

The development of allergy in high-risk children

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Summary

Background It is uncertain as to what extent the development of allergic disease in childhood is predictable during early infancy. A number of environmental factors have been suspected of increasing the risk of acquiring allergy, but the evidence is conflicting.

Objective To observe the development of atopy and allergic disease in a cohort of high-risk children so as to determine the importance of certain environmental factors and to study the relationship between early and later manifestations.

Methods A cohort of infants, all at high risk of allergy, was followed up from birth to the age of 7 years. In half, selected at random, cow's milk protein was avoided for 4 months. Skin-prick tests were performed and serum IgE measured in infancy and at 7 years, when an AlaTOP test was also performed.

Results Skin sensitivity to egg in the first year of life was strongly associated with eczema, asthma, mite sensitivity and serum IgE at the age of 7 years, when mother's atopic history was associated with AlaTOP status, father's atopic history with skin sensitivity, and male sex with both. Maternal smoking during pregnancy was associated positively with IgE at 3 months and negatively with skin sensitivity at 7 years. The development of allergy was unrelated to infant feeding method or number of older siblings.

Conclusion Allergic disease in childhood is to a large degree determined before birth or during infancy.

Keywords: asthma, eczema, hay fever, allergy, atopy, IgE, prediction

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Introduction

The ability to predict which infants will acquire allergic disease is potentially important in two ways. Firstly, it reflects the extent to which babies arrive in the world already predisposed to become allergic. This predisposition will of course have a genetic component, but it may also involve environmental factors that operate antenatally and are in principle open to intervention. Secondly, in so far as allergic disease can be predicted, it is possible to identify infants at very high risk in whom the benefits of prophylactic intervention (by allergen avoidance or

medication) are more likely to be found and will be most worthwhile.

A first degree family history of atopic disease is known to carry a higher risk for the infant. Cord blood IgE concentration was thought to be a good predictive test [1,2]; but more recent studies have shown that its sensitivity is rather low [3–5]. During infancy IgE levels have some predictive value; in an American cohort, serum IgE at 9 months of age was higher in children who wheezed up to the age of 6 years than in other children [6].

Various environmental factors have been suspected to influence the risk of allergy antenatally or neonatally, such as maternal smoking, breast-feeding, other foods (particularly cow's milk), number of siblings, birthweight, and exposure to inhaled allergens, such as the house dust mite. Much of the evidence is conflicting — thus early feeding

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with cow's milk has been associated with allergy both positively [7–9] and negatively [10].

A cohort study was set up comprising infants with a family history of atopy. It incorporated a randomized trial of withholding cow's milk protein from half the participants during the first 4 months of life [11]; other potential determinants were recorded prospectively. This paper presents the development of atopy and allergic disease up to the age of 7 years in this cohort; other findings have already been published [12].

Subjects and methods

The subjects in this study formed a cohort that was identified antenatally as being at high risk of allergy. A questionnaire completed by women in the antenatal clinics of two areas of south Wales enquired whether they, their husband or their children had ever had asthma, eczema or hay fever. Those who answered affirmatively were invited to participate in this study. A randomized controlled trial was conducted, half the mothers being advised to avoid giving their babies any food containing cow's milk protein for 4 months, while a soya preparation was given to those who were not breast feeding. Samples of maternal and cord blood were taken for measurement of IgE and IgG4 concentrations; further samples were taken from the babies when they were 3 months. The intention was to repeat the blood tests at 12 months, but it was found that venepuncture at this age caused some distress to the infants and their mothers, so the procedure was discontinued and results are available only for a subset. Skin tests for common allergens were performed at 6 and 12 months. The parents were asked at 3, 6 and 12 months whether the child had wheezed or been treated by a doctor for eczema. Various other details were recorded, including weight and head circumference at birth, duration of breast feeding (if any), pet ownership, and the presence of damp patches and mould on the inside walls of the house. About the time of the second to the sixth birthdays the parents were sent an annual questionnaire asking whether they had consulted a doctor about the child, whether the child had wheezed, and whether the child had been treated for eczema, during the past 12 months. About the time of the seventh birthday each child was invited to a clinic where a questionnaire was administered, skin tests were performed (for egg, milk, cat, mite, grass pollen and mixed moulds), blood was taken for AlaTOP testing, and the children were examined by a paediatrician.

Sera were analysed for Total IgE (AlaSTAT® EIA – Diagnostic Products Corp., Los Angeles, USA) and for inhalant IgE antibodies using the AlaTOP – EIA multi-allergen screen (Diagnostic Products Corp.) according to the manufacturers' recommendations [13]. The AlaTOP® test comprises aero-allergens from 12 sources: timothy grass,

Bermuda grass, birch tree, Japanese cedar tree, ragweed, plantain, *Parietaria*, *D. pteronyssinus*, cat, dog, *Penicillium notatum* and *Alternaria tenuis*; the test is designed for use in a wide variety of countries, so not all of the constituent allergens are encountered in the UK.

Association between categorical variables was examined using χ^2 tests; where one variable was ordinal, the χ^2 test for trend was used. The distributions of some of the variables were highly non-normal; in some cases transformations were used to reduce the skewness before comparing means, while in others non-parametric tests were employed to compare medians. In investigating possible risk factors, multiple logistic regression was used to identify factors which made independent contributions. The analysis was performed using SPSS for Windows.

The approval of the local Ethics Committee was obtained for both stages of the study.

Results

Of the 497 babies in the original cohort, 440 were seen at the age of 7 years, and detailed questionnaires were completed for another 13 children who were living outside the original area. Because of the missing information on some children at each stage in the study, there were differences in the numbers available for the various analyses. Skin tests were performed on 437 children at age 7; 109 of these had at least one weal of diameter 3 mm or more and were designated as atopic, while the other 328 children were considered to be non-atopic.

Table 1 shows the numbers of children who had positive skin tests (of 3 mm diameter or more) to the five antigens that were used on all three occasions. Egg was the antigen that most commonly gave a positive reaction at 6 months and one year (in 7% of children on each occasion), but it had declined in importance by 7 years to affect only 1%. Cat allergy increased from 1% at 6 months to 5% at 1 year, with a further rise to 9% by 7 years. A striking rise in mite sensitivity appeared between 1 and 7 years, to become the most frequent allergy (19%). Grass pollen sensitivity, rare in

Table 1. Numbers (%) of positive skin tests to certain antigens on different occasions

Antigen	6 months <i>n</i> = 478	1 year <i>n</i> = 477	7 years <i>n</i> = 437
Egg	34 (7.1)	34 (7.1)	4 (0.9)
Milk	3 (0.6)	3 (0.6)	4 (0.9)
Cat	5 (1.0)	25 (5.2)	40 (9.2)
Mite	1 (0.2)	8 (1.7)	84 (19.2)
Grass pollen	1 (0.2)	2 (0.4)	55 (12.6)

Table 2. Relationship between egg skin test at 6 months and serum IgE

Age (years)	Egg positive at 6 months		Egg negative at 6 months		P-value
	No.	Median IgE kU/L	No.	Median IgE kU/L	
3 months	32	2.85	413	1.4	0.00017
1 year	6	74	60	6.4	0.004
7 years	24	162.5	315	40	0.0001

Table 3. Relationship between symptoms reported annually and positive egg skin test at 6 months

Age (years)	Odds ratios (95% CI) for positive egg test		
	Eczema	Asthma	Wheeze
0–1	5.57 (2.70, 11.5)	–	0.93 (0.44, 1.97)
0–2	3.65 (1.74, 7.68)	2.38 (0.50, 11.2)	0.61 (0.28, 1.34)
0–3	1.90 (0.85, 4.25)	1.87 (0.53, 6.62)	1.43 (0.69, 2.94)
0–4	1.10 (0.37, 3.27)	4.09 (1.62, 10.3)	2.20 (1.08, 4.50)
0–5	1.52 (0.56, 4.14)	2.70 (1.10, 6.63)	1.70 (0.82, 3.52)
0–6	1.59 (0.58, 4.34)	2.58 (0.99, 6.69)	2.02 (0.98, 4.18)
0–7	3.55 (1.70, 7.43)	2.63 (1.26, 5.51)	2.56 (1.25, 5.24)
0–7	4.25 (1.80, 10.0)	2.23 (1.07, 4.66)	0.85 (0.41, 1.78)

the first year of life, also became common (12.6%) at 7 years. Of the other antigens that were used, none produced positive reactions in more than five subjects (1%) at 6 months, but at one year 26 children (5.5%) were sensitive to feathers and 17 (3.6%) to house dust, while at 7 years eight children (1.8%) were sensitive to a mould mixture that included *Alternaria* and *Cladosporium*. There was a strong relationship between egg sensitivity at 6 months and mite sensitivity at 7 years among the 427 children who were skin-tested on both occasions: 16 out of 31 who were egg-positive, and 66 out of 396 who were egg-negative, became mite-positive at 7 years ($P < 0.001$).

Table 2 shows median IgE concentrations in the children who had positive and negative skin tests to egg at 6 months. It is clear that egg sensitivity at that age is associated with higher IgE levels, not only in infancy but at the age of 7 years. The children destined to become atopic at the age of 7 years had significantly higher IgE levels at birth, at 3 months, and at 7 years, when median IgE concentrations were 148 and 31 kU/L in atopics and nonatopics, respectively.

Table 3 shows the relationship between a positive egg skin test at 6 months and the occurrence of eczema, asthma

Table 4. Relationship between symptoms reported annually and AlaTOP status at age 7

Age (years)	Odds ratios (95% CI) for positive AlaTOP test		
	Eczema	Asthma	Wheeze
0–1	2.42 (1.43, 4.09)	–	0.94 (0.58, 1.55)
0–2	1.58 (0.87, 2.86)	0.96 (0.24, 3.8)	0.76 (0.47, 1.24)
0–3	1.67 (0.93, 3.01)	2.68 (1.99, 7.15)	1.22 (0.74, 1.99)
0–4	1.66 (0.81, 3.44)	2.92 (1.22, 7.00)	1.96 (1.20, 3.18)
0–5	1.43 (0.70, 2.90)	2.46 (1.15, 5.85)	1.77 (1.08, 2.90)
0–6	0.98 (0.45, 2.13)	2.87 (1.31, 6.27)	1.95 (1.19, 3.22)
0–7	1.41 (0.87, 2.27)	2.76 (1.60, 4.76)	2.29 (1.40, 3.76)
0–7	1.64 (1.03, 2.64)	3.09 (1.83, 5.24)	1.25 (0.75, 2.07)

and wheeze as reported by the parents during each of the 7 years (except for asthma in the first year). For eczema and asthma all the odds ratios are greater than 1 (i.e. there is a positive relationship between the skin test and the symptom), significantly so on several occasions, including the first two years for eczema and the seventh year for both diseases. The year-to-year variations may be attributable to the width of the confidence intervals. The odds ratios for wheeze were lower than those for asthma. At each year, asthma was also associated with positive skin tests to cats and feathers at 1 year of age, the odds ratios for ages 0–7 years being 5.54 for cats (95% CI 2.41, 12.8) and 3.22 for feathers (95% CI 1.38, 7.54). For eczema these relationships were less consistent.

The AlaTOP test was performed in 338 children at age 7. Among the 104 who were AlaTOP-positive, 79 were atopic as judged by skin tests, and among the 234 who were AlaTOP-negative 232 were non-atopic. Table 4 shows the odds ratios for eczema, asthma and wheeze in relation to a positive AlaTOP. There was a significant association with eczema during the first year of life, and a significant association with asthma after the age of 2 years, showing that AlaTOP-positive children at age 7 have been at higher risk of atopic disease since birth. Again, the relationship with wheeze was similar to that with asthma, only weaker. Information about hay fever was available only at age 7; a history of the disease at any time was strongly related to a positive AlaTOP test (odds ratio 2.65, 95% CI 1.43, 4.88).

The results of univariate logistic regression analysis of various factors in relation to the skin sensitivity and AlaTOP test are shown in Table 5. Significant associations with either or both of these tests occurred for parental history, male sex, maternal IgE, cord IgE, and 3 months IgE (positive), and for maternal smoking during pregnancy and pet ownership at 1 year (negative). Maternal smoking habits in pregnancy and at 1 year were so similar that their

Table 5. Results of univariate logistic regression analysis of associations between skin sensitivity and AlaTOP test at 7 years and variables recorded in infancy

Variable	Skin sensitivity		AlaTOP test	
	Direction of association	P-value	Direction of association	P-value
Father's history	Positive	0.02	Positive	0.39
Mother's history	Positive	0.09	Positive	0.005
Weeks breast fed	Positive	0.06	Positive	0.63
Male sex	Positive	0.045	Positive	0.01
No. older siblings	Negative	0.13	Negative	0.12
Maternal smoking	Negative	0.003	Negative	0.05
Mould on walls	Negative	0.09	Negative	0.83
Pets	Negative	0.12	Negative	0.02
Maternal IgE*	Positive	0.005	Positive	0.004
Cord IgE*	Positive	0.01	Positive	0.08
3 months IgE*	Positive	0.02	Positive	0.003

* log values.

effects could not be distinguished. The negative relationship between pets and AlaTOP was marginally greater for dogs than for cats. There was a weak negative association between mould growth and skin sensitivity (not statistically significant). Further analysis showed no associations between skin sensitivity or AlaTOP test and randomization group, social class, dampness, birthweight, head circumference, or serum IgG4 in the mother, in cord blood, or at three months. Multivariate logistic regression analysis was then undertaken, using nine variables: paternal and maternal allergic histories, maternal smoking, social class, randomization group, sex, number of older siblings, duration of breast-feeding, and pet ownership. The skin sensitivity was positively associated with father's allergic history ($P = 0.018$) and negatively associated with maternal smoking ($P = 0.003$); the AlaTOP status was significantly and positively associated with mother's allergic history ($P = 0.022$) and male sex ($P = 0.007$), and negatively associated with the ownership of pets ($P = 0.048$).

The univariate analysis was repeated with the same variables, using the consultant's diagnosis of asthma, eczema and hay fever at 7 years as outcome measures. Male sex was associated positively with asthma and negatively with eczema; there were no other significant associations.

Maternal smoking during pregnancy was examined in relation to serum IgE concentrations. The number of cigarettes smoked per week during pregnancy was positively associated with log IgE at 3 months ($P = 0.01$). There was no association with log IgE in the cord blood or at 7 years; the relationship at 1 year was not examined as the numbers

were small. The number of prolonged colds during the first year of life was not related to atopic status at age 7. The number of older siblings was associated with the proportion who wheezed at the age of 7 in the non-atopics ($\chi^2 = 10.67$, $P = 0.0011$) but not in the atopics.

Discussion

The 7-year follow-up of these children shows that the groups destined to be atopic and non-atopic at the age of 7 years were different in several respects during the first year of life. Thus eczema in the first year of life was associated with AlaTOP status at age 7, egg sensitization at 6 months was strongly associated with serum IgE, mite sensitivity and asthma at age 7, and IgE levels over the whole period were related to atopic status. The relationship between cord IgE and subsequent atopy, although statistically significant, was too weak to be of much practical value in predicting which children would become atopic, confirming our earlier findings on this cohort [3] and reports from other workers [4,5]. In so far as atopy at age 7 is predictable in the first year of life, its predictability probably represents early manifestations of genetic predisposition, although it may also reflect some environmental factors that operate antenatally or in infancy.

The repeat skin tests show the order of appearance of different sensitivities and a marked change in their relative frequency over time. Of the antigens tested, egg was by far the most important among 6-month-old babies; during the second 6 months of life the prevalence of egg sensitivity remained constant while that of cat sensitivity rose steeply.

By the age of 7 years the pattern had changed completely: mite, grass pollen and cat became the predominant sensitivities, very few children being now sensitive to egg. Broadly similar findings were reported in a smaller study in which skin tests were performed annually up to the age of 5 years [14]. There are three possible explanations of this sequence. Firstly, it may represent the order in which the allergens are first encountered by the children. This does not seem very likely. Secondly, egg antigen may be peculiarly effective in switching on the allergic process, which then responds to other antigens. If so, withholding egg in infancy should prevent the development of allergy. Avoidance of ingested and inhaled allergens has been shown to reduce the incidence of allergy up to 2 years [15], but avoidance of food allergens (including egg) alone does not seem to be effective [16]. Thirdly, the response to egg antigen may be an early marker (though not a cause) of an allergic propensity, which later responds to inhaled allergens. In this case, egg avoidance would merely postpone and not prevent the appearance of allergic disease. Whatever the mechanism, it is clear that a positive response to egg at 6 months predicts mite-sensitivity and asthma at age 7.

The IgE-based AlaTOP test is designed to distinguish atopic from non-atopic persons in a wide variety of countries. It showed good overall agreement with the skin tests, and the two indices of allergy were broadly consistent in their relationship with the various factors examined in the univariate analysis. The association with male sex is well established. Parental history of allergy is also well known to be a risk factor for atopy, and it was on the basis of a first-degree family history that the children were selected in the first place. Somewhat surprisingly, maternal history was associated with AlaTOP status and paternal history with positive skin tests. Other studies have tended to suggest a stronger role for maternal than for paternal history [17,18]; it is, however, possible that inaccuracies in the paternal history (especially when it is obtained from the mother) cause its importance to be underestimated.

Maternal cigarette smoking appeared to raise IgE levels in infancy, as reported by Magnusson [19]. The increase in serum IgE seemed to be transitory and was not associated with atopy or disease at the age of 7 years. More unexpected was the negative association between maternal smoking during pregnancy and atopy (as judged by skin tests) at 7 years. Some studies have reported that maternal smoking is related to asthma [20,21]. Adult smokers tend to have higher serum IgE levels than non-smokers [22,23]; in one survey they also had a higher prevalence of positive skin tests [22] but in another survey their prevalence of skin sensitivity was significantly lower [23]. In the latter study the authors suggested that the findings might reflect a tendency for atopic subjects to avoid smoking, but it is quite possible that smoking affects IgE and skin sensitivity in different ways.

In the present cohort, maternal smoking was related to reported wheezing in the non-atopic but not in the atopic children [12]; it was not possible to distinguish between the effects of antenatal and postnatal maternal smoking.

Reported relationships between breast-feeding and atopy have been conflicting: several studies have shown a negative association [7,9,24–27], some have shown no association [14,28–30], while others have shown a positive association [31,32]. In the present study, duration of breast-feeding showed a non-significant positive association with atopic status in the univariate analysis; it appeared to protect against wheeze up to the age of 7 years in the non-atopics only [12]. Replacement of cow's milk by a soya preparation did not confer any protection, contrary to the findings of an earlier randomized trial, but this also involved the exclusion of beef, chicken, egg and wheat products for the first 9 months of life [8].

Several studies have reported that the number of older siblings is negatively associated with skin-prick reactivity [33,34], hay fever [35,36], wheeze [37], and asthma [36]. These associations were not confirmed in the present study, although the number of older siblings was related to wheeze in the non-atopics. Maternal smoking, breast-feeding and older siblings probably influence the risk of infection; the relationship between atopy and infection may not be the same in different populations.

Seidman *et al.* [38] reported an increased incidence of asthma among children whose birthweight was less than 2500 g. In the present study, birthweight was not related to any of the outcome variables studied; the numbers were very much lower than in Seidman's study, however, and babies weighing under 2000 g at birth were excluded. We did not confirm the reported association with head circumference [39]. If these associations occur, they probably have only marginal importance in the overall cause of allergic disease.

Unexpectedly, pet ownership in infancy was negatively associated with AlaTOP status at 7 years. This relationship may be attributable to chance or confounding variables (e.g. a strong family history of allergy, which operates against the keeping of pets [40]), but it suggests that in this population early exposure to pets is unlikely to increase the risk of allergy to any great degree. As previously reported, cat ownership during infancy was not related to skin sensitivity to cat antigen, nor was the level of mite antigen in household dust related to the development of mite sensitivity [12]. These antigens may be sufficiently ubiquitous for most susceptible children to become sensitized to them. The presence of moulds in infancy did not increase the risk of allergy; in fact there was a (non-significant) negative relationship. An association between current mould growth and wheeze has been reported [41,42] but was not found in this cohort [12].

In conclusion, the results of this follow-up study draw attention to the continuity in the manifestations of allergy and atopy over the first 7 years of life. To some extent this continuity reflects the genetic component in allergic disease. In so far as environmental factors influence the development of allergy, they must be looked for during infancy or in areas that were not investigated in this cohort.

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References

- 1 Croner S, Kjellman N-I M, 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.
- 2 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.
- 3 Merrett TG, Burr ML, Butland BK, Merrett J, Miskelly FG, Vaughan-Williams E. Infant feeding and allergy: 12-month prospective study of 500 babies born into allergic families. *Annals of Allergy* 1988; 61:13–20.
- 4 Ruiz RGG, Richards D, Kemeny DM, Price JF. Neonatal IgE: a poor screen for atopic disease. *Clin Exp Allergy* 1991; 21:467–72.
- 5 Hide DW, Arshad SH, Twiselton R, Stevens M. Cord serum IgE: an insensitive method for prediction of atopy. *Clin Exp Allergy* 1991; 21:739–43.
- 6 Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, and the Group Health Medical Associates. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; 332:133–8.
- 7 Grulee CG, Sanford HN. The influence of breast and artificial feeding on infantile eczema. *J Pediatrics* 1936; 9:223–5.
- 8 Johnstone DE, Dutton AM. Dietary prophylaxis of allergic disease in children. *N Engl J Med* 1966; 274:715–9.
- 9 Lucas A, Brooke OG, Morley R, Cole TJ, Bamford MF. Early diet of preterm infants and development of allergic or atopic disease: randomised prospective study. *Br Med J* 1990; 300:837–40.
- 10 Lindfors ATB, Danielsson L, Enocksson E, Johansson SGO, Westin S. Allergic symptoms up to 4–6 years of age in children given cow milk neonatally. *Allergy* 1992; 47:207–11.
- 11 Miskelly FG, Burr ML, Vaughan-Williams E et al. Infant feeding and allergy. *Arch Dis Child* 1988; 63:388–93.
- 12 Burr ML, Limb ES, Maguire MJ et al. Infant feeding, wheezing, and allergy: a prospective study. *Arch Dis Child* 1993; 68:724–8.
- 13 Merrett J, Merrett TG. Screening for IgE-mediated allergy. *J Clin Immunoassay* 1993; 16:164–72.
- 14 Cogswell JJ, Mitchell EB, Alexander J. Parental smoking, breast feeding, and respiratory infection in development of allergic diseases. *Arch Dis Child* 1987; 62:338–44.
- 15 DW, Matthews S, Matthews L, Stevens M, Ridout S, Twiselton R, Grant C, Arshad SH. Effect of allergen avoidance in infancy on allergic manifestations at age two years. *J Allergy Clin Immunol* 1994; 93:842–46.
- 16 Zeiger RS, Heller S, Mellon MH, Halsey JF, Hamburger RN, Sampson HA. Genetic and environmental factors affecting the development of atopy through age 4 in children of atopic parents: a prospective randomized study of food allergen avoidance. *Pediatr Allergy Immunol* 1992; 3:110–27.
- 17 Ownby DR. Environmental factors vs. genetic determinants of childhood inhalant allergies. *J Allergy & Clinical Immunol* 1990; 86:279–87.
- 18 Halonen M, Stern D, Taussig LM et al. The predictive relationship between serum IgE levels at birth and subsequent incidences of lower respiratory illnesses and eczema in infants. *Am Rev Respir Dis* 1992; 146:866–70.
- 19 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.
- 20 Weitzman M, Gortmaker S, Walker DK, Sobol A. Maternal smoking and childhood asthma. *Pediatrics* 1990; 85:505–11.
- 21 Martinez FD, Cline M, Burrows B. Increased incidence of asthma in children of smoking mothers. *Pediatrics* 1992; 89:21–6.
- 22 Zetterström O, Osterman K, Machado L, Johansson SGO. Another smoking hazard: raised serum IgE concentration and increased risk of occupational allergy. *Br Med J* 1981; 283:1215–7.
- 23 Cline MG, Burrows B. Distribution of allergy in a population sample residing in Tucson, Arizona. *Thorax* 1989; 44:425–31.
- 24 Chandra RK. Prospective studies of the effect of breast feeding on incidence of infection and allergy. *Acta Paediatr Scand* 1979; 68:691–4.
- 25 Hide DW, Guyer BM. Clinical manifestations of allergy related to breast and cows' milk feeding. *Arch Dis Child* 1981; 56:172–5.
- 26 Moore WJ, Midwinter RE, Morris AF, Colley JRT, Soothill JF. Infant feeding and subsequent risk of atopic eczema. *Arch Dis Child* 1985; 60:722–6.
- 27 Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet* 1995; 346:1065–9.
- 28 Gordon RR, Noble DA, Ward AM, Allen R. Immunoglobulin E and the eczema–asthma syndrome in early childhood. *Lancet* 1982; I:72–4.
- 29 Kramer MS, Moroz B. Do breast-feeding and delayed introduction of solid foods protect against subsequent atopic eczema? *J Pediatrics* 1981; 98:546–50.
- 30 Gustafsson D, Löwhagen T, Andersson K. Risk of developing atopic disease after early feeding with cows' milk based formula. *Arch Dis Child* 1992; 67:1008–10.
- 31 Taylor B, Wadsworth J, Golding J, Butler N. Breast feeding, eczema, asthma and hayfever. *J Epidemiol Community Health* 1983; 37:95–9.
- 32 Astarita C, Harris RI, De Fusco R, Franzese A, Biscardi D,

- Mazzacca FRM, Altucci P. An epidemiological study of atopy in children. *Clinical Allergy* 1988; 18:341–50.
- 33 von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Reitmeir P, Thiemann H-H. Skin test reactivity and number of siblings. *Br Med J* 1994; 308:692–5.
- 34 Strachan DP, Harkins LS, Johnston IDA, Anderson HR. Childhood antecedents of allergic sensitization in young British adults. *J Allergy Clin Immunol* 1997; 99:6–12.
- 35 Strachan DP. Hay fever, hygiene and household size. *Br Med J* 1989; 299:1259–60.
- 36 Jarvis D, Chinn S, Luczynska C, Burney P. The association of family size with atopy and atopic disease. *Clin Exp Allergy* 1997; 27:240–5.
- 37 Crane J, Pearce N, Shaw R, Fitzharris P, Mayes C. Asthma and having siblings. *Br Med J* 1994; 309:272.
- 38 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.
- 39 Godfrey KM, Barker DJP, Osmond C. Disproportionate fetal growth and raised IgE concentration in adult life. *Clin Exp Allergy* 1994; 24:641–8.
- 40 Brunekreef B, Groot B, Hoek G. Pets, allergy and respiratory symptoms in children. *Int J Epidemiol* 1992; 21:338–42.
- 41 Platt SD, Martin CJ, Hunt SM, Lewis CW. Damp housing, mould growth, and symptomatic health state. *Br Med J* 1989; 298:1673–8.
- 42 Dales RE, Zwanenburg H, Burnett R, Franklin CA. Respiratory health effects of home dampness and molds among Canadian children. *Am J Epidemiol* 1991; 134:196–203.