

The role of indoor allergen exposure in the development of sensitization and asthma

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The role of indoor allergen exposure in the development of sensitization and asthma remains a subject of controversy. From a number of cross-sectional and longitudinal studies we can conclude that there is a very close association between allergen exposure and the sensitization of an individual. The dose-response relationships seem to differ between allergens; house dust mite and cockroach allergens appear to have a positive linear relationship, whereas cat allergens appear to act quite differently, with maximum sensitization developing at moderate exposure levels. Very low levels of cat allergen exposure are likely to induce no response and very high levels are likely to develop a form of tolerance, with a modified T helper cell type 2 response and the production of IgG4 antibodies and but not IgE. The relationship between indoor allergen exposure and asthma is, however, less clear. The proposed mechanism for the development of disease is that allergen exposure causes sensitization, and continued exposure leads to airway responsiveness and inflammation. As yet, the evidence for allergen exposure being a primary cause of asthma remains weak, and the results of ongoing prospective, randomized allergen avoidance trials are awaited to clarify this issue. *Curr Opin Allergy Clin Immunol* 1:407–412. © 2001 Lippincott Williams & Wilkins.

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Abbreviations

CBMC	cord blood mononuclear cells
ELISA	enzyme-linked immunosorbent assay
Th	T helper

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Introduction

In recent years a number of authors have argued that indoor allergen exposure is the primary cause of asthma [1–4]. Increases in the prevalence of asthma throughout the world could be secondary to increased time spent indoors [2] because of changes in lifestyle, or increases in indoor allergen levels [4] as a result of changes in housing (increased soft furnishings, increased room temperatures, decreased ventilation).

The relationship between allergen exposure, sensitization and asthma development is a complex one, and has recently been a subject of controversy. Pearce *et al.* [5] suggested that only 50% of asthma cases are attributable to atopy. A recent systematic review [6•] concluded that current evidence did not support the view that allergen exposure is a major risk factor for asthma. However, many studies examining this subject are retrospective, differ in the assessment of exposure, and have included subjective outcome measures. Peat and Li [7], in a comprehensive meta-analysis, evaluated several environmental factors thought to be responsible for the incidence and severity of asthma, and concluded that indoor allergen exposure was the environmental factor with by far the strongest effect on the manifestation of asthma.

There is certainly biological plausibility for the role of allergens in the development of asthma, in that proteolytic enzymes within allergens can damage airway epithelium [8•]. All the other Bradford-Hill criteria [9] can be fulfilled, (9 criteria proposed by Bradford-Hill in the 1960's which if all fulfilled suggest causation eg. temporal sequence, strength of association, biological plausibility, consistency of findings) suggesting a possible causal relationship between allergens and asthma [3].

In this review, we examine current evidence for the role of indoor allergens in the development of sensitization and asthma. We commence by discussing the evidence for the priming of the immune system *in utero* and early life towards the development of an atopic state. We then address the behaviour of different allergens in inducing sensitization and consider evidence, from various cross-sectional and longitudinal studies, for the role of allergen exposure in the development of asthma.

In-utero and early exposure to allergens: when does sensitization occur?

It has been hypothesized that atopy in children represents the persistence of prenatal and neonatal

allergen specific T helper (Th) type 2 responses, caused by failure of immune deviation mechanisms that promote the Th1 state of the normal, mature immune system. An analysis of cytokine profiles of allergen-stimulated cord blood mononuclear cells (CBMC) has demonstrated polarization towards the Th2 cytokine phenotype, characterized by the production of IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13 [10,11]. In addition, decreased production of the Th1 cytokine IFN- γ has been reported in those infants at high risk of developing allergic disease [12] and also in those who subsequently go on to develop allergic disease in childhood [13–15]. Although IgE production starts in the 11th week of gestation, no specific sensitization to food or inhalant allergens, as measured by elevated serum IgE antibodies, has been detected using current methods.

The human fetus is capable of making immune responses from the third trimester. Several groups have tried to establish whether T cell priming of the fetus by allergens can occur during pregnancy. There is evidence that some infants have positive food allergen-specific CBMC proliferation responses [16], and there is also evidence to suggest that some have inhalant allergen CBMC proliferation responses [17], suggesting in-utero priming to these allergens. However, one would expect the magnitude of these proliferative responses to relate to maternal allergen exposure during pregnancy. Several authors have reported on the relationship between maternal exposure and CBMC proliferative responses. Szepefalusi *et al.* [18^{*}] found that proliferative responses to Bet v 1 and Phl p 1 were no more likely to occur if the mother had been exposed to birch or grass pollen during pregnancy than if she had not been exposed. Smillie *et al.* [19] also found no relationship between CBMC immunoproliferative responses and the levels of inhalant allergen that mothers were exposed to during pregnancy, despite 21 000-fold differences between the lowest and highest maternal mattress Der p 1 levels.

It is unclear how this priming process may be triggered. It may be caused by the transplacental leakage of allergen from the maternal circulation, or the transplacental transfer of maternal antibodies against allergens. Recently, an in-vitro placental study [20^{*}] showed the active transfer of both Bet v 1 (birch pollen allergen) and beta-lactoglobulin (milk allergen) across the placenta. Holloway *et al.* [21^{*}] demonstrated the presence of Der p 1 in matched maternal blood and amniotic fluid at 16–17 weeks' gestation and also of Der p 1 in matched maternal and umbilical-cord blood at term, suggesting both transamniotic and transplacental allergen transfer. Allergen levels in amniotic fluid and cord plasma increased with increasing maternal allergen concentrations. However, concentrations of Der p 1, which were measured in the amniotic fluid, were equivalent to up to

6 years' cumulative inhaled house dust mite exposure, which has been estimated to be approximately 10 ng per day [22^{**}], raising questions about the specificity of the Der p 1 enzyme-linked immunosorbent assay (ELISA) used. Other groups have shown the presence of Fel d 1–IgG immune complexes in cord blood, again using ELISA, indicating the transplacental transfer of cat allergen in the form of immune complexes with maternal-derived IgG antibodies [23^{*}].

A recent review article [22^{**}] suggested that the evidence for sensitization or priming of the fetus was unconvincing, and that, at least for inhalant allergens, proliferation responses were neither consistent nor related to maternal exposure, and did not predict outcome for the infant in terms of either sensitization or disease.

It may be, however, that early postnatal exposure to allergens is important in priming T cells. Two recent studies have shown that inhalant allergen exposure in the first few months of life is associated with peripheral blood mononuclear cell proliferative responses. Smillie *et al.* [19] found proliferative responses in children at 1 year of age to increase significantly with increasing exposure to Der p 1 early in life. Also, Finn *et al.* [24^{*}] found proliferative responses in children at 2 years of age to increase significantly with increasing exposure to Bla g 1 at 3 months of age.

At present, it remains unknown whether it is exposure at a particular time of life (during pregnancy or in infancy, or perhaps both) or cumulative exposure that is of importance in the development of atopy.

Allergen exposure and the development of sensitization

Individuals will only develop an immune response if exposed to sufficient allergen. Allergen measurement has become easier and more reliable. We can now measure representative allergens from cat, dog, dust mites and cockroach [25–28]. Also, the relationship between airborne levels of allergen and floor or reservoir levels has been established [29–31]. However, this does not amount to an accurate measurement of exposure, i.e. actually how much allergen is inhaled over a period of time.

Despite this inaccuracy of exposure measurement, there appears to be a dose–response relationship between reservoir allergen levels and sensitization. For house dust mite, a dose–response relationship has been shown within communities [4,32,33^{**},34^{*}] and also between communities with different climates [1,35]. The threshold concentration for developing mite sensitivity in atopic children was confirmed by Kuehr *et al.* [36] as 2 μ g

Der p 1 antigen per gram of dust, but in non-atopic children only a high cut-off limit of 80 $\mu\text{g/g}$ gained significance. For other indoor allergens the relationship between exposure and sensitization is less well-defined, partly because fewer studies have been conducted.

For areas in the world where cockroach infestation is commonplace, allergens derived from the cockroach are an important source of sensitization. Several studies [34,37,38] have shown that with increasing cockroach allergen exposure, children are more likely to become sensitized. Increasing exposure to mouse allergen has recently been found to be associated with increased sensitization to mouse allergen [39]. Interestingly higher levels of mouse allergen have been associated with evidence of cockroach infestation, and both are widely distributed throughout poorer inner-city homes [40].

Cat and dog allergens differ from the above in that they remain airborne. There is thus a different relationship between reservoir measurements and the amount of inhaled allergen. The major cat allergen, Fel d 1, is primarily produced in the skin, and is probably carried on flakes of dander. Both Fel d 1 and Can f 1 can become adherent to walls, carpets and clothing, facilitating their transfer to offices and homes without a pet [41,42]. They can remain airborne for hours. Recent population studies [38,43,44] suggested that having a cat as a pet in the house as a child (i.e. living in a very high cat allergen environment) could decrease the risk of sensitization to cat later. Explanations for this phenomenon include the possibility that allergic families actively avoid taking pets, that the presence of pets increases microbiological exposure and thus enhances Th1 immunity, or that current methods of cat allergen measurement do not accurately reflect exposure. Recently, Platts-Mills *et al.* [45] proposed an alternative hypothesis. In this important study, children exposed to the highest levels of cat allergen were less likely to be sensitized to cat and were more likely to have IgG4 antibodies to cat allergens. A high prevalence of allergen-specific IgG antibodies has previously been reported among animal handlers and beekeepers [46,47]. Animal handlers over a few years develop IgG antibodies to rat urinary allergen without developing IgE antibodies, and similarly bee keepers who have had multiple stings develop IgG4 without IgE antibodies. As IgG4 antibodies are part of a Th2 response, the primary cytokine inducing the gene for IgG4 in human B cells being IL-4, this appears to be a modified Th2 response or tolerant immune response.

It appears that with cat allergen the maximum prevalence of sensitization to cat develops with moderate exposure (1.7–23 $\mu\text{g/g}$). Very low levels of exposure are likely to induce no immune response, and very high

levels are likely to induce a modified Th2 response with the production of IgG4 antibodies and the absence of symptoms. However, given that some children in the study by Platts-Mills *et al.* [45], who were exposed to high levels of cat allergen did become sensitized, perhaps there is also a genetic component. In general, the findings of the study bring into question the advice that is often given to families about avoiding having pets to prevent sensitization in their children.

The other issue raised by their study is why the same effect was not seen with house dust mite allergen. The exposure levels of dust mite allergen compared with cat allergen could explain this. Platts-Mills *et al.* [45] found mite allergen levels to be lower than those for Fel d 1. However, in studies from New Zealand [48], where mite allergen levels are much higher, evidence of tolerance development, with the detection of IgG4 antibodies, has not been reported. As cat allergen, unlike mite allergen, is persistently airborne, the quantity of inhaled cat allergen is probably much greater than that of dust mite. Although both allergens are measured in μg per gram of dust, it cannot be assumed that the biological potency of 1 μg mite allergen is the same as 1 μg of cat allergen. For cat allergen, a graph of exposure versus sensitization appears to be a bell-shaped curve. For mite allergen this is a positive linear relationship (Fig. 1). It is possible that if mite allergen inhalation levels were sufficiently high, an effect similar to cat may be seen.

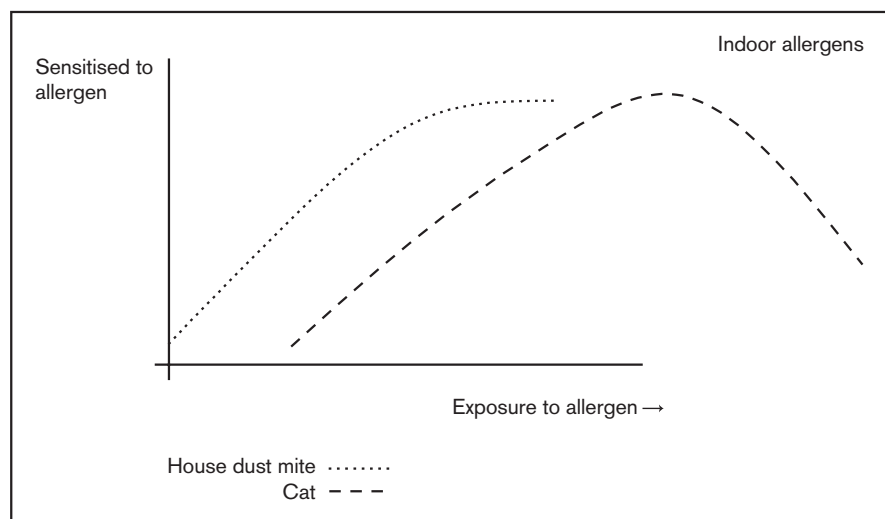
Allergen exposure and the development of asthma

It is well established that allergen exposure is a secondary cause of asthma; allergen exposure can trigger an exacerbation of asthma in a sensitized individual, and prolonged exposure can lead to the persistence of symptoms [1,49]. However, the evidence for allergen exposure being a primary cause of asthma is not so clear. The most relevant evidence to date comes from longitudinal studies, in which infants are followed from birth, and the association between allergen exposure early in life and the subsequent development of asthma is examined.

Evidence from longitudinal studies

Sporik *et al.* [4] followed 67 children, with a family history of atopy, from birth to 11 years. They found a significant correlation between early dust mite exposure and current wheeze, with the age at which children first wheezed being inversely proportional to the level of exposure at 1 year of age. All but one of the children with asthma at 11 years of age had been exposed to greater than 10 μg of Der p 1 per gram of dust at 1 year of age. They found no correlation between current exposure and current wheeze.

Figure 1. Proposed relationship between exposure to cat and house dust mite and sensitisation to that allergen



In 1993, Burr *et al.* [50] published their results of a birth cohort study of 453 infants. Infants were randomly assigned to cows' milk protein avoidance for the first 3 months of life or a normal regime, and were followed until 7 years of age. Levels of dust mite allergen were determined in mattress and carpet dust in the first and seventh years of life. Doctor-diagnosed asthma or wheezing at 7 years of age was not associated with mite allergen levels in the first or seventh year of life. Withholding cows' milk protein had no effect on the incidence of allergy or wheezing, and thus it seems likely that the lack of association between mite allergen exposure and asthma symptoms can be explained by confounding effects of the intervention.

A total of 1314 children were enrolled in the German Multicentre Allergy Study [33•] and followed prospectively. At 7 years of age, complete data were available on 648 children. There was a strong association between sensitization to mite and cat allergens and wheezing, which became significant at 3 years of age. Sensitized children also showed higher bronchial reactivity at 7 years of age. Indoor allergen exposure was strongly related to specific sensitization at 3 and 7 years. However, the authors were unable to detect a consistent dose-response relationship for early allergen exposure and doctor-diagnosed asthma, wheezing within the past 12 months or wheezing ever.

Litonjua *et al.* [51•] followed 222 children (median age at enrolment 2.87 years), who were siblings of an ongoing longitudinal study, over a 2 year period, and examined the relationship between home allergen levels at the beginning of the study and the development of asthma. They found exposure to cockroach allergen to be a

significant predictor of incident asthma (developing asthma over the follow-up period). In addition, they found a dose-response relationship. The relative risk of incident asthma for an exposure level of 0.05 to less than 2 U/g cockroach allergen in the multivariate model being 9.22 [95% confidence interval (CI) 1.24–68.49] and the relative risk for an exposure level over 2 U/g being 26.47 (95% CI 2.06–339.46). Neither dust mite nor cat allergen levels were found to be associated with incident asthma. The numbers of children, however, developing incident asthma in the study were very small (5.9%), and we have no information as to exposure earlier in their lives.

Evidence from intervention studies

In the Isle of Wight Study [52] infants were randomly assigned to avoidance of allergenic food and a reduction of dust mite allergen by acaricide treatments up to the age of 9 months (prophylactic group, $n = 58$) or a 'normal' lifestyle (control group, $n = 62$). Children were then followed prospectively and seen at 1, 2 and 4 years of age [53], and most recently at 8 years of age [54]. There was significantly less sensitization in the prophylactic group compared with the control group at all age reviews. There was a significant reduction in wheezing at 1 year of age and non-significant reductions at 2 and 4 years. At 8 years of age there was a significant reduction in nocturnal cough ($P = 0.02$) and a non-significant reduction in wheezing ($P = 0.07$), but the forced expiratory volume in 1 s and bronchial responsiveness were no different. Unfortunately, the numbers in the study were small, and it was impossible to separate out the effects of food allergen avoidance from mite allergen reduction. In addition, it must be noted that house dust mite reduction methods only resulted in the reduction of allergen levels to a mean of 6 μg Der p 1 per gram of

dust. This level may be insufficient in atopic children to prevent sensitization [36], and thus show a statistical difference in symptoms.

The Manchester Asthma and Allergy Study [55••], a pre-natally randomized controlled trial of allergen avoidance in high-risk infants, has recently reported their 1-year outcomes. Parents of infants in the intervention group used mite-proof bedding for themselves and their infant, used a high expiratory pressure air filter vacuum cleaner, applied high efficiency particulate air (HEPA) filter acaricides to carpets and soft furnishings, hot washed bed linen weekly, washed all soft toys, and kept no pets. Infants were reviewed at 1 year of age, and were found to have lower estimates of relative risk for a range of respiratory symptoms; wheezing after playing or crying [relative risk (RR) 0.18; 95% CI 0.04, 0.79]; wheeze with breathlessness (RR 0.44; 95% CI 0.2, 1.0); and wheeze requiring inhaled treatment (RR 0.58; 95% CI 0.36, 0.95). The authors acknowledge that it is important not to over-interpret the findings in view of the fact that the children have only been followed for a short period.

Conclusion

From a number of cross-sectional and longitudinal studies we can conclude that there is a close association between exposure to some of the indoor allergens and sensitization to that specific allergen. A dose-response relationship has been demonstrated for both house dust mite (positive linear relationship) and cat allergen (bell-shaped relationship) exposure and the development of IgE-mediated sensitization to mites and cats, respectively. However, as far as the development of asthma is concerned, the situation remains unclear. It is possible that sensitization may be regulated differently from the manifestation of airway inflammation and asthma [56].

The relationship between allergen exposure and disease is confounded by a number of factors. The measurement of reservoir allergen levels is at best only an estimate of personal inhaled allergen. Also, in real life, individuals are exposed not only to a mixture of allergens but also to other pollutants and irritants (tobacco smoke, ozone, nitrogen dioxide), and we know little about any synergistic effects, if any. In addition, in terms of study design, disease outcome measures must be clearly defined and objective, as well as subjective outcomes measured.

To elicit the true role of allergen exposure in the development of sensitization and asthma it is necessary to conduct a large prospective randomized trial of allergen avoidance, with an accurate measurement of allergen exposure throughout, confirming adequate allergen reduction in the avoidance group. Children will need to be followed for many years in order to

distinguish true asthma symptoms from early viral wheeze. As yet, the evidence for allergen exposure being primarily involved in the development of asthma is inconclusive.

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