

## Prevention of allergic disease during childhood by allergen avoidance: The Isle of Wight prevention study

Syed Hasan Arshad, DM,<sup>a</sup> Belinda Bateman, MRCP,<sup>a</sup> Alireza Sadeghnejad, MD, PhD,<sup>b</sup> Carole Gant, SRD,<sup>a</sup> and Sharon M. Matthews, RGN<sup>a</sup> *Isle of Wight, United Kingdom, and Winston-Salem, NC*

**Background:** Early life allergen exposure may increase the risk of childhood allergy, but the protective effect of reduction in allergen exposure remains uncertain.

**Objective:** To evaluate the effect of reduction in food and house dust mite (HDM) allergen exposure in infancy in preventing asthma and allergy.

**Methods:** Infants, at higher risk because of family predisposition, were recruited prenatally and randomized to prophylactic (n = 58) and control (n = 62) groups. Prophylactic group infants were either breast-fed with mother on a low allergen diet or given an extensively hydrolyzed formula. Exposure to HDM was reduced by the use of an acaricide and mattress covers. The control group followed standard advice. Development of allergic diseases and sensitization to common allergens (atopy) was assessed blindly at ages 1, 2, 4, and 8 years in all 120 children.

**Results:** Repeated measurement analysis, adjusted for all relevant confounding variables, confirmed a preventive effect on asthma: adjusted odds ratio (OR), 0.24; 95% CI, 0.09-0.66; *P* = .005; atopic dermatitis, OR, 0.23; CI, 0.08-0.64; *P* = .005; rhinitis, OR, 0.42; CI, 0.19-0.92; *P* = .03; and atopy, OR, 0.13; CI, 0.05-0.32; *P* < .001. The protective effect was primarily observed in the subgroup of children with persistent disease (symptoms at all visits) and in those with evidence of allergic sensitization.

**Conclusion:** Allergic diseases can be reduced, for at least the first 8 years of life, by combined food and HDM allergen avoidance in infancy.

**Clinical implications:** Strict food and HDM allergen avoidance should be considered for prevention of allergy in high-risk infants. (*J Allergy Clin Immunol* 2007;119:307-13.)

**Key words:** Atopy, allergy, asthma, rhinitis, atopic dermatitis, food allergy, prevention, diet, house dust mite, randomized controlled trial

Atopy is defined as the genetic propensity to generate IgE antibodies against common environmental allergens. Asthma, atopic dermatitis (AD), and rhinoconjunctivitis are the clinical expressions of atopy. These diseases are major causes of mortality and morbidity in childhood and through into adulthood.<sup>1</sup> Thus, attempts at successfully preventing the development of these diseases must take priority. Because genetic manipulation is not yet in sight, attention is focused on environmental factors, particularly exposure to allergens, in genetically predisposed infants.

Food allergy and AD are common in the first few years of life, followed by asthma and allergic rhinitis, in genetically at-risk children.<sup>2</sup> The heritability of atopic diseases is well known and has been used to identify children at risk of developing these diseases to achieve a greater effect of preventive measures.<sup>3,4</sup>

Studies into the preventive effect of breast-feeding on allergic diseases have produced conflicting results.<sup>5</sup> The lack of a clear beneficial effect of breast-feeding may be attributed to the small amount of intact food protein passed through the breast milk.<sup>6</sup> Studies that restricted maternal food during lactation have met with greater success in reducing the incidence of AD and food allergy.<sup>7</sup> In addition, there is strong evidence linking exposure to house dust mite (HDM) with the development of allergic diseases.<sup>8</sup>

This study aimed, for the first time, to reduce exposure to food as well as HDM allergen. We hypothesize that in infants genetically predisposed to atopy, allergen exposure in infancy plays a critical role in the development of phenotypic manifestations, and allergen avoidance in this period may lead to a reduction in the development of allergic diseases with the benefit continuing beyond the actual period of avoidance.

Children were recruited into this birth cohort in 1990 and assessed at the ages of 1, 2, 4, and 8 years. Cross-sectional data at these follow-ups have been reported previously.<sup>9-12</sup> This article describes an overall effect of intervention on the natural history and development of allergic diseases prospectively from birth to the age of 8 years.

From <sup>a</sup>the David Hide Asthma and Allergy Research Center, St Mary's Hospital, Newport, Isle of Wight; and <sup>b</sup>the Center for Human Genomics, Wake Forest University School of Medicine, Winston-Salem.

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Reprint requests: Syed Hasan Arshad, DM, David Hide Asthma and Allergy Research Center, St Mary's Hospital, Newport, Isle of Wight PO30 5TG, United Kingdom. E-mail: sha@soton.ac.uk.

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*Abbreviations used*

AD: Atopic dermatitis  
HDM: House dust mite  
SPT: Skin prick test

**METHODS****Subjects**

This was a randomized, controlled study with blind assessments. The study was approved by the Local Research Ethics Committee, and informed consent was obtained from the parents at recruitment and at each follow-up visit. In 1990, 120 infants at high risk were prenatally recruited and randomized (using random allocation numbers) into prophylactic ( $n = 58$ ) and control ( $n = 62$ ) groups. The criteria for high risk were 2 or more members of the immediate family affected with an allergic disease (asthma, AD, or allergic rhinitis) or either parent or sibling affected with an allergic disease plus cord serum IgE  $> 0.5$  kilo units (kU)/L. At recruitment, the parents completed a questionnaire seeking information on family history of allergy, household pets, and smoking habits.

**Intervention**

Preventive measures have been described in detail in earlier reports.<sup>9</sup> Briefly, this included strict elimination of common food allergens (dairy products, egg, wheat, nuts, fish, soya) in infants to the age of 12 months. Lactating mothers, for the duration of breast-feeding, followed the same restricted diet (except wheat). Maternal compliance with restricted diet was checked by analysis of random samples of breast milk for cow's milk proteins ( $\beta$ -lactoglobulin and casein), because cow's milk was considered to be the most difficult to avoid completely during lactation. Extensively hydrolyzed formula (Aptamil HA, Milupa, Oxbridge, United Kingdom) was given as a supplement to the child from birth or when breast-feeding was discontinued before 9 months. Reduction in exposure to HDM allergen was achieved with treatment of the carpets and upholstery in the infant's bedroom and lounge with an acaricide (Acarosan; Crawford Chemicals, Milton Keynes, United Kingdom) and the use of polyvinyl impermeable mattress covers for infants' cots. Infants in the control group followed standard recommendations prevailing at that time.

**Follow-up**

Blind assessments have been made at 1, 2, 4, and 8 years of age in all 120 children. These included questionnaires (including standardized International Study of Asthma and Allergic Disease in Children questionnaire),<sup>13</sup> physical examination, and skin prick tests (SPTs) to common food and aeroallergens (ALK, Hørsholm, Denmark). These included *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, grass pollen mix, tree pollen mix, cat, milk, egg, fish (cod), and peanut. Positive (histamine) and negative (saline) controls were used. A positive reaction was defined as a mean wheal diameter of 3 mm or greater during all follow-ups.

**Outcomes**

Presence of allergic diseases (asthma, AD, rhinitis, and food allergy) and sensitization to common allergens were predetermined outcomes for this study.

**Asthma**

The definition of asthma was investigator-diagnosed asthma on the basis of the minimum criteria of a history of physician-diagnosed asthma plus at least 1 episode of wheezing in the last 12 months. In addition, during the early childhood period, an alternative minimum

criterion for asthma diagnosis was a history of 3 separate episodes of persistent wheezing ( $\geq 3$  days duration), because asthma diagnosis is often not given to infants/young children.

**Atopic dermatitis**

The diagnosis of AD was made using the 16 criteria of Hanifin and Rajka.<sup>14</sup>

**Rhinitis**

The diagnosis of rhinitis was made when typical nasal blockage, rhinorrhea, and sneezing were present all year round or during the summer season.

**Food allergy**

Diagnosis of food allergy required typical symptoms (rash, vomiting, diarrhea) within 2 hours of ingestion of the suspected food on 2 or more occasions.

**Atopy**

Atopy was defined as positive reaction on SPT to 1 or more allergens.

Children with clinical manifestations were further defined as allergic if there was evidence of allergic sensitization on SPT. For example, a child with asthma and positive reaction on SPT to 1 or more allergens was said to have allergic asthma. Similarly, those with rhinitis, AD, and food allergy and positive skin test were said to have allergic rhinitis, allergic AD, and IgE-mediated food allergy, respectively.

**Analysis**

Data were double-entered onto SPSS (v10.0; SPSS Inc., Chicago, Ill) and imported into SAS/STAT Software (SAS Institute Inc, Cary, NC). To make a comprehensive assessment of the effect of intervention throughout the first 8 years of life, we analyzed our data in 2 ways. The total number of children diagnosed with an allergic condition at any time point during this period is reported and compared between the groups by using  $\chi^2$  analysis. However, this analysis does not differentiate between children with transient or persistent disease. Therefore, we performed repeated measurement analysis by using generalized estimating equations<sup>15</sup> with and without adjustment for relevant confounders. To provide an unbiased parameter estimate and SE, this method takes into account correlation of observations collected on the same subject across successive points in time. Generalized estimated equation models were applied by using the GENMOD procedure in SAS/STAT Software.<sup>16</sup>

**RESULTS**

All 120 children have been seen at all follow-ups (3 children, all asymptomatic, did not have SPT at 8 years). Prophylactic and control groups were compared for their demographic and other characteristics.<sup>9</sup> Despite randomization, some differences were noted. For instance, sibling allergy and maternal asthma were more common in the prophylactic group, whereas more children in the control group were first born and exposed to maternal cigarette smoke (Table I). Prospective data from 1 to 8 years of age reveal that the pattern of occurrence of allergic symptoms and sensitization was influenced by both their natural history and the preventive measures undertaken in the first year of life (Figs 1 and 2).

## Asthma

Asthma prevalence increased in both groups to the age of 4 years and then stabilized (Fig 1, A). When children diagnosed with asthma at least once during 8 years were compared, the difference did not reach statistical significance (Table II). However, persistent disease was disproportionately more common in the control group. Only 1 (1.7%) child in the prophylactic group had persistent asthma (asthma diagnosed at all ages), compared with 7 (11.3%) children in the control group ( $P = .04$ ). Repeated measurement analysis, which gives appropriate weighing to the repeated occurrence over time, confirmed that a significant difference (unadjusted  $P = .03$ ) existed between the 2 groups (Fig 1, A). When adjusted for all relevant confounding variables, the difference in the groups was highly significant (Table III).

## AD

Prevalence of AD in the prophylactic group was reduced to 50% of that in the control group throughout the first 8 years of life (Fig 1, B). Repeated measurement analysis, adjusted for confounders, confirmed that the difference was statistically significant ( $P = .005$ ), with further amplification of the protective effect seen in children with allergic sensitization (Table III).

## Rhinitis

Rhinitis was not diagnosed in any child at the age of 1 year. From 2 years, the prevalence of rhinitis increased in both groups with age, with a difference of 5% to 10% persisting between the groups, but these differences were not statistically significant (Fig 1, C). However, allergic rhinitis (rhinitis with positive SPT) was significantly reduced in the prophylactic group (Table II), and adjusting for confounders in repeated measurement analysis further increased the difference (Table III).

## Food allergy

As expected, the prevalence of food allergy was high in the first 2 years of life and then decreased sharply in both groups. The prevalence was consistently lower (a 50% or more reduction) in the prophylactic group, but the numbers were relatively small, and the difference failed to reach statistical significance with repeated measurement analysis (Fig 1, D). Crude analysis of children with food allergy at 1 or more visit showed a significant reduction in food allergy in the prophylactic group (Tables II), but the difference disappeared in adjusted repeated measurement analysis (Tables III).

## Allergic sensitization

Sensitization to HDM increased with age in both groups, but the gap widened between the groups as the children reached age 8 years (Fig 2, A). Food sensitization increased in early childhood and then, as expected, decreased by the age of 8 years. However, the difference between the groups persisted so that no child in the prophylactic group was sensitized to food at 8 years, compared with 5 in the control group (Fig 2, B). Overall, 37

**TABLE I.** Demographic characteristics and potential risk factors in the 2 groups\*

| Allergic disease                  | Prophylactic group (n = 58) | Control group (n = 62) | P value |
|-----------------------------------|-----------------------------|------------------------|---------|
| Age (y), mean (SD)                | 8.46 (0.20)                 | 8.49 (0.27)            | .49     |
| Male sex                          | 28 (48.3)                   | 33 (53.2)              | .59     |
| Maternal allergy                  | 42 (72.4)                   | 41 (66.1)              | .46     |
| Paternal allergy                  | 31 (53.4)                   | 34 (54.8)              | .88     |
| Sibling allergy                   | 36 (62.1)                   | 31 (50.0)              | .18     |
| Maternal asthma                   | 17 (29.3)                   | 12 (19.4)              | .20     |
| Paternal asthma                   | 15 (25.9)                   | 13 (21.0)              | .53     |
| Sibling asthma                    | 20 (34.5)                   | 12 (19.4)              | .06     |
| High (>0.5 kU/L) cord IgE         | 15 (36.6)                   | 19 (38.8)              | .83     |
| Position of child in the family   |                             |                        | .06     |
| First                             | 14 (24.1)                   | 26 (41.9)              |         |
| Second                            | 29 (50.0)                   | 19 (30.6)              |         |
| Third or more                     | 15 (25.9)                   | 17 (27.4)              |         |
| Mother left education at 16       | 27 (47.4)                   | 36 (58.1)              | .24     |
| Separate bedroom                  | 26 (47.3)                   | 25 (46.3)              | .92     |
| Gas cooker                        | 26 (44.8)                   | 24 (38.7)              | .50     |
| Maternal smoking during pregnancy | 8 (13.8)                    | 15 (25.0)              | .12     |
| Maternal smoking at age 8 years   | 16 (27.6)                   | 23 (37.1)              | .27     |
| Paternal smoking at age 8 years   | 12 (22.2)                   | 16 (28.1)              | .48     |
| Pets (cat and/or dog)             |                             |                        |         |
| At birth                          | 36 (62.1)                   | 38 (61.3)              | .93     |
| At 1 year                         | 36 (62.1)                   | 38 (61.3)              | .93     |
| At 2 years                        | 35 (60.3)                   | 44 (71.0)              | .22     |
| At 4 years                        | 30 (51.7)                   | 38 (61.3)              | .29     |
| At 8 years                        | 33 (56.9)                   | 47 (75.8)              | .03     |
| Total duration (y), mean (SD)     | 4.62 (3.72)                 | 5.61 (3.81)            | .15     |

\*Values are n (%) unless otherwise indicated.

(59.7%) children were sensitized to 1 or more allergens at any time in the control group and 14 (25.5%) in the prophylactic group (OR, 0.23; CI, 0.11-0.51;  $P < .001$ ). Repeated measurement analysis confirmed significant differences in allergic sensitization throughout the first 8 years of life (Fig 2, C). When adjusted for confounders, the OR (CI) were as follows: foods, 0.15 (0.03-0.80); HDM, 0.07 (0.02-0.23); and any sensitization, 0.13 (0.05-0.32).

## DISCUSSION

This report from the Isle of Wight prevention study confirms a sustained preventive effect of allergen avoidance in infancy over the period of the first 8 years of life. Cross-sectional data at each follow-up have been reported previously,<sup>9-12</sup> but the usefulness of the preventive efforts cannot be assessed unless a comprehensive assessment of the overall effect is performed. Conforming to the presumed sequence, allergen exposure → sensitization → allergic disease, we found a larger preventive effect on allergen sensitization and a smaller, but clinically

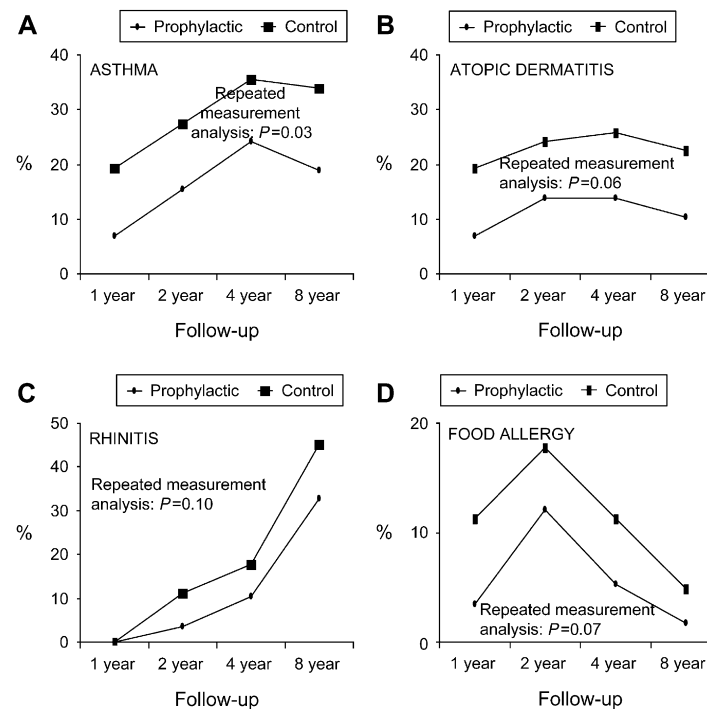


**FIG 1.** Period prevalence of allergic manifestations at each follow-up in prophylactic and control group children. The graphs demonstrate pattern of natural history of allergic disease during childhood and the effect of intervention: (A) asthma, (B) atopic dermatitis, (C) rhinitis, and (D) food Allergy.  $P$  values shown are unadjusted repeated measurement analysis.

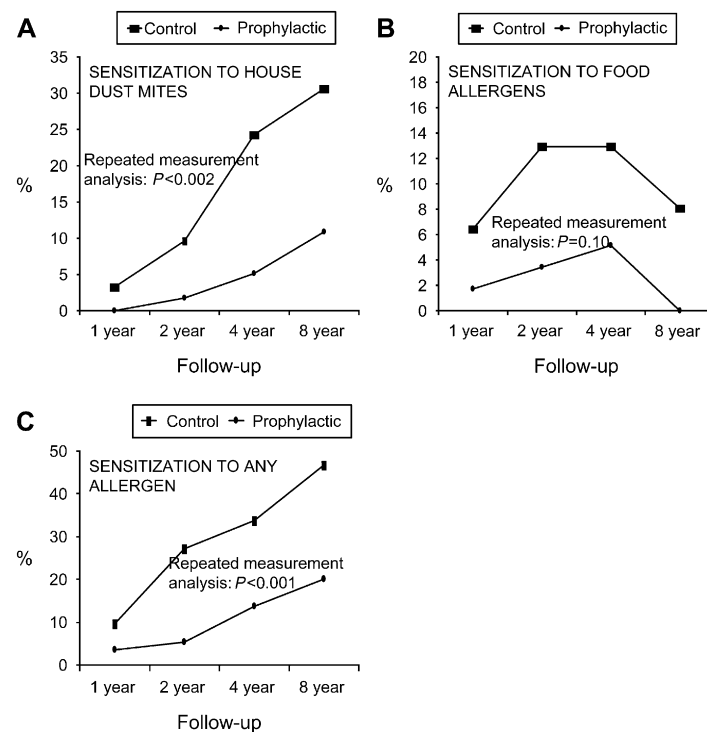


**FIG 2.** Sensitization to house dust mites, food, and any (tested) allergen during the first 8 years of life and the effect of intervention: (A) HDM, (B) food allergens, and (C) any allergen.  $P$  values shown are unadjusted repeated measurement analysis.

**TABLE II.** Clinical allergic disease\* diagnosed at least once during the first 8 years of life in prophylactic and control groups (univariate analysis)

| Allergic disease            | Prophylactic group (n = 58) | Control group (n = 62) | OR   | 95% CI    | P value |
|-----------------------------|-----------------------------|------------------------|------|-----------|---------|
|                             | N (%)                       | N (%)                  |      |           |         |
| Asthma                      | 23 (39.7)                   | 30 (48.4)              | 0.70 | 0.34-1.45 | .22     |
| Allergic asthma             | 7 (12.7)†                   | 16 (25.8)              | 0.42 | 0.16-1.11 | .06     |
| Atopic dermatitis           | 21 (36.2)                   | 29 (46.8)              | 0.65 | 0.31-1.34 | .16     |
| Allergic atopic dermatitis  | 5 (9.1)†                    | 17 (27.4)              | 0.27 | 0.09-0.78 | .01     |
| Rhinitis                    | 19 (32.8)                   | 28 (45.2)              | 0.59 | 0.28-1.24 | .11     |
| Allergic rhinitis           | 7 (12.7)†                   | 19 (30.6)              | 0.33 | 0.13-0.86 | .02     |
| Food allergy                | 11 (19.0)                   | 26 (41.9)              | 0.32 | 0.14-0.74 | .005    |
| Food allergy (IgE-mediated) | 5 (9.1)†                    | 16 (25.8)              | 0.29 | 0.10-0.85 | .02     |

\*For definition of disease, see text.

†n = 55 because skin tests at 8 years were not performed in 3 prophylactic group children.

meaningful and statistically significant, effect on allergic manifestations. Interestingly, the effect was sustained over the duration of follow-up with no narrowing of the difference. Indeed, in cross-sectional analysis, a statistically significant difference in the prevalence of allergic rhinitis appeared for the first time at the age of 8 years (prophylactic, 6 of 54; control, 17 of 62;  $P = .03$ ). This is consistent with the natural history of the disease (rise in the prevalence of allergic rhinitis in late childhood), unmasking the preventive effect of early intervention.

The assertion that allergen exposure early in life leads to the development of allergic disease is biologically plausible, and there is considerable evidence in the literature to support this notion. A dose-dependent relationship between allergen exposure and sensitization<sup>17,18</sup> and between sensitization and the development of allergic disease<sup>19</sup> is well established. There is also some evidence to support that early exposure to cow's milk and to HDM may be risk factors for the development of asthma.<sup>20,21</sup> Although Lau et al,<sup>22</sup> reporting on a German cohort, could not find a direct relationship between allergen exposure and the development of asthma, a recent report from the same cohort indicates that early life allergen exposure is an important determinant of the development of airways obstruction and bronchial hyperresponsiveness at age 13 years in children sensitized to the respective allergen before the age of 3 years.<sup>23</sup> Overall, the evidence weighs in favor of early allergen exposure and sensitization as significant risk factors for later development of asthma and other allergic diseases, and thus prevention by early allergen avoidance seems a logical step in high-risk children.

A number of studies have attempted to prevent the development of allergy.<sup>24</sup> Exclusive breast-feeding with maternal avoidance during lactation<sup>25</sup> and use of hypoallergenic formula<sup>26</sup> have shown mixed effects, whereas avoidance of HDM has been generally disappointing.<sup>27-29</sup> Studies assessing combined food and aeroallergen avoidance have met with greater success.<sup>30</sup> However, none of the primary prevention studies have tried such stringent measures, including strict dietary restriction during lactation, as this study did. The compliance to dietary

**TABLE III.** Adjusted risk for prophylactic group (compared with control group) for the presence of clinical allergic diseases during the first 8 years of life (repeated measurement analysis)\*

|                             | OR   | CI (95%)  | P value |
|-----------------------------|------|-----------|---------|
| Asthma                      | 0.24 | 0.09-0.66 | .005    |
| Allergic asthma             | 0.18 | 0.06-0.58 | .004    |
| Atopic dermatitis           | 0.23 | 0.08-0.64 | .005    |
| Allergic atopic dermatitis  | 0.04 | 0.00-0.24 | .0003   |
| Rhinitis                    | 0.42 | 0.19-0.92 | .03     |
| Allergic rhinitis           | 0.14 | 0.05-0.41 | .0003   |
| Food allergy                | 0.75 | 0.27-2.10 | .59     |
| Food allergy (IgE-mediated) | 0.41 | 0.11-1.53 | .18     |

\*Variables included in the model were age; sex; maternal, paternal, and sibling allergy; maternal, paternal, and sibling asthma; high cord IgE; first born child; maternal education; separate bedroom; gas cooking; maternal smoking during pregnancy; maternal and paternal smoking at age 8 years; pet cat; and pet dog. For definition of disease, see text.

restriction was remarkably high, as assessed by testing of breast milk samples,<sup>9</sup> and extensive HDM avoidance measures were implemented by health care professionals.<sup>9</sup> It is possible that reduction of allergen exposure to very low levels works better than simply handing out impermeable mattress covers.<sup>28</sup> Even when more stringent environmental measures were taken to reduce HDM allergen exposure, the effect was modest,<sup>27</sup> highlighting the importance of exposure to food allergens in early life.

Repeated measurement analysis was used to make an overall assessment of the effect of intervention with sequential data points from birth to 8 years. It is known that children can be affected transiently with allergic diseases. However, when they have the disease, they do suffer and may use health care resources. Thus, a total effect could not be ascertained unless every child with or without a specific condition at any time during the assessment period was included in the analysis. A disadvantage of cross-sectional analysis using data for each point in time is that persistent disease and transient disease are not differentiated. We could not analyze specifically the subset of children with persistent disease because the

numbers were too small. In general, transient disease was more common in the prophylactic group, and the control group bore the brunt of persistent disease. For example, 7 children in the control group had persistent asthma and 6 persistent AD, whereas the corresponding figures for the prophylactic group were 1 and 2. Analysis of repeated measurement (age 1, 2, 4, 8) focuses on repeatedness and is a good approximation of the risk for persistent occurrences. Therefore, the differences in asthma and atopic dermatitis, nonsignificant when disease at 1 or more follow-up was analyzed, achieve statistical significance with repeated measurement analyses (Fig 1).

Baseline characteristics were distributed unequally in the 2 groups, although none were significantly different except pets (cat and dog) at 8 years (Table I). Atopic heredity, especially maternal and sibling allergy, was more common in the prophylactic group, whereas children in the control group had more frequent maternal smoking, first born child, low maternal education, and pets at 8 years. We adjusted for these differences by using standard statistical methods and included all relevant variables in the model (Table III). This increased the statistical significance in favor of prophylactic group (Fig 1 vs Table III). The explanation probably lies in the fact that atopic heredity has a strong influence on the development of asthma and allergy in children, whereas unequal distribution of environmental factors had minor effect. Among the environmental factors, the effect of parental smoking was observed only on asthma at 1 year,<sup>9</sup> whereas maternal and sibling allergy had a significance influence, independent of group allocation, at all ages.<sup>9-11</sup> The augmentation of protective effect, after adjustment for confounders, has been reported previously—for example, for asthma symptoms at age 8 years.<sup>12</sup>

Although these conditions are broadly termed *allergic*, evidence of IgE-mediated allergy is not found in a significant minority, where benefit of allergen avoidance may not be expected. We therefore analyzed the subset of children with diagnosed clinical condition as well as evidence of allergic sensitization on SPT. As expected, the preventive effect was more prominent in those with evidence of IgE-mediated allergy (Tables II and III). To exclude the possibility of prophylactic measures being a risk factor for nonatopic allergic diseases, we analyzed the subgroup with clinical disease without evidence of atopy and found no significant differences (data not shown). This further supports the hypothesis that allergen exposure leads to sensitization and clinical disease and therefore, allergen avoidance prevented only IgE-mediated allergic disease.

A limitation of this study was single-blindness. Great care was taken to keep the assessing pediatric allergist blind to group allocation. However, with the kind of extensive intervention measures used, it was not possible to keep the parents blind to their group allocation. We tried to keep the parents of control and prophylactic groups separate (eg, clinical assessments were made at different times). However, it is possible that some control group parents took allergen avoidance measures without

reporting this to the study team. We do not think this was an issue because the rigorous measures used in this study were difficult to adhere to without substantial guidance and support. In any case, this would actually mask or reduce a preventive effect. It is also possible that the prophylactic group children continued to be subjected to allergen avoidance measures by their parents beyond the planned duration of intervention, the first year of life. Dietary restrictions were definitely lifted by the age of 12 months, but some parents may have continued to take HMD allergen avoidance measures. It would have been both interesting and useful if there had been an assessment of ongoing allergen avoidance at later follow-ups. Another limitation of this study is small sample size. This has led to statistical significance not being achieved even with an OR of less than 0.5, because the CIs were wide (eg, allergic asthma; Table II). The small sample size, to some extent, has been compensated for by excellent retention with zero attrition throughout the life of this cohort.

The analysis in its present form with its multiple outcome measures is in danger of reporting results vulnerable to type 1 error (false-positive because of chance occurrence). However, assessment of various allergic diseases was the predetermined outcome at the beginning of this intervention study. Moreover, the intervention effect detected in our analyses is uniformly in 1 direction—reduction of allergic disease in the prophylactic group—sometimes not reaching statistical significance, indicating the possibility of type 2 (rather than type 1) error (false-negative).

The original hypothesis stated that in infants genetically predisposed to atopy, allergen avoidance in infancy will reduce development of phenotypic manifestations, with the benefit continuing beyond the period of avoidance. Our data support this hypothesis, showing an overall effect of reduction in allergic sensitization, as well as clinical manifestations of allergy. This benefit, in our view, justifies the stringent measures applied in these highly selected (high-risk children and highly motivated parents) families. Further follow-up of this cohort is essential to assess whether the beneficial effect continues through to adolescence and early adult life. In addition, future studies should enroll larger cohorts of children and families, but still need to apply combined and stringent intervention measures.

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