

Allergen Avoidance as Primary Prevention

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Susanne Lau

*Children's Hospital Charity Campus Virchow, Augustenburger Platz 1, Berlin, Germany;
E-mail: susanne.lau@charite.de*

Abstract

There has been a dramatic increase in the prevalence of atopic diseases, such as atopic dermatitis, food allergy, allergic rhinitis, and allergic asthma. Because environmental factors such as early allergen exposure to nutritional and inhalant allergens have been suspected as potential environmental factors favoring the development of allergic diseases and asthma, primary prevention studies have begun to investigate the effect on sensitization and wheezing. Designs of the studies are different and, therefore, are not completely comparable. Although no clear primary prevention study is available for pets, mite allergen avoidance during infancy can achieve a reduction of specific sensitization and, in some studies, can also produce a slight effect on respiratory symptoms.

Index Entries

Allergy prevention; childhood; allergen avoidance; asthma; prevention studies.

Introduction

In recent decades, a dramatic increase in atopic diseases and asthma during childhood has been observed in industrialized countries (1). This trend seems to be real and is not only a result of increased awareness (2). Asthma is the most frequent chronic disease in childhood, with multiple gene–environment interactions. If phenotypical 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 (3). Epidemiological studies indicate that various lifestyle and environmental factors, such as indoor allergen exposure (mites and pets; refs. 3 and 4), pollutants, dietary modifications, and infectious factors (ref. 3; the latter supporting the hygiene hypothesis [5]), play an important role in the development of the multifactorial entity of atopy and childhood asthma.

Sensitization to house dust mites (HDMs), a perennial allergen in Europe, the United States, Australia, New Zealand, Taiwan, South America, and many other places in the world, plays a key role in the pathogenesis of asthma (6–8). In areas of the world where mite allergen exposure (*Dermatophagoides* spp.) is highest, asthma prevalence among children was also found to be highest, for example, in Australia and New Zealand (9,10). However, children living at altitudes with low levels of HDMs were not found to have any significant decrease in the development of asthma (11).

The best single predictors for childhood asthma are positive maternal history for asthma and allergic sensitization to HDMs (4,7). HDM sensitization often occurs early in childhood and depends on the level of domestic exposure (4,12,13). Sensitization rates increase by age during the first two decades of life. Because sensitization often precedes allergic airway disease, it is logical to attempt to reduce exposure before sensitization occurs.

Although allergen avoidance has been shown to be successful as tertiary prevention in the treatment of asthmatic patients who are allergic to mites (14,15), the effect of indoor allergen avoidance as primary prevention to prevent early sensitization and later allergic airway disease remains under investigation (16–18). The earliest trial, the Isle of Wight Study, started to recruit newborns in 1990 to 1991, and children are now ages 13 to 14 yr.

Ongoing primary prevention cohort studies attempt to evaluate the effect of different intervention strategies. Most of the birth cohort studies have introduced dietary intervention or avoidance of HDM allergens. End points of trials in which a significant decrease in environmental indoor allergen exposure is achieved involve specific sensitization and airway symptoms—that is, cough and wheeze. Comparing the different studies is usually not easy, because all studies use different study designs and some studies combine different intervention procedures, such as dietary intervention plus avoidance of HDM and pet allergens as well as tobacco smoke.

This article briefly presents study designs and results of the following trials:

- The Isle of Wight Study (birth cohort).
- The Study of Prevention of Allergy in Children in Europe (SPACE) interventional, prospective birth cohort and second cohort with schoolchildren.
- The Prevention of the Incidence of Asthma and Mite Allergy (PIAMA) study birth cohort (Netherlands).
- Canadian Allergy and Asthma Prevention Study (birth cohort).
- Manchester Allergy and Asthma Study (MAAS; birth cohort).
- Children's Asthma Prevention Study (CAPS) from Australia (birth cohort).

The Isle of Wight Study (19–22)

A birth cohort of 120 infants at high risk for atopy (double-positive family history or one parent with positive food hypersensitivity

for atopy plus elevated cord blood immunoglobulin E [IgE] >0.5 kU/L) were recruited prenatally and randomized into prophylactic ($n = 58$) and control ($n = 62$) groups. Allergen avoidance measures were instituted from birth in the prophylactic group: infants were either breastfed with the mother on a low-allergen diet or given an extensively hydrolyzed formula. Exposure to house dust was reduced by the use of an acaricide and mattress covers. The control group followed standard advice as normally given by the health visitors. Blind assessments were made at ages 1, 2, and 4 yr in all 120 children. These included questionnaires, physical examination, and skin prick tests (SPTs) to common food and aero-allergens. At age 8 yr, all 120 children completed a questionnaire, and 110 (92%) had all assessments (SPT, spirometry, and methacholine bronchial challenges). In the prophylactic group, 8 children (13.8%) had current wheeze, compared with 17 (27.4%) in the control group ($p = 0.08$). Respective figures were 8 (13.8%) and 20 (32.3%) for nocturnal cough ($p = 0.02$), and 11 of 55 (20%) and 29 of 62 (46.8%) for atopy ($p = 0.0003$). 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] 0.07–0.96; $p = 0.04$), nocturnal cough (OR = 0.22, CI 0.06–0.83; $p = 0.02$), asthma as defined by wheeze plus bronchial hyperreactivity ($PC_{20} < 8$ mg/mL) (OR = 0.11, CI 0.01–1.02), atopy (OR = 0.21, CI 0.07–0.62; $p = 0.005$), and mite sensitization (OR = 0.08, CI 0.02–0.36; $p = 0.002$). Authors concluded that strict dietary allergen and mite allergen avoidance during infancy in high-risk children reduced the development of allergic sensitization to HDM and nocturnal cough, indicating that this may prevent some cases of childhood asthma.

Comments

The effect on asthma symptoms, pulmonary function, and bronchial hyperreactivity was less marked. The development of asthma

is only partially determined by atopy, providing an explanation for the more modest improvements seen in asthma-related features in this study, although a considerable reduction in sensitization was achieved. A major problem in the interpretation of data is the combination of two interventional procedures.

The Canadian Asthma and Allergy Prevention Study (23)

A total of 545 high-risk infants (infants with at least one first-degree relative with asthma or two first-degree relatives with other IgE-mediated diseases) were identified before birth, and environmental measures to decrease HDM and pet allergens as well as environmental tobacco smoke, were instituted. If a supplement was required, breastfeeding and supplemented breastfeeding with a partially hydrolyzed formula was encouraged for the first year of life. At age 12 mo, 38 (15.1%) of the 252 infants available for assessment in the intervention group and 49 (20.2%) of the 242 infants available for assessment in the control group fulfilled the criteria of asthma (adjusted relative risk [RR] = 0.66; 90% CI 0.44–0.98). Also, 16.7% of the infants in the intervention group and 27.3% of infants in the control group developed rhinitis without colds (RR = 0.51; CI 0.35–0.74). At age 24 mo, the prevalence of asthma in the intervention group remained significantly lower (16.3%) than that in the control group (23%; RR = 0.61; 90% CI 0.41–0.9).

The Manchester Allergy and Asthma Prevention Study (24–26)

In this study, 291 high-risk infants (with both parents atopic) without pets were recruited. They were randomized, and 142 were allocated to an active group and 136 were allocated to a control group. Two further prospective groups were followed: 161 high-risk babies with pets in the home and 168 low-risk babies whose parents were both nonatopic. In the active group, vinyl flooring in the child's room, an allergen-

impermeable cot mattress, a hot-washable toy, and mite allergen-impermeable encasings to the parental bed and to the child's bed (when older) were introduced. Furthermore, high-filtration vacuum cleaning and regular hot-washing of bedding were introduced. Intervention was started in early pregnancy. Dust samples were taken from the parental mattress, living room floor, child's mattress, and floor at baseline (pregnancy), birth, and at age 3 yr and were analyzed for Der p 1, Fel d 1, and Can f 1. A total of 278 families completed the baseline visit, 259 completed the birth visit, and 239 completed the 3-yr visit. In the active group at age 3 yr, 58% remained compliant with all measures likely to reduce the child's exposure to allergen, and 77% of parents still used encasings in their bed. Levels of Der p 1, Fel d 1 and Can f 1 were significantly lower in the active group in the child's floor and child's mattress at 3 yr compared with the control group ($p < 0.001$). For the parental mattress, the levels of Der p 1 and Fel d 1 were lower in the active group ($p < 0.001$), and there was a strong trend toward lower Can f. Custovic et al. (24) instituted several avoidance measures to decrease inhalant allergen exposure in these families and demonstrated that the avoidance measures used were capable of achieving and maintaining an environment with low dust mite allergens during pregnancy and for the first 3 yr of life. During the first year of life, children in the active group were less likely to have respiratory symptoms than those in the control group. The most pronounced differences were in the relative risks for severe wheeze with shortness of breath (RR = 0.44, 95% CI 0.2–1); prescribed medication for the treatment of wheezy attacks (RR = 0.58, CI 0.36–0.95); and wheezing after vigorous playing, crying, or exertion (RR = 0.18, CI 0.04–0.79). Follow-up studies will show whether the frequency of respiratory symptoms will remain significantly different. Cat ownership was also significantly

associated with sensitization to cats (RR = 24.6, CI 3.04–199.05; $p = 0.003$).

The SPACE Study (27,28)

As a part of a multicenter study (SPACE), 242 children (ages 5–7 yr) in three European countries (United Kingdom, Greece, and Lithuania) were randomized to prophylactic group ($n = 127$) and control group ($n = 115$). At randomization, these children were required to have a family history of atopy and positive SPT to an aero-allergen but not HDM. Children in the prophylactic group were provided with dust-mite-impermeable mattress covers and advice regarding environmental measures to reduce exposure to dust mite allergen. Control group children were given nonspecific advice. After 12 mo, a standardized questionnaire was completed and SPT were performed. Ten children in the prophylactic group and 19 in the control group were lost to follow-up. Three of 117 (2.56%) children in the prophylactic group and 9 of 96 (9.38%) in the control group developed sensitization to dust mites. Logistic regression analysis confirmed an independent effect of prophylactic measures (adjusted OR = 0.14, 95% CI 0.03–0.79; $p = 0.03$). Fifteen children needed to be treated to prevent sensitization in one.

Furthermore, a total of 696 newborns were included from Austria, the United Kingdom, and Germany. Inclusion criteria were: a positive history of parental allergy, and a positive SPT or specific IgE against at least one out of a panel of common aero-allergens in one or both parents. Families were randomized into active and placebo groups as mentioned earlier. At age 1 yr, the overall sensitization rate against the tested allergens (*D. pteronyssinus* and *farinae* and food allergens [egg and milk]) was 6.12% in the prophylactic group vs 10.6% in the control group. The prevalence of sensitization to *Dermatophagoides* was 1.86% in the prophylactic group and 5% in the control group.

The CAPS (29–31)

The CAPS was a randomized, controlled trial in Australia to measure whether the incidence of atopy and asthma could be reduced by HDM allergen reduction, a diet supplemented with ω -3 fatty acids, or a combination of both interventions. In CAPS, 616 pregnant women whose unborn children were at high risk of developing asthma because of a family history were randomized prenatally. Study groups were as follows: group A (placebo diet intervention, no HDM reduction), group B (placebo diet intervention, active HDM reduction), group C (active diet intervention, no HDM reduction), and group D (active diet intervention, active HDM reduction). The HDM reduction intervention uses physical and chemical methods to reduce allergen contact. The dietary intervention uses daily oil supplement from 6 mo or at onset of bottle-feeding, as well as margarine and cooking oil based on sunflower or canola oils to increase ω -3 dietary intake. Data are collected quarterly until the infant is age 1 yr and are then collected every 6 mo until age 5 yr. Questionnaires are used to collect respiratory illness history and information about diet and home environment. Dust is collected from the child's bed and bedroom and playroom floors. Blinded assessments are conducted at 18 mo, 3 yr, and 5 yr. SPTs to common allergens, blood tests, and detailed illness; medication use; and vaccination histories are collected. Primary outcomes are the development of allergic sensitization and the presence and severity of asthma. The study is designed to measure the effectiveness of allergen reduction and dietary supplementation, both separately and in combination, for the primary prevention of atopy and asthma. In the highly exposed Australian environment, the reduction achieved was above the exposure levels achieved in the United Kingdom by the MAAS. In the control group, Der p 1 levels were found to be 22 μ g/g of mattress dust, whereas in the intervention

group, levels were 6 μ g/g of mattress dust after 18 mo. No clinical effect was observed in the group with single HDM avoidance; however, in the group with supplementation of ω -3 fatty acids, a decreased prevalence of wheeze was observed during the first 18 mo.

The PIAMAS (32–34)

The PIAMA birth cohort study was initiated in 1996. Children born to allergic mothers were enrolled in a double-blind, placebo-controlled trial for evaluating the use of mite-impermeable mattress and pillow covers. Children born to allergic and nonallergic mothers were enrolled in a "natural history" study to assess the role of environmental and dietary risk factors for the development of allergic diseases in childhood. Recruitment started by distributing a validated screening questionnaire among more than 10,000 pregnant women during their first visit to a prenatal health clinic. Allergic mothers-to-be were invited to participate in the intervention study. Allergic and a random sample of nonallergic mothers-to-be were invited to participate in the natural history arm of the study. In the intervention study, homes were visited before birth and at 3 and 12 mo after birth for the collection of dust samples from floors and mattresses, and Der p 1 and Der f 1 were determined per square meter. The intervention began with 855 participants, and the natural history part of the study began with 3291 participants. Participation rate at the follow-up age of 3 yr was less than 90%. In the intervention trial, 416 families were allocated to the active group, receiving HDM allergen-impermeable mattress covers for the parents' and child's mattress during the third trimester of pregnancy. A total of 394 were allocated to the placebo group and received placebo covers. A second control group ($n = 472$) was also followed and received no intervention. Parents completed questionnaires during pregnancy, as well as when the children were ages 3 mo, and

1, 2, and 5 yr. Blood samples were collected and serum IgE to HDM, cat, dog, and food allergens were determined at age 1 and 5 yr.

At ages 1 and 2 yr, mite allergen levels were lower than were found in previous Dutch studies. The intervention measure had a significant effect on mite allergen levels, without important clinical benefits up to age 2 yr. The prevalence of night cough without a cold in the second year of life was lower in the group with active covers compared with the group with placebo covers (adjusted OR = 0.65, 95% CI 0.4–1). No effect of the intervention was observed for other respiratory symptoms, atopic dermatitis, and total and specific IgE.

Conclusion

Although avoidance of ingested allergens (i.e., cow's milk in early infancy) clearly can prevent early allergy and atopic dermatitis (German Infant's Nutritional Investigation; ref. 35), results of primary prevention trials avoiding indoor allergens—especially HDM allergens—indicate that sensitization rates can be reduced in childhood. However, the impact of school-age asthma appears to be rather weak. Because some of the participating children are still fairly young, further long-term follow-up data will demonstrate whether early avoidance of HDM allergens can reduce the prevalence of school-age and teenage asthma. One major problem is the fact that all primary prevention trials have different study protocols, often combining two or more intervention strategies (nutritional plus indoor allergens), and comparability is not really provided.

Regarding pets, it is still unclear how early life exposure is related to children's risk of developing allergic sensitization and asthma (4,22,25,36–42). There is no single primary prevention study that only avoids pet allergens. Some primary prevention studies, such as the MAAS and the Canadian trial, avoid pet allergen in addition to the avoidance of HDM allergens.

Thus far, recommendations to families for primary prevention of asthma should be given with caution, because none of the single approaches can actually prevent children from asthma to a larger extent. Because smoking in families—especially during pregnancy—favors later sensitization in the children, and sensitization to inhalant allergens is a risk factor for wheezing, it is highly recommendable to avoid smoking during pregnancy and early infancy. The avoidance of indoor allergens, especially HDMs, appears to at least delay the onset of allergy (i.e., sensitization). Sensitization to mite is a major risk factor for asthma; therefore, the severity of childhood asthma may be influenced by avoiding early HDM sensitization by introducing mite-impermeable encasings and so forth. Data are still controversial for pets, but families with infants at risk for atopy should not be encouraged to keep cats or dogs, because the Isle of Wight Study, the German Multicentre Allergy Study, and the MAAS have shown that high cat allergen exposure favors sensitization, at least during the first years of life.

However, a more global and more promising approach in allergy and asthma prevention seems to be the development of an allergy vaccination that attempts to modulate immune responses in the correct way early in life.

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