ASTHMA

Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study

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Background: Recent increases in the prevalence of asthma and atopy emphasise the need for devising effective methods for primary prevention in children at high risk of atopy.
Method: A birth cohort of genetically at risk infants was recruited in 1990 to a randomised controlled study. Allergen avoidance measures were instituted from birth in the prophylactic group (n=58). Infants were either breast fed with mother on a low allergen diet or given an extensively hydrolysed formula. Exposure to house dust mite was reduced by the use of an acaricide and mattress covers. The control group (n=62) followed standard advice as normally given by the health visitors. At age 8, all 120 children completed a questionnaire and 110 (92%) had all assessments (skin prick test, spirometry, and bronchial challenges).
Results: In the prophylactic group eight children (13.8%) had current wheeze compared with 17 (27.4%) in the control group (p=0.08). Respective figures were eight (13.8%) and 20 (32.3%) for nocturnal cough (p=0.02) and 11 of 55 (20.0%) and 29 of 62 (46.8%) for atopy (p=0.003). After adjusting for confounding variables, the prophylactic group was found to be at a significantly reduced risk for current wheeze (odds ratio (OR) 0.26 (95% confidence interval (CI) 0.07 to 0.96)), nocturnal cough (OR 0.22 (95% CI 0.06 to 0.83)), asthma as defined by wheeze and bronchial hyperresponsiveness (OR 0.11 (95% CI 0.01 to 1.02)), and atopy (OR 0.21 (95% CI 0.07 to 0.62)).
Conclusion: Strict allergen avoidance in infancy in high risk children reduces the development of allergic sensitisation to house dust mite. Our results suggest that this may prevent some cases of childhood asthma.

Asthma is a major cause of morbidity and mortality at all ages.[1] Repeated cross sectional studies have confirmed a rise in prevalence that is not entirely explained by changes in diagnostic practices.[2] This increase in prevalence has focused attention on the role played by environmental factors.[3] If phenotypic expression is the result of an interaction between genetic predisposition and environment, this provides potential for manipulating the environment of high risk individuals and hence reducing the prevalence of the disease.[4] A family history of atopy remains the most useful way of identifying infants at high risk of atopy. A prevalence rate of 40–80% is suggested in children with bi-parental atopy.[5] Cord IgE is not very sensitive but has a relatively high specificity[6] and may add to the family history in predicting the risk of developing atopy in the newborn.[7]

Atopic disease manifests itself when the genetically predisposed individual is exposed to various trigger factors. Many such triggers are allergens to which the infant appears particularly vulnerable.[8] Early exposure to cows' milk, egg protein, and other food allergens may cause food allergy and atopic eczema.[9 10] There is evidence linking exposure to aeroallergens in infancy, particularly house dust mite, with the development of asthma later in life.[11]

Avoidance of cows' milk by the infant and lactating mother does seem to protect against the development of food allergy and eczema during early childhood.[12] The effect of house dust mite avoidance during infancy has also been investigated.[13] Our study aimed for the first time to control for both variables—food allergens and house dust mite exposure.[14] We hypothesise that, in infants genetically predisposed to atopy, allergen exposure in infancy plays a critical role in the development of phenotypic manifestations. Allergen avoidance in this period may lead to a reduction in the prevalence of asthma, other allergic disorders, and skin sensitisation. Moreover, the benefit might continue beyond the actual period of avoidance.

This birth cohort was recruited in 1990 and children were seen at 1, 2, and 4 years of age. Previous follow up had shown significant benefit in reducing allergic disorders and sensitisation to common allergens in the prophylactic group.[14–16] Assessment at the age of 8 years was thought to be crucial for the outcome of this study as it is critical to know if the benefit of allergen avoidance in infancy continues beyond early childhood. Moreover, at this age the diagnosis of asthma could be more objectively made.

METHODS

Subjects

The recruitment procedures and intervention measures have been described in detail previously.[14] Briefly, from February 1990 to February 1991 120 infants at high risk of developing atopy were recruited antenatally and randomised (using random allocation numbers) into prophylactic (n=58) and control (n=62) groups. The criteria for "high risk" were two or more members of the immediate family affected with an allergic disorder (asthma, atopic eczema or allergic rhinitis) or either parent or sibling affected with an allergic disorder plus cord serum IgE >0.5 kU/l in the infant. At recruitment parents completed a questionnaire seeking information on family history of allergy, household pets, and smoking habits. Sample size calculation was based on the expected cumulative incidence of allergic disorders at 1 year.[14]

The study was approved by the local research ethics committee and written informed consent was obtained from the parents at recruitment and each follow up.

Table 1 Demographic characteristics and potential risk factors in the two groups*

	Control (n=62)	Prophylactic (n=58)
Mean (SD) age	8.49 (0.27)	8.46 (0.20)
Male sex	33 (53.2)	28 (48.3)
Dual heredity	42 (67.7)	51 (87.9)
Maternal allergy	41 (66.1)	42 (72.4)
Paternal allergy	34 (54.8)	31 (53.5)
Sibling allergy	31 (50.0)	36 (62.1)
Maternal asthma	12 (19.4)	17 (29.3)
Paternal asthma	13 (21.0)	15 (25.9)
Sibling asthma	12 (19.4)	20 (34.5)
High (>0.5 kU/l) cord IgE†	19 (38.8)	15 (36.6)
Maternal smoking during pregnancy	15 (24.2)	8 (13.8)
Mother left education at 16	36 (58.1)	27 (46.6)
Cat‡	28 (45.2)	25 (43.1)
Dog‡	32 (51.6)	20 (34.5)
First born child	26 (41.9)	14 (24.1)
Gas cooker	35 (56.5)	37 (63.8)

*Values are n (%) unless otherwise stated.
†Cord IgE was available in 41 children in the prophylactic group and 49 children in the control group.
‡Current exposure to pets.

Preventive measures during infancy

A programme of reduced allergen exposure (food and aeroallergen) was instituted from birth for the infants in the intervention group.[14] Dairy products, egg, wheat, nuts, fish and soya were excluded from the diet of the infants (and lactating mothers) for the first 9 months of life. Extensively hydrolysed hypoallergenic formula was given as a supplement when needed. These foods were gradually introduced from 9 months onwards. Compliance with maternal diet was excellent, as assessed by analysis of random samples of breast milk for cows' milk proteins (β-lactoglobulin and casein).

Cot mattresses were covered with a polyvinyl impermeable cover. The carpets and upholstery in the bedroom and lounge in the homes of the infants were repeatedly treated with an acaracide from just before birth and then at 3 monthly intervals to the age of 9 months. This resulted in a fivefold reduction in dust mite antigen in the homes of the prophylactic group, while no significant change was observed in the control group.[17] Infants in the control group followed national guidelines recommended at that time.

Follow up

Blind assessments were made at 1, 2, and 4 years of age in all 120 children. These included questionnaires, physical examination, and skin prick tests to common food and aeroallergens (Biodiagnostics, Germany). The children have now been assessed at 8 years. All study procedures were performed blind to the patients' allocation to study group.

Two questionnaires were used to assess symptoms suggestive of allergic disease—the study questionnaire used in a previous follow up study and the standardised ISAAC (International Study of Asthma and Allergic Disease in Children) questionnaire.[18] Skin prick tests were done to common food and aeroallergens (ALK, Denmark) including *Dermatophagoides pteronyssinus*, *D farinae*, grass pollen mix, tree pollen mix, cat, milk, egg, cod and peanut. Positive (histamine) and negative (saline) controls were used. A positive reaction was defined as a mean wheal diameter 3 mm or more than the negative control.

Baseline pulmonary function (forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), and subdivisions of forced expiratory flow) was measured using Koko spirometry software (Pds Instrumentation, USA) and standardised methodology.[19] All children attending the centre performed a methacholine bronchial challenge to assess non-specific bronchial responsiveness using a Koko dosimeter (Pds Instrumentation, USA) with compressed air source at 8 l/min and nebuliser output 0.8 l/min. Initial inhalation of 0.9% saline was followed 1 minute later by spirometry recording to obtain a baseline value. Incremental doses from 0.0625 mg/ml to 16 mg/ml of methacholine were then serially administered.[20] The methacholine concentration causing a 20% fall in FEV_1 from the post-saline value was interpolated and expressed as $PC_{20}FEV_1$. To perform this test, children were required to be free from respiratory infection for 14 days, not taking oral steroids, not taken β_2 agonist for 6 hours, and to abstain from caffeine intake for at least 4 hours. Blood was taken for measurement of total serum IgE and an inhalant screen (qualitative) for IgE antibody to common inhalant allergens (Phadiatop; Pharmacia, Uppsala, Sweden).

Analysis of data

The primary outcome variable at 8 years was current wheeze (in the last 12 months). Secondary outcome variables included cough, exercise induced wheeze, lung function, bronchial responsiveness, asthma (defined as wheeze plus bronchial hyperresponsivenss (PC_{20} <8 mg/ml)), and atopy (defined as a positive reaction to one or more allergens on skin testing).

The data were double entered into SPSS program Version 10.0. Means for continuous variables were analysed (with log transformation where necessary) using the independent samples *t* test. Differences in proportions between groups were tested (two tailed) using χ^2 analysis (with Fisher's exact test where indicated by low expected cell counts). To obtain the independent effect of intervention measures, all variables of interest were entered into a logistic regression model. Stepwise backward (likelihood ratio) logistic regression was used for this purpose. Separate models were constructed for each outcome variable entered as a dependent variable with a number of explanatory variables as factors. Each asthma related feature (current wheeze, nocturnal cough, exercise induced wheeze, bronchial hyperreactivity, and asthma) was adjusted in the multivariate regression model for maternal, paternal, and sibling asthma, high cord IgE, firstborn child, gas cooking, maternal smoking during pregnancy, male sex, pet cat, and pet dog as confounding variables. For allergy related features (atopy and positive skin test to house dust mite), maternal, paternal and sibling allergy replaced maternal, paternal and sibling asthma as confounding variables.

RESULTS

All 120 children were contacted soon after their eighth birthday and, at the very least, their parents completed a questionnaire; 117 children (98%; prophylactic group=55, controls=62) were seen by the study doctor who was blind to the

Table 2 Prevalence of asthma related symptoms during the last 12 months, bronchial hyperresponsiveness, current asthma and skin prick test at age 8 (univariate analysis)

	Control	Prophylactic	OR (95% CI)	p value
Symptoms	N=62	N=58		
Current wheeze*	17 (27.4)	8 (13.8)	0.42 (0.17 to 1.08)	0.08
Nocturnal cough*	20 (32.3)	8 (13.8)	0.34 (0.13 to 0.84)	0.02
Exercise induced wheeze*	11 (17.7)	6 (10.3)	0.54 (0.18 to 1.56)	0.30
BHR	n=58	n=52		
PC_{20} <8mg/ml	25 (43.1)	17 (32.7)	0.64 (0.29 to 1.40)	0.33
Current asthma†	9 (15.5)	5 (9.6)	0.58 (0.18 to 1.86)	0.40
Skin test positive	n=62	n=55		
House dust mite‡	19 (30.7)	6 (10.9)	0.28 (0.10 to 0.76)	0.01
Grass pollen	14 (22.6)	10 (18.2)	0.76 (0.31 to 1.89)	0.65
Tree pollen	7 (11.3)	1 (1.8)	0.15 (0.02 to 1.22)	0.07
Cat	10 (16.1)	4 (7.3)	0.41 (0.12 to 1.38)	0.16
Any aeroallergens	28 (45.2)	11 (20.0)	0.30 (0.13 to 0.70)	0.006
Cows' milk	4 (6.5)	0	–	0.12
Peanut	1 (1.6)	0	–	1.0
Any food allergens§	5 (8.1)	0	–	0.06
Any allergen (atopy)	29 (46.8)	11 (20.0)	0.28 (0.12 to 0.65)	0.003
IgE	n=60	n=53		
Inhalant screen positive	22 (36.7)	14 (26.4)	0.62 (0.28 to 1.39)	0.31
Total IgE¶	91.69 (5.4)	103.60 (5.5)	1.13 (0.68 to 2.14)	0.71

Values are n (%).
BHR=bronchial hyperresponsiveness; OR=odds ratio; 95% CI=95% confidence interval.
*As a yes response to ISAAC questions: have you had wheezing or whistling, nocturnal cough or exercise induced wheeze in the last 12 months.
†Current asthma: current wheeze plus bronchial hyperresponsiveness (PC_{20} <8 mg/ml).
‡Skin test positive to either *D pteronyssius* or *D farinae*.
§There were no skin test positive reactions to egg or fish in either group.
¶Geometric means (SD), means difference and 95% CI are given.

group allocation. In addition, in seven children (four controls, three in prophylactic group) a valid PC_{20} was not obtained on bronchial challenge measurements. In two children parental consent was not given for bronchial challenge, two children were seen in a peripheral clinic without facilities for bronchial challenge, and in three children a challenge could not be completed because of poor coordination. Prophylactic and control groups were compared for their demographic and other characteristics. Despite randomisation some differences were noted—for example, sibling and maternal allergy was more common in the prophylactic group whereas more children in the control group were firstborn and exposed to maternal cigarette smoke (table 1).

Period prevalence of asthma related symptoms, as assessed by the ISAAC questionnaire, was higher in the control group than in the prophylactic group (table 2). However, with univariate analysis the difference was statistically significant only for nocturnal cough (p=0.02). Although the trend for increased prevalence persisted across all symptoms, severity indices and treatment requirement, none of the differences reached statistical significance.

Percentage predicted peak flows were lower in both groups while FEV_1 values were within normal limits, indicating the possibility that the technique was not adequate in every child (table 3). Overall, there was a trend for higher spirometric values in the prophylactic group. Similarly, more children in the control group were hyperresponsive to methacholine (PC_{20} <8 mg/ml) but univariate analysis did not reveal significant differences (table 2). However, when bronchial responsiveness was analysed as a continuous variable (dose response), children in the prophylactic group were significantly less responsive to methacholine (table 3).

Thirty three children (27.5%) from the whole sample were sensitised to at least one of the allergens tested and were thus defined as "atopic". Atopy was considerably higher in the control group (46.8%) than in the prophylactic group (20%). Sensitisation to most aeroallergens was higher in the control group, particularly for house dust mite (table 2). Although 50% more children in the control group (36.7%) than in the prophylactic group (26.4%) proved to be sensitised on serological testing (qualitative inhalant screening), this failed to reach statistical significance. Interestingly, the levels of total serum IgE were remarkably similar between the two groups (table 2).

Despite randomisation there were important differences between the groups with regard to heredity and some

Table 3 Pulmonary function on spirometric testing and bronchial responsiveness as assessed by methacholine challenge in the two groups at age 8

	Control (n=61)	Prophylactic (n=54)	Mean difference (95% CI)	p value (*t* test)
FEV_1 (% predicted)	92.6	95.0	2.39 (–1.43 to 6.21)	0.22
Peak flow (% predicted)	76.2	81.3	5.13 (–0.78 to 11.05)	0.08
$FEF_{25–75}$ (% predicted)	75.1	82.5	7.45 (–1.64 to 16.53)	0.11
Bronchial responsiveness*	12.3	2.7	4.54 (1.20 to 17.12)	0.03

FEV_1=forced expiratory volume in 1 second; $FEF_{25–75}$= mid forced expiratory flow.
*Dose response: maximum change in FEV_1 divided by cumulative dose of methacholine given for each subject.
Values are given as geometric means with mean difference and 95% confidence intervals of the difference in means.

Table 4 Adjusted risk for prophylactic group compared with control group for the presence of asthma related features at 8 years (multivariate logistic regression analysis)

	Odds ratio	95% CI	p value
Current wheeze	0.26	0.07 to 0.96	0.04
Nocturnal cough	0.22	0.06 to 0.83	0.02
Exercise induced wheeze	0.24	0.05 to 1.11	0.07
Bronchial hyperresponsiveness	0.51	0.18 to 1.48	0.21
Asthma (wheeze + BHR)	0.11	0.01 to 1.02	0.05
Atopy (positive skin test)	0.21	0.07 to 0.62	0.005
Positive skin test to house dust mite	0.08	0.02 to 0.39	0.002

environmental factors such as exposure to smoking and pets. To adjust for these and other confounding variables, independent risk was calculated for characteristic features of asthma including typical symptoms, bronchial hyperresponsiveness, atopy and asthma, as defined by wheeze plus bronchial hyperresponsiveness (table 4). A 2–10-fold reduction in the risk for all features of asthma was seen.

DISCUSSION

We were able to assess the prevalence of allergic symptoms in all children, maintaining the zero attrition rates achieved at previous follow ups. A full assessment was done in more than 90% of children, ensuring validity of the results. All assessments were blind and carried out by a paediatric allergist (BB) not previously involved with this study. Parents and children were specifically instructed not to disclose their group allocation. Parents knew their group allocation and this may introduce bias in reporting. However, this is less likely at this stage as active intervention was discontinued after infancy.

Analysis of multiple outcome measures has the risk of reporting statistical significance on one or more variables merely by chance (type I error). However, this was inevitable as there is no single symptom or objective measurement which can define asthma. The diagnosis of asthma is usually based on reported typical symptoms, supported by evidence of reversible bronchial obstruction and/or measures of bronchial hyperreactivity.[1] Three key symptoms (wheezing, nocturnal cough, and exercise induced wheezing) were used in addition to objective measurements of pulmonary function and bronchial responsiveness. A type I error is unlikely as the outcome is in one direction for all the variables analysed. Indeed, persistent non-significant differences such as those for lung function and severity indices in one direction indicate the possibility of a type II error due to small sample size.

The benefit of allergen avoidance was remarkably consistent for nearly all characteristics associated with asthma, but the size of the effect varied depending on the phenotype characteristic examined. Atopy was reduced to the greatest degree, with significant reductions in both food and aeroallergen sensitisation. The adjusted risk for the control group was five times for sensitisation to any allergen and more than 10 times for sensitisation to house dust mite. The effect on asthma symptoms, pulmonary function, and bronchial hyperreactivity was less marked. Bronchial responsiveness as assessed by PC_{20} was not significant, but this parameter is less sensitive as it relies on an arbitrary cut off for the change in FEV_1 (20%) and the dose of methacholine (8 mg/ml). Analysis of the dose-response curve is more sensitive when comparing groups for the effect of a treatment as it includes all children whether or not a PC_{20} was achieved.[21] The differential effect on symptoms could be explained by parental knowledge of their child's group allocation; however, this would not explain the reduction in bronchial responsiveness and consistent (albeit non-significant) improvement in lung function. A more likely explanation may be that the development of asthma is only partially determined by atopy,[22] providing an explanation for the more modest improvements seen in asthma related features in the face of a considerable reduction in sensitisation.

The eventual phenotype in asthma results from a complex interplay of genetic and environmental factors.[23] Several factors such as level of exposure to allergens and infections during infancy may influence the direction of immune responses. It can be hypothesised that a significant reduction in allergen exposure may inhibit the development of Th2 responses in the atopic infant and thus achieve a more balanced Th1/Th2 immune response.

Our original hypothesis was that allergen avoidance in infancy, in infants genetically predisposed to atopy, would reduce the development of asthma and atopy and the benefit would continue beyond the period of avoidance. These results confirm the second part of our hypothesis, as benefit was still seen 7 years after the discontinuation of active allergen avoidance. There was a continued effect on sensitisation to common allergens and a less marked, but statistically significant, effect on the development of symptomatic asthma and bronchial responsiveness. It is possible that partial allergen avoidance measures continued in the prophylactic group, especially to indoor allergens. It would have been both interesting and useful if there had been an assessment of ongoing allergen avoidance.

Prospective birth cohort studies of the effect of allergen avoidance are few and most have focused on food, particularly the avoidance of cows' milk allergen in infancy.[9 10] Zeiger *et al*,[12] in their study of food allergen avoidance, showed a beneficial effect on the development of eczema and food allergy only in the first 2 years of life. Cross sectional and prospective data indicate the importance of exposure to inhalant allergens, particularly house dust mite, as a risk factor for the development of asthma.[11 24 25] A recent study has, however, challenged this view, suggesting that exposure to allergen causes sensitisation but not asthma.[26]

The possible beneficial effect of combined food and aeroallergen avoidance in infancy has rarely been studied.[27] In our study the dietary measures applied were stringent to ensure a reduction in exposure to allergenic foods in early infancy. A significant reduction in the level of dust mite allergen was also demonstrated.[14] The study was performed in a controlled environment with a group of highly motivated mothers who were closely observed by the research physicians and dietitian. We therefore consider this as a "proof of concept" study. Combined reduction in allergen exposure in the critical period of early infancy seems to be effective in preventing asthma and atopy, possibly by the modulation of immune responses in high risk children. The design of the study does not allow us to speculate whether the benefit was due to specific allergen avoidance (food or dust mite) or a combined effect. Further large prospective studies are needed to evaluate the preventive effect of a reduction in indoor allergen exposure as well as investigating other possible ways of immune modulation.

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