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

S H Arshad, B Bateman, S M Matthews

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 childhoo...
Preventive measures during infancy

A programme of reduced allergen exposure (food and aeroallergen) was instituted from birth for the infants in the intervention group. Dairy products, egg, wheat, nuts, fish and soy 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).

Got 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, and skin prick tests to common food and aeroallergens (ALK, Denmark) including Der pteronyssinus, D farinae and aeroallergens—the study questionnaire used in a previous follow up study and the standardised ISAAC (International Study of Asthma and Allergic Disease in Children) questionnaire. Skin prick tests were done to common food and aeroallergens (ALK, Denmark) including Dermatophagoïdes 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 (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF), and subdivisions of forced expiratory flow) was measured using Koko spirometry software (Pds Instrumentation, USA). 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 hyperresponsiveness (PC20 <8 mg/ml)), and atopy (defined as a positive reaction to one or more allergens on skin testing).

Analysis of data

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 χ2 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 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)        |
| Maternal allergy                | 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                 | 13 (21.0)        | 15 (25.9)        |
| Paternal asthma                 | 19 (4.9)         | 17 (29.3)        |
| Sibling asthma                  | 12 (19.4)        | 20 (34.5)        |
| High (>0.5 kU/l) cord IgE       | 19 (33.8)        | 15 (26.6)        |
| Maternal smoking during pregnancy | 13 (24.2)      | 8 (15.3)         |
| Maternal and sibling education at 16 | 30 (50.0)     | 27 (46.6)        |
| Cat‡                           | 28 (45.2)        | 25 (43.1)        |
| Dog†                           | 32 (51.6)        | 20 (34.5)        |
| First born child                | 25 (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.
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 characteristics. Despite randomisation there were important differences between the groups with regard to heredity and some possibility that the technique was not adequate in every child (table 2). 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) 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 IgE were remarkably similar between the two groups (table 2).

## Table 2

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Control</th>
<th>Prophylactic</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current wheeze*</td>
<td>N=62</td>
<td>N=58</td>
<td>17 (27.4)</td>
<td>20 (32.3)</td>
</tr>
<tr>
<td>Nocturnal cough*</td>
<td>8 (13.8)</td>
<td>8 (13.8)</td>
<td>0.34 (0.13 to 0.84)</td>
<td>0.02</td>
</tr>
<tr>
<td>Exercise induced wheeze*</td>
<td>11 (17.7)</td>
<td>6 (10.3)</td>
<td>0.54 (0.18 to 1.56)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

## Table 3

<table>
<thead>
<tr>
<th>Pulmonary function on spirometric testing and bronchial responsiveness as assessed by methacholine challenge in the two groups at age 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=61)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>FEV_{1} (%) predicted</td>
</tr>
<tr>
<td>Peak flow (% predicted)</td>
</tr>
<tr>
<td>FEF_{25-75} (% predicted)</td>
</tr>
<tr>
<td>Bronchial responsiveness*</td>
</tr>
</tbody>
</table>

FEV_{1} = forced expiratory volume in 1 second; FEF_{25-75} = mid forced expiratory flow.

*As a yes response to ISAAC questions: 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. pteronyssinus or D. farinae.
¶Geometric means (SD), means difference and 95% CI are given.
§Current asthma: current wheeze plus bronchial hyperresponsiveness (PC_{20} < 8 mg/ml).
¶Geometric means (SD), means difference and 95% CI are given.
††Skin test positive to either D. pteronyssinus or D. farinae.
§§Geometric means (SD), means difference and 95% CI are given.
†††Skin test positive to either D. pteronyssinus or D. farinae.
‡‡‡Geometric means (SD), means difference and 95% CI are given.

Values are n (%).

BHR = bronchial hyperresponsiveness; OR = odds ratio; 95% CI = 95% confidence interval.

As a yes response to ISAAC questions: 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. pteronyssinus 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.

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 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 variability in the prevalence of certain symptoms and the levels of total IgE. However, the overall trend of higher spirometric values and bronchial responsiveness in the control group suggests that allergen avoidance in infancy may have a protective effect on the development of asthma and atopy.
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 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, 27 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 hyperresponsiveness. 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. 23 Zeiger et al, 14 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. 21, 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 aero-allergen 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. 28 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.

### 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)

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