. Blood was collected from the umbilical cord of 1106 infants. Total IgE was measured using a new enzyme immunoassay [24] EIA ULTRA® (Pharmacia Diagnostics AB, Uppsala, Sweden). Contamination of cord blood by maternal blood during

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sampling was excluded by measurement of cord IgA. Eighty-six infants were excluded from analysis involving cord IgE as cord IgA was found to be higher than 10 mg/l. Cord IgE data were available on 1020 infants.

Data on the estimated date of delivery (EDD) and birth weight were taken from the record books of the labour ward. Week of gestation was calculated from the EDD and the date of birth.

Data on the occupation of father and mother were obtained from hospital maternity notes. The children were classified by the father's occupation; the mother's occupation was coded if she was a single parent or if her husband was unemployed and she was employed. The social classes were formed according to the Registrar General's classification. To highlight the effect of socio-economic class, analysis was performed with classes 1, 2 and 3 grouped together as higher socio-economic (S-E) group (professionals and skilled workers) and classes 4 and 5 (semi-skilled, unskilled and unemployed) grouped together as lower S-E group. Unfortunately entries of parents' occupation were incomplete in the maternity notes and the data were available for only 685 infants. However, children where social class was known were compared to those where it was not known for various confounding variables [3]. There were no significant differences. To analyse the effect of season of birth, children were classified into four groups according to month of birth. Children born in December, January and February were defined as winter births. Those born in March, April and May as spring births, June, July and August as summer births and September, October and November as autumn births.

Follow-up

A research nurse contacted all parents when the infants were between the ages of 21 months and 24 months. The nurse completed a questionnaire. Information was obtained regarding any allergic symptoms since the first follow-up at one year. If any symptoms were present the parents were invited to attend the hospital clinic. A clinical assessment was made and SPT performed using allergen extracts (Soluprick ALK, Denmark) against Timothy grass pollen, cat dander, house dust mite (HDM), egg white and cows' milk in every child with a positive and negative control. Other allergens were added if the history suggested it appropriate to do so. A weal of the same size as the histamine response (1 mg/ml) was regarded as + + +, and of half that size as + +. Flare alone was ignored. + + or more was considered positive [25]. Allergic disorders were defined as follows:

- 1 Asthma: three or more separate episodes of cough and wheezing.

Table 1. Prevalance of allergic disorders at the age of 2 years ($n = 1174$)

	Symptoms only	Symptoms with positive Skin-prick test
Asthma	128 (10.9)	18 (1.5)
Eczema	126 (10.7)	30 (2.6)
Rhinitis	38 (3.2)	10 (0.9)
Food intolerance	53 (4.5)	20 (1.7)
Total	275 (23.4)	60 (5.1)

- 2 Eczema: chronic or chronically relapsing, itchy dermatitis (lasting more than 6 weeks) with characteristic morphology (areas of scaly, erythematous, pruritic lesions) and distribution (face, post-auricular area, scalp, extensor surface of extremities and flexural creases).
- 3 Rhinitis: recurrent nasal discharge or blockage with attacks of sneezing and itchy eyes.
- 4 Food reactions: a history of vomiting, diarrhoea, colic or rash within 4 hr of ingestion of a particular food on at least two occasions.

Infants breast fed exclusively for 3 months were classified as breast fed and the remainder as formula fed. Information on pets and tobacco smoking inside the house was updated at 2 years on all children.

Statistical methods

The chi-square test with Yates's correction and Fisher's exact test were employed for analysis of difference between proportions. Sensitivity, specificity and predictive values were calculated as described by Galen [26]. Logistic regression analysis was used in order to obtain the independent contribution of factors to the risk of allergic disorders. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated. Statistical analyses were carried out using SPSS/PC+ V4 (SPSS Inc., Chicago, IL, U.S.A.).

Results

Out of 1215 infants followed up at one year, information was available on 1174 for the second year follow-up. Four-hundred and thirty-six children were assessed and skin tested in the hospital clinic. Two-hundred and seventy-five of these were confirmed to have allergic disorder. Table 1 shows the prevalence of various allergic disorders. The prevalence varied from 3.2% for rhinitis to 10.9% for asthma. Fifty-three children were intolerant to

Table 2. Genetic and environmental factors and development of allergic disorders at 2 years

	Total	+ SPT	Asthma	Eczema	Rhinitis	Food intolerance
<i>Family history</i>						
Positive (<i>n</i> = 661)	27.7***	5.5	12.6*	14.4***	4.1	5.3
Negative (<i>n</i> = 511)	17.8	4.7	8.6	6.1	2.2	3.5
<i>Cord IgE (ku/l)</i>						
> 0.5 (<i>n</i> = 109)	25.7	8.3	9.2	16.5*	1.8	5.5
< 0.5 (<i>n</i> = 911)	22.9	4.5	10.9	9.9	3.5	4.4
<i>Sex</i>						
Male (<i>n</i> = 594)	24.8	6.1	13.0*	9.9	2.7	5.1
Female (<i>n</i> = 580)	22.1	4.1	8.8	11.6	3.8	4.0
<i>Birth weight (kg)</i>						
< 2.5 (<i>n</i> = 38)	36.8*	15.8**	26.3**	7.9	2.6	7.9
> 2.5 (<i>n</i> = 1105)	22.9	4.8	10.5	10.7	3.4	4.4
<i>Method of feeding</i>						
Formula (<i>n</i> = 733)	23.7	5.7	12.1	10.0	3.1	4.5
Breast (<i>n</i> = 436)	22.9	4.1	9.0	12.2	3.2	4.6
<i>Maternal smoking</i>						
Smoking (<i>n</i> = 257)	27.6	4.7	17.9***	8.2	3.1	4.7
No Smoking (<i>n</i> = 915)	22.2	5.3	8.9	11.5	3.3	4.5
<i>Season of birth</i>						
Summer (<i>n</i> = 273)	23.8	4.0	12.1*	8.8	3.7	5.1
Autumn (<i>n</i> = 262)	25.2	6.1	12.6*	12.2	5.0	3.8
Spring (<i>n</i> = 272)	25.0	4.4	12.9*	10.3	2.6	6.3
Winter (<i>n</i> = 367)	20.7	5.7	7.4	11.4	2.2	3.3
<i>Socio-economic group</i>						
Lower (<i>n</i> = 367)	25.6	6.3	14.2*	9.3	5.5	5.5
Higher (<i>n</i> = 318)	23.6	4.1	8.5	12.6	2.5	5.4
<i>Cats and/or dogs</i>						
Yes (<i>n</i> = 700)	22.4	4.1	11.0	10.9	3.1	2.7
No (<i>n</i> = 474)	24.9	6.5	10.8	10.6	3.4	7.2***

P* < 0.05, *P* < 0.01, ****P* < 0.001 (χ^2 test with Yates's correction).

All figures are percentages.

foods. The most frequent was cows' milk in 21 children, followed by egg (19), wheat (6) and other foods (15) such as orange, fish, strawberry and peanut.

Table 2 shows the percentages of children with allergic disorders in relation to various hereditary and environmental factors. Some of these risk factors are inter-related. Cord IgE levels are higher in male infants and those with a family history of atopy. Formula fed infants more often belong to a lower socio-economic group and are more exposed to passive smoking than breast fed infants. To obtain the independent effect of these factors, multivariate logistic regression analysis was used to

obtain adjusted odds ratios for each factor. The baseline for each factor was defined as:

Family history:	negative family history
Cord IgE:	low IgE (< 0.5 ku/l)
Sex:	female
Birth weight:	normal birth weight (> 2.5 kg)
Method of feeding:	breast feeding
Smoking:	no maternal smoking
Season of birth:	winter births
S-E Groups:	higher S-E group
Pets:	no cats or dogs

Table 3. Effect of various risk factors on prevalence of allergic disorders at two years evaluated with logistic regression analysis ($n = 1136$)

Risk factors	Allergic symptoms	Positive	
		skin-prick test	Asthma
<i>Positive Family history</i>	1.8 (1.3–2.4)**	—	1.7 (1.1–2.5)*
Maternal allergy	1.4 (1.1–1.9)	—	—
Sibling allergy	1.9 (1.3–2.7)**	—	—
<i>Male sex</i>	—	1.8 (1.0–3.2)	1.6 (1.1–2.3)
<i>Low birth weight</i>	2.0 (1.0–4.0)	3.5 (1.1–10.7)	3.0 (1.4–6.5)*
<i>Maternal smoking</i>	—	—	2.2 (1.5–3.4)**
<i>Season of birth</i>			
Spring	—	—	2.0 (1.2–3.5)*
Summer	—	—	1.7 (1.0–2.9)
Autumn	—	—	1.9 (1.1–3.3)

Odds ratio (95% confidence limits) are given. Other factors evaluated but found to be non-significant were paternal allergy, formula feeding, high cord IgE and pets. * $P < 0.01$. ** $P < 0.001$. All others listed, $P = < 0.05$. Non-significant relative risk are not listed for clarity.

Table 4. Effect of various risk factors on prevalence of allergic disorders at two years evaluated with logistic regression analysis ($n = 1136$)

Risk factors	Eczema	Rhinitis	Food intolerance
<i>Positive Family history</i>	2.5 (1.6–3.8)**	1.9 (1.0–4.0)	—
Maternal allergy	1.7 (1.2–2.4)*	—	—
Sibling allergy	3.1 (1.9–5.0)*	—	—
<i>Low birth weight</i>	—	—	5.2 (1.3–21.1)
<i>Season of birth</i>			
Autumn	—	2.9 (1.1–7.4)	—
<i>Cats and/or dogs</i>	—	—	0.6 (0.4–0.9)**

Non-significant relative risk are not listed for clarity.

Various allergic disorders were analysed (as dependent variables) to all risk factors of interest (Tables 3 and 4). Children who were skin tested ($n = 436$) had significantly more positive family history (OR, 1.4; CL, 1.1–1.7) than those who were not tested. Distribution of other risk factors did not differ significantly. Sixty children gave 89 positive reactions on SPT. House dust mite was the commonest reaction in 37 children followed by egg (17), cat (13), grass-pollen (7), dog (5) and other reactions (10) which included cows' milk, budgie, fish, strawberry and peanut. Logistic regression was used to obtain independent effect of the factors on skin test reactivity to these allergens.

Family history

Positive family history was a significant risk factor for total allergy, asthma, eczema and rhinitis (Tables 3 and 4). Data were analysed separately for maternal, paternal and sibling allergy. Maternal and sibling allergy were significant for total allergy and eczema. Paternal allergy was not a significant risk for any of the allergic disorders.

Cord IgE

A significantly higher percentage of children with high IgE (> 0.5 ku/l) developed eczema (Table 5) but when adjusted for other variables this became non-significant.

Table 5. Sensitivity, specificity and predictive value (in per cent) with 95% confidence limits, of cord IgE (ku/l) at various cut-off levels in relation to development of allergy

Cord IgE	Sensitivity	Specificity	Predictive value
> 0.2	41.77 (38.7–44.9)	58.62 (55.5–61.7)	23.40 (20.7–26.1)
> 0.5	11.81 (9.8–13.8)	89.66 (87.8–91.6)	25.69 (22.9–28.4)
> 0.8	5.48 (4.1–6.9)	94.64 (93.2–96.1)	23.64 (21.0–26.3)
> 1.0	4.64 (3.3–6.0)	96.93 (95.9–98.0)	31.43 (28.5–34.3)

The only significant effect of high cord IgE was seen on skin test reactivity to egg (OR, 6.5; CL, 1.8–22.9).

The sensitivity, specificity and predictive value of cord IgE at various cut-offs was estimated (Table 5). When detectable IgE (> 0.2 ku/l) was considered as high IgE, the sensitivity and specificity were both low and predictive value was only 23%. As the cut-off level is increased specificity improves but sensitivity becomes too low to be of any value.

Sex

Male children developed asthma and positive SPT more often than female (Tables 3 and 4).

Birth weight

Low birth weight (< 2.5 kg) children developed total allergy, asthma, food intolerance and positive SPT significantly more often than those with normal birth weight (Tables 3 and 4). Low birth weight was also a significant risk for skin-test reactivity to house dust mite; 3.4 (1.0–11.7).

Method of feeding

No significant relationship could be detected between method of feeding and various allergic manifestations in the second year of life.

Maternal smoking

Asthma was significantly related to maternal smoking but no effect of paternal smoking was observed (Tables 3 and 4).

Season of birth

Children born during winter months had significantly less asthma compared to other months. A higher percentage

of children born during autumn months developed rhinitis. When adjusted for other variables this was significant (Tables 3 and 4).

Socio-economic group

The percentage of children who developed asthma and rhinitis was higher among lower S-E groups (Table 2). When adjusted for other variables the risk was significant for rhinitis (2.6 [1.1–6.3]) but not for asthma.

Pets

There was no effect of presence of furry pets (cat and/or dogs) on the development of allergy. A curious relationship was observed with significantly less food intolerance in children with furry pets inside the house (Tables 3 and 4).

Positive SPT

When positive SPT was added to the regression model, it was found to be significant for eczema (3.6 [1.9–6.5]), rhinitis (2.8 [1.3–6.3]) and food intolerance (5.1 [5.6–10]).

Discussion

There are several problems in the epidemiological study of allergic disorders during infancy and early childhood. Parents tend to attribute a wide variety of symptoms to allergy. Investigations such as lung function tests are not appropriate at this age. A correct clinical diagnosis of asthma or eczema does not always represent type I IgE mediated allergy.

A subgroup of children was defined whose symptoms were backed by relevant positive skin test. Among those children who were seen in the clinic but did not fulfil the criteria, very few (5 of 161) had positive skin tests. Although they might develop clinical disorder in future, for the present analysis they were considered non-allergic.

Skin tests were done after the diagnosis was made so there was no bias in the reporting of clinical diagnosis. Possible bias can not be excluded, however, for the information that was available at the time of assessment. This includes sex, method of feeding, parental smoking, month of birth and presence of pets.

Maternal and sibling allergy were significant but paternal allergy was not a significant risk factor for any of the disorders. In most instances the history was taken from the mother and this lack of effect might be due to inaccurate information about the father's allergy. Other investigators have reached similar conclusions. Michel *et al.* [6] found that allergy in the infant doubled if the mother was allergic but no relationship to the father's allergy was detected. Happle and Schnyder [27] evaluated the children of men and women with atopic asthma. In children of atopic fathers, 32 of 98 (33%) were affected by some form of atopic disease compared to 45 of 93 (48%) of children of atopic mothers. They believed that this difference in hereditary risk was due to the Carter effect [28] providing evidence for polygenic inheritance in allergy. Another interesting finding was the relationship to sibling allergy. Among the immediate relatives the effect of a sibling with an allergic disorder was most closely related to the child's allergy. A similar observation was reported by Lebowitz [29] for serum IgE in children which was related to sibling, maternal and paternal IgE in that order of significance.

Several studies have found cord IgE to be useful in predicting atopy in children [6–10]. In the present study the first year results were confirmed at 2 year follow-up that cord IgE is a poor predictor of allergic disease.

In line with previous studies [3–5] male children were found to be at a higher risk for developing asthma. Although serum IgE levels are usually found to be higher in males compared to females [30,31] there is no such consensus for allergic disorder apart from asthma. Some studies have found males to be at a higher risk [7,10,32] but others could not find a difference in the incidence of allergy between sexes [33,34]. We were unable to find a difference between sexes for eczema, rhinitis or food intolerance or when any allergy was considered. There was however evidence that males are more prone to allergic sensitization. The risk for developing positive SPT was twice in males compared to females.

Low birth weight was found to be a highly significant risk factor for allergic disorders. The effect was stronger than that of family history of atopy. These children were also at risk to develop sensitivity to house dust mite by the age of 2 years. Low birth weight infants are said to be at risk of developing asthma in later childhood and adolescence [35]. An immunological immaturity may exist in the early months of life and exposure to allergens at this

vulnerable period leads to development of allergy later in life [36]. It is possible that low birth weight infants are particularly at risk because the immaturity of their immune system renders them liable to sensitization by various allergens. No relationship of allergic disorders or positive skin tests could be found to prematurity when calculated from week of gestation but information on week of gestation is not always accurate.

Breast feeding did not protect against allergic disorders. Data were repeatedly analysed with various definitions of breast feeding but the outcome was not different. As Sauls [37] points out mothers who choose to breast feed and formula feed their infants differ in several variables which affects the development of allergic disease. Some of the studies [11–13] claiming benefit from breast feeding have failed to adjust for these confounding variables. In this study there were significant differences in parental smoking habits and social class among the two groups. When analysing the effect of method of feeding all variables should be taken into account.

Wheezy illness is a strong risk factor for childhood asthma [38]. It has been shown in longitudinal studies that infants with recurrent wheezing share several characteristics with asthmatic children [4]. In the absence of more objective parameters this remains the best indicator for later childhood asthma. We found a highly significant effect of maternal smoking on the development of asthma. This may just be an irritant effect on the children's airways and may not lead to permanent bronchial hyperreactivity although children of smoking parents suffer from more frequent wheeze and lower FEV₁ than those of non-smoking parents [17]. A longer follow-up is required to clarify this effect. Maternal smoking has been associated with increased cord IgE levels [39] and exposure to passive smoking may increase serum IgE level in children [16]. Paternal smoking was not a risk factor for any of the allergic disorders. The likely explanation would be that fathers do not frequently smoke in the vicinity of the child.

Asthma occurred least frequently in children born in winter months. It can be hypothesized that this effect is due to the high concentration of tree and grass pollens during spring and summer respectively and house dust mite during autumn months. Although at this age there was no evidence of increased sensitivity to these allergens for the appropriate months other workers have found this relationship [18–20] at a later age.

Genetic and environmental factors are important in the predisposition and expression of allergic disorders. Among the genetic factors, maternal and sibling allergy and male sex are significant. The important environmental factors include low birth weight, maternal smoking and season of birth.

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References

- 1 Ownby DR. Environmental factors versus genetic determinants of childhood inhalant allergies. *J Allergy Clin Immunol* 1990; 86:279-87.
- 2 Kaufman HS, Frick OL. The development of allergy in infants of allergic parents: a prospective study concerning the role of heredity. *Ann Allergy* 1976; 37:410-15.
- 3 Horwood LJ, Fergusson DM, Shannon FT. Social and familial factors in the development of early childhood asthma. *Pediatrics* 1985; 75:859-68.
- 4 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.
- 5 Martin AJ, McLennan LA, Landau LI, Phelan PD. The natural history of childhood asthma to adult life. *Br Med J* 1980; 1397-400.
- 6 Michel FB, Bousquet J, Greillier P, Robinet-Levy M, Coulomb Y. Comparison of cord blood immunoglobulin E concentration and maternal allergy for the prediction of atopic disease in infancy. *J Allergy Clin Immunol* 1980; 65:422-30.
- 7 Croner S, Kjellman NIM, Eriksson B, Roth A. IgE screening in 1701 newborn infants and the development of atopic disease during infancy. *Arch Dis Child* 1982; 57:364-8.
- 8 Businco L, Marchetti F, Pellegrini G, Perlini R. Predictive value of cord blood IgE levels in at risk newborn babies and influence of type of feeding. *Clin Allergy* 1983; 13:503-8.
- 9 Chandra RK, Puri S, Cheema PS. Predictive value of cord blood IgE in the development of atopic disease and role of breast feeding in its prevention. *Clin Allergy* 1985; 15:517-22.
- 10 Magnusson CGM. Cord serum IgE in relation to family history and as a predictor of atopic disease in early infancy. *Allergy* 1988; 43:241-51.
- 11 Grulee CG, Sanford HN. The influence of breast and artificial feeding on infantile eczema. *J Pediatr* 1936; 9:223-5.
- 12 Saarinen UM, Kajosaari M, Backman A, Siimes MA. Prolonged breast-feeding as prophylaxis for atopic disease. *Lancet* 1979; ii:163-6.
- 13 Gruskay FL. Comparison of breast, cow, and soy feeding in the prevention of onset of allergic disease. *Clin Pediatr* 1982; 21:486-91.
- 14 Hide DW, Guyer BM. Clinical manifestations of allergy related to breast and cows' milk feeding. *Arch Dis Child* 1981; 56:172-5.
- 15 Halpern SR, Sellars WA, Johnson RB, Anderson DW, Saperstein S, Reisch JS. Development of childhood allergy in infants fed breast, soy, or cow milk. *J Allergy Clin Immunol* 1973; 51:138-51.
- 16 Kjellman NIM. Effect of parental smoking on IgE levels in children. *Lancet* 1981; i:993-4.
- 17 Murray AB, Morrison BJ. The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma. *J Allergy Clin Immunol* 1986; 77:575-81.
- 18 Bjorksten F, Suoniemi I. Dependence of immediate hypersensitivity on the month of birth. *Clin Allergy* 1976; 6:165-71.
- 19 Bjorksten F, Suoniemi I, Koski V. Neonatal birch-pollen contact and subsequent allergy to birch pollen. *Clin Allergy* 1980; 10:585-91.
- 20 Bjorksten F, Suoniemi I. Time and intensity of first pollen contacts and risk of subsequent pollen allergies. *Acta Med Scand* 1981; 209:299-303.
- 21 Hide DW, Arshad SH, Twiselton R, Stevens M. Cord serum IgE: An insensitive method for the detection of atopy. *Clin Exp All* 1991; 21:739-43.
- 22 Arshad H. Pets and atopic disorders in infancy. *Br J Clin Prac* 1991; 45:88-9.
- 23 Arshad SH, Hide DW. Effect of environmental factors on the development of allergic disorders in infancy. *J Allergy Clin Immunol* 1992; 95:235-41.
- 24 Arshad H, Twiselton R, Smith J, Hide DW. The influence of genetic and environmental factors on the level of IgE at birth. *Pediatr Allergy Immunol* 1992; 3:79-83.
- 25 Aas K. Some variables in skin prick testing. *Allergy* 1980; 35:250-2.
- 26 Galen RS, Gambino SR. Beyond normality: the predictive value and efficiency of medical diagnosis. John Wiley: New York, 1975:9-29.
- 27 Happle R, Schnyder UW. Evidence for the Carter effect in atopy. *Int Arch Allergy Appl Immunol* 1982; 68:90-2.
- 28 Carter CO. Genetics of common disorders. *Br Med Bull* 1969; 25:52-7.
- 29 Lebowitz MD, Barbee R, Burrows B. Family concordance of IgE, atopy, and disease. *J Allergy Clin Immunol* 1984; 73:259-64.
- 30 Barbee RA, Halonen M, Lebowitz M, Burrows B. Distribution of IgE in a community population sample: correlation with age, sex, and allergen skin test reactivity. *J Allergy Clin Immunol* 1981; 68:106-11.
- 31 Orren A, Dowdle EB. The effect of sex and age on serum IgE concentration in three ethnic groups. *Int Arch Allergy Appl Immunol* 1975; 48:824-35.
- 32 Astarita C, Harris RI, Fusco R *et al.* An epidemiological study of atopy in children. *Clin Allergy* 1988; 18:341-50.
- 33 Kjellman NIM. Atopic disease in seven year old children—incidence in relation to family history. *Acta Paediatr Scand* 1977; 66:465-71.
- 34 Luoma R, Koivikko A, Viander M. Development of asthma, allergic rhinitis and atopic dermatitis by the age of five years. A prospective study of 534 newborns. *Allergy* 1983; 38:339-46.

- 35 Seidman DS, Laor A, Gale R, Stevenson DK, Danon YL. Is low birth weight a risk factor for asthma during adolescence. *Arch Dis Child* 1991; 66:584-7.
- 36 Suoniemi I, Bjorksten F, Haahtela T. Dependence of immediate hypersensitivity in the adolescent period on factors encountered in infancy. *Allergy* 1981; 36:263-8.
- 37 Sauls HS. Potential effect of demographic and other variables in studies comparing morbidity of breast-fed and bottle-fed infants. *Pediatrics* 1979; 64:523-7.
- 38 Gurwitz D, Mindorff C, Levison H. Increased incidence of bronchial reactivity in children with a history of bronchiolitis. *Pediatrics* 1981; 98:551-5.
- 39 Magnusson CGM. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. *J Allergy Clin Immunol* 1986; 78:898-904.