

Allergen avoidance in infancy and allergy at 4 years of age

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In an attempt to prevent or reduce the manifestations of atopic disease, a group of infants considered to be genetically at high risk of atopy was entered in a prenatally randomized, controlled study. A prophylactic group ($n=58$) was either breast-fed with their mothers excluding foods regarded as highly antigenic from their diets, or given an extensively hydrolysed formula. In addition, strenuous efforts were made to reduce exposure to the house-dust mite by application of acaricide to the bedroom and living room carpets and upholstered furniture. A control group ($n=62$) was fed conventionally by breast or on formula, and no specific environmental measures were taken. The results (previously reported) after 1 year showed significantly less total allergy, asthma, and eczema in the prophylactic group. Similar results were obtained at 2 years although the reduction in asthma no longer achieved statistical significance. However, there was significantly less sensitization, as shown by a battery of skin prick tests (SPTs), to both dietary allergens and aeroallergens in the prophylactic group. All the children have now been reviewed at the age of 4 years, and SPTs to a wide range of dietary allergens and aeroallergens have been performed. The control group continues to show more total allergy (odds ratio [OR] 2.73, 95% confidence interval [CI] 1.21–6.13, $P<0.02$), definite allergy (allergic symptoms plus positive SPT) (OR 5.6, CI 1.8–17.9, $P<0.005$), and eczema (OR 3.4, CI 1.2–10.1, $P<0.05$). More control children have positive SPTs (OR 3.7, CI 1.3–10.0, $P<0.02$). A dual approach to the prevention of allergic disease, avoiding as far as possible sensitization to food and aeroallergens, significantly reduces the risk of atopic disease. This should be reserved for infants considered at very high risk of atopy, and close medical and dietetic supervision must be available.

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Atopic disease develops in those who have a genetic predisposition to become sensitized to allergens which they inhale or ingest. It is widely believed that the newborn infant is particularly vulnerable to sensitization, although the extent to which this may occur prenatally remains contentious (1).

Attempts to reduce atopy by limiting the exposure of vulnerable infants to potentially allergenic foods by restricting the diet of the lactating mother, or by feeding so-called hypoallergenic formulas, have been successful in reducing cow's milk allergy and atopic dermatitis, at least in the early years of childhood. Even so, the prevalence rates tend to converge with those of a control population by the age of 4 years (2, 3). By the age of 7, the period prevalence of food allergy, asthma, atopic eczema, allergic rhinitis, any atopic disease, and sensitization was similar in the

prophylactic and control groups in the study of food allergen avoidance reported by Zeiger & Heller from San Diego (4). In the Isle of Wight study, not only were high-risk infants protected from exposure to food antigens, but strenuous efforts were made to reduce house-dust mite contact in the first year of life. The results of the study after 1 and 2 years have been reported (5, 6).

The entire cohort has now been followed into the fifth year of life, and once again all the children have been assessed by a paediatric allergist ignorant of their original allocation to a control or a prophylactic group.

Material and methods

A detailed account of the selection of subjects and methodology of the study has been published (5).

Briefly, a cohort of mothers with a strong family history of atopy was recruited (either two first-degree relatives of the infant with atopy or one first-degree relative with a high level of cord-blood IgE [>0.5 kU/l]). The infants were prenatally randomized into prophylactic and control groups. A total of 136 mothers met the criteria and entered the study. For various reasons, 16 (11 prophylactic and five control) subjects left the study, leaving 58 in the prophylactic group and 62 in the control group. All these children have been seen at ages 1, 2, and 4 years.

Children in the prophylactic group were either breast-fed with their mothers excluding dairy products, eggs, fish, and nuts, or were given a soya-based protein hydrolysate (Aptamil HA, Milupa, UK). The infant's diet excluded dairy products, egg, wheat, soya (unhydrolysed), orange, fish, and nuts. These foods were gradually introduced after the age of 9 months. Lactating mothers received supplements of calcium and vitamins.

The homes of children in the prophylactic group were treated with an acaricide, Acarosan (Crawford Chemicals, UK), energetically applied by one of the research team to the infant's bedroom carpet, the living room carpet, and upholstered furniture. The procedure was repeated at 3-month intervals until the infant was 9 months old. Quantitative measurements of house-dust mite antigen were made before and after treatment.

Children in the control group were fed conventionally by breast or formula. No specific environmental measures were recommended. It should be noted that infants in both groups slept on polyvinyl-covered mattresses, the usual practice in the UK.

All children in this study were seen regularly, and "blind review" was carried out at 12, 24, and 48 months by a paediatric allergist. Standard criteria were used for the diagnosis of atopic disease, and the SCORAD index was employed in assessing the degree of atopic dermatitis (7). Total atopy implies that the child met defined criteria for a clinical diagnosis of asthma, seasonal or perennial rhinoconjunctivitis, atopic dermatitis, or food allergy/intolerance. The child was recorded as having definite atopy if the clinical manifestations were accompanied by positive skin prick tests. The term "latent allergy" is used for those with one or more positive skin tests but no other clinical manifestations of allergic disease.

A battery of skin prick tests (Soluprick, ALK, Denmark) was used on all children at each review except for one child in the control group whose mother preferred serologic radioallergen sorbent testing (RAST) to skin tests. A skin test was considered positive if the mean wheal diameter equalled or

exceeded 3 mm and was at least half the size of the wheal of the histamine control.

Information on exposure to passive smoking and contact with pets was updated.

Logistic regression analysis was used to assess independent factors that might contribute to the risk of allergic disorders. Statistical analysis was done with the SPSS for Windows, Version 6.0 (SPSS, Chicago, IL, USA).

A separate study, assessing the development of atopic disease in an entire infant population born on the Isle of Wight in 1989, is being undertaken by the same investigators (8–10). This provides a unique opportunity to compare the development of atopy in the two study groups, drawn from high-risk families, with that found in an entire, unselected population.

Results

Acaricidal treatment produced an overall reduction in mean levels of *Der p 1* from 25.9 to 6.0 $\mu\text{g/g}$ dust after four applications in the homes of children in the prophylactic group. Considerable variation in the effect of the acaricide occurred from home to home and in the sites treated. These have been reported elsewhere (11). No significant change occurred in *Der p 1* levels in the control group.

The number of children developing clinical manifestations of allergic disease in the control and prophylactic groups at the ages of 1, 2, and 4 years is given in Table 1.

There was significantly less total atopy in the prophylactic group than the control at all three reviews. At the 2- and 4-year follow-ups, there were significantly fewer children with definite allergy and with positive skin tests. When these figures are compared with those of the whole population born the previous year, but also assessed after their fourth birthday, it can be seen that, as expected, infants in the high-risk control group manifest more total and definite atopy. However, the 1990 high-

Table 1. Clinical manifestations of allergy at ages 1, 2, and 4 years

	1 year		2 years		4 years	
	Prophylactic control		Prophylactic control		Prophylactic control	
	(58)	(62)	(58)	(62)	(58)	(62)
Total allergy	8	25	17	36	19	34
Definite allergy	2	6	3	16	5	19
Asthma	4	12	9	17	14	22
Eczema	4	12	8	15	8	15
Rhinitis	—	—	2	7	6	11
Food intolerance	2	7	7	11	3	7
Positive SPT	2	5	3	16	8	21

risk prophylactic group are actually manifesting less definite atopy than that found in the total population born in 1989 (Table 2).

As previously, multivariate logistic regression analysis was carried out to control for potential confounding factors. At the 1-year, 2-year, and now the 4-year review, the control group showed significantly more total allergy and eczema (Table 3). We were unable to demonstrate any difference in the severity of the eczema between the two groups as judged by SCORAD (data not shown). At 2 years and again at 4, there was significantly more definite allergy in the control group. As positive SPT is a component of definite allergy, it is not surprising that this occurs more frequently in this group.

Asthma, defined as recurrent cough and wheezing, occurred more often in the control group at 1 year, and although a similar trend was found at 2 and 4 years, the statistical significance is lost.

A profound effect of parental smoking on the presence of asthma, defined as recurrent wheeze, had been noted at 1 year. This effect was still present but weaker at 2 years. The influence of passive smoking apparently continues to decline and cannot be identified as a risk factor at the 4-year follow-up.

The influence of pets, specifically cats and dogs, cannot be shown definitely to influence the development of atopic disease, although seven children in the control group have been sensitized to the cat

allergen *Fel d 1*, compared to only one in the prophylactic group. It has been suggested that any difference could be explained either by an unexpected effect of the acaricide on *Fel d 1* or by the fact that the allergen-avoidance regimen results in a general reduction in sensitization and is not confined only to the allergens targeted.

At age 2 years, a highly significant difference was found in the number of positive SPTs between the prophylactic and control groups. After 4 years, a significant advantage of the prophylactic group remains (Table 4). At this review, only three children in the prophylactic group had become sensitized to house-dust mite, compared to 15 control children. One of the three had in fact been exposed to house-dust mite during infancy (unknown to us, she had been cared for in a child-minder's house on weekdays). Not only were significantly more control children sensitized (21 versus eight), but they collectively showed 50 positive reactions to the SPT battery compared with 12 in the prophylactic group.

Table 4. Positive skin prick tests at age of 4 years

	Prophylactic	Control
Total tested	58	62*
Skin test positivity (%)	8 (13.8)**	21 (33.9)
No. positive tests	12	50
Aeroallergens		
House-dust mite	3 (5.2)**	15 (24.2)
Grass pollen	3 (5.2)	9 (14.5)
Cat	1 (1.7)	7 (11.3)
Dog	2 (3.4)	4 (6.5)
Moulds	1 (1.7)**	10 (16.2)
Food allergens		
Milk	0	3 (5.1)
Egg	2 (3.4)	4 (6.5)
Wheat	0	1 (1.7)
Fish	1	0

* One child tested by radioallergen sorbent tests (RAST battery) at mother's request.

** $P < 0.02$; all other figures nonsignificant.

Table 2. Clinical manifestations of allergy at age of 4 years

	Prophylactic group (<i>n</i> = 58)		Control group (<i>n</i> = 62)		1989 cohort (<i>n</i> = 981)	
	No.	%	No.	%	No.	%
Total allergy	19	(32.8)	34	(54.8)	365	(37.2)
Definite allergy	5	(8.6)	19	(30.6)	115	(11.7)
Latent allergy	3	(5.3)	2	(3.3)	78	(7.9)
Positive SPT	8	(13.8)	21	(33.9)	193	(19.7)

Table 3. Effect of risk factors on expression of allergy at 4 years (regression analysis)

	Odds ratios (with 95% confidence intervals) <i>n</i> = 120		
	Control group	Male sex	Maternal allergy
Total allergy	2.7 (1.2–6.1)**	NS	NS
Definite allergy	5.6 (1.8–17.9)***	3.5 (1.2–10.2)*	NS
Positive SPT	3.7 (1.3–10.0)**	3.0 (1.2–7.9)*	NS
Asthma	NS	NS	3.0 (1.0–9.9)*
Eczema	3.4 (1.2–10.1)*	NS	NS
Rhinitis	NS	4.9 (1.4–7.0)**	NS

* $P < 0.05$; ** $P < 0.02$; *** $P < 0.005$; NS: nonsignificant.

Other factors included in regression model, paternal and sibling allergy, exposure to passive smoking, and presence of cats and dogs, were all nonsignificant for allergic disorders. Food intolerance was not influenced by any of the risk factors and is not shown.

Discussion

Attempts at primary prevention of atopic disease take two forms. The first assumes that sensitization of the vulnerable foetus may take place during intrauterine life; therefore, the intervention measures are instituted well before birth. Until recently, prenatal sensitization appeared improbable, as specific IgE is unusual in cord blood. Moreover, a trial in which the mothers of high-risk infants restricted their own diets from the 28th week of pregnancy resulted in no less allergy in the first 5 years of life than among the infants of mothers who maintained a normal diet (12). Recently, a number of studies have found evidence of intrauterine programming (13, 14). The finding of raised peripheral blood mononuclear proliferative responses and impaired interferon-gamma (IFN- γ) production in the cord blood of high-risk infants suggests that the vulnerable period for sensitization could well precede birth. Implementation of a programme of allergen avoidance at this time has very substantial risks attached – to the normal growth and development of the foetus and to maternal nutrition (15). A great deal more immunologic data are required before prenatal intervention can be recommended.

Manipulation of the diet of the lactating mother by restricting potentially allergenic foods also has dangers and should only be entertained where the family history suggests a high risk of atopy, and with professional dietetic support available. The use of hydrolysed formulas in allergy-prevention programmes as an alternative or supplement to breastfeeding remains debatable (16). Even the extensively hydrolysed formulas can elicit an allergic response on rare occasions (7). They are also expensive and, to the adult taste at least, unpalatable. There is a need for reassurance that hydrolysed formulas, whatever their degree of hydrolysis, are nutritionally as good as natural milk (17).

Other advice commonly given in a programme to prevent allergy is less contentious. It is wise not to give weaning foods until at least the age of 4 months (18). Those foods regarded as allergenic should be delayed until 6 months at the earliest.

It is disappointing that this study has not shown a significant reduction in asthma at 2 and 4 years. The trend to less asthma, shown at 2 and 4 years, and the reduction in sensitization to aeroallergens does suggest that a larger study might well confirm the benefit of this approach.

The influence of passive smoking to trigger recurrent wheeze is now well known (19). The effect of sensitization to pets, particularly cats and dogs, has been less easy to determine (20). However, there is good *a priori* reason to discourage exposure to furry

animals as much as possible. The major sensitizing aeroallergen in the UK is the house-dust mite. By the age of 4 years, 12% of children in the 1989 cohort born on the Isle of Wight had been sensitized to this allergen (10). Antimite measures are an essential element of any programme of allergen avoidance. These can include modifying the internal environment to make it less conducive to the mite; the use of mite-impermeable mattress, duvet, and pillowcases; and/or the use of acaricides. Acaricides are expensive and there may be problems of toxicity although these do not appear to be great. They reduce, but by no means exterminate, the mites, whose antigenicity largely resides in the faecal residue (11). We had hoped to ascertain whether the beneficial effect of the acaricide persisted at 2 and 4 years, but, unfortunately, too many families changed their residence to make a valid assessment. The significant difference in sensitization to house-dust mite between the prophylactic and control groups in this study is encouraging, suggesting that this approach to allergy prevention deserves further investigation. Indeed, it would be very reasonable to institute antimite measures before the child is born. Overall, a combination of dietary and environmental measures continues to show a significant reduction in definite atopy and in sensitization to the common food allergens and aeroallergens in high-risk children now in the fifth year of life. Although the numbers are relatively small, compliance has been excellent with no children lost to follow-up other than the 16 (11 prophylactic and five control) subjects who dropped out in the early weeks of the study. One infant in the prophylactic group was inadvertently given cow's milk in the neonate nursery, and 10 mothers found the diet too restrictive. In the control group, two families left the area and three defaulted from follow-up. A close relationship developed between the mothers and the research team with frequent home visits. The investigators were convinced that compliance with a difficult diet was good but emphasize that such contact is necessary if a protocol such as this is to be followed. The conclusions of the first 2 years have been discussed widely and we are aware of no major criticism of the methodology. We would like others to confirm the benefits of this approach to allergy prevention. In this study, the two groups were closely matched for maternal, paternal, and sibling allergy; mean cord-blood IgE levels; socioeconomic group; pets in the household; and paternal smoking. However, there were fewer mothers in the first year who smoked in the prophylactic group than in the control group (eight versus 16). Analysis of the data, excluding those families where the mother smoked, did not produce any significant difference in the conclusions. There were rather

more children with dual heredity in the prophylactic group (51 versus 42). If anything, we would have expected this to influence the results in favour of the control group. We recommend attempting to match all confounding variables in any future study, but this may be impossible to achieve.

Other workers have shown that dietary intervention measures reduce atopic dermatitis and food-related allergy, particularly in the first years of life, but that there then is a tendency for prevalence rates to converge with those of control children (3, 4). A controlled study from Denmark, combining either breast-feeding or the use of a hydrolysed formula with general environmental advice, found less asthma, eczema, and food-related symptoms in the prophylactic group of high-risk infants when they were reviewed at the age of 18 months (21).

The Isle of Wight study, combining dietary and environmental approaches, has shown a sustained benefit to the intervention group. We now recommend that this policy be considered for families with high risk of allergic disease who ask, "Can we do anything to prevent allergy in our next baby?" If they are willing to comply with a demanding protocol, and the necessary medical and dietetic support is available, it is likely that the risk of atopic disease can be reduced significantly.

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