

Exposure and sensitization in infants and children

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The complex relationship between allergen exposure, atopic sensitization and asthma in individuals and in populations has recently been a subject of controversy. A number of studies have demonstrated that allergen exposure in sensitized asthmatic individuals increases the severity of disease. A simple dose–response relationship between mite allergen exposure and specific sensitization in infants and children has been confirmed. However, the concept that there is a direct relationship between allergen exposure and the initiation of asthma has been challenged. The relationship between allergen exposure and subsequent disease development is complex, and is confounded by a number of important factors. Populations and individuals are exposed to a mixture of several allergens, irritants and pollutants, and we know very little about the impact of these mixtures and their possible synergistic effect. The dose–response relationship between allergen exposure and allergic disease may not be linear, and may be different for different allergens. For example, a protective effect of cat ownership on sensitization and allergic disease has been reported, raising the question of whether the dose–response relationship between exposure and sensitization may be different for cat compared with mite allergen. It has been suggested that many children who are exposed to a high level of cat allergen make a modified T helper type 2 response, characterized by the presence of IgG4 antibody to cat proteins without becoming allergic (i.e. no IgE response), which could be regarded as a form of tolerance. This could explain a decreased risk of asthma in children living in homes with cats,

without invoking a concept of a shift in the balance of T helper types 1 and 2 responses. Cat allergen is ubiquitous, and passive exposure (e.g. home without cats and public places) may induce specific IgE responses in non-cat owners, whereas those exposed to very high levels of cat allergen may initially mount an IgE response, which may be replaced by a modified T helper type 2 response (tolerance). It is likely that the population susceptibility to allergic sensitization and also end-organ responsiveness has altered, and allergen exposure may still be important in initiating disease in an increasingly susceptible population, although the pattern may differ for different allergens. *Curr Opin Allergy Clin Immunol* 1:133–138. © 2001 Lippincott Williams & Wilkins.

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Abbreviations

CBMC cord blood mononuclear cells
PBMC peripheral blood mononuclear cells

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Introduction

The relationship between allergen exposure, atopic sensitization and asthma in individuals and in populations is a complex one, which has recently been a subject of controversy. Pearce *et al.* [1] suggested that the proportion of asthma cases that are attributable to atopy is usually less than half, and after reviewing the data challenged the concept that there is a relationship between allergen exposure and the development of asthma [2•].

First of all, it is important to be precise about the issues and definitions. There are few similarities between different studies in the assessment of exposure (e.g. when has exposure occurred and how has it been estimated; questionnaire versus objective measurement) and outcome measures (atopy, wheeze, 'asthma', airway reactivity). As allergen exposure is strongly associated with sensitization, it is often difficult to separate the effect of sensitization from that of allergen exposure on the initiation of asthma. Although evidence is mounting that allergen exposure in sensitized asthmatic individuals may increase the severity of disease [3–6], the role of allergen exposure in the initiation of asthma appears less clear. Too many studies are retrospective and are open to selection bias.

Allergen exposure and lymphocyte responses in early life

Several studies have reported differential stimulation of cord blood mononuclear cells (CBMC) [7–10], and infant peripheral blood mononuclear cells (PBMC) by mitogens and allergens in advance of the development of disease itself [7,9,10]. The induction of T lymphocyte activation and consequent cytokine production may lead to a cascade of responses including IgE-mediated sensitization, and perhaps airway inflammation. Cytokine expression profiling of CBMC immunoproliferative responses has revealed a strong T helper type 2 bias at birth [7,11,12], and reduced IFN- γ production by antigen-stimulated CBMC has been associated with the subsequent development of allergic disease [13].

Is inhaled allergen exposure during pregnancy important?

It has been suggested that maternal allergen exposure beyond the 22nd week of pregnancy may play a role in fetal T cell priming. The allergen-specific differences in CBMC immunoproliferative responses between neonates at high and low risk of developing allergic disease, and the fact that immunoproliferative responses to the bacterial antigen controls (e.g. tetanus toxoid) were not observed, have been suggested as evidence of in-utero sensitization to inhaled allergens [7,9]. This would suggest that the neonate immune system could be committed, rather than merely biased,

towards the development of atopic disease. This has important implications for disease prevention, indicating that any prophylactic intervention(s) need to be implemented before the second and third trimesters of pregnancy. However, a recent study (FI Smillie, AJ Elderfield, F Patel, *et al.*, in preparation) demonstrated that whereas the level of maternal dust mite allergen exposure during pregnancy did not affect proliferative responses at birth, the immunoproliferation at 1 year of age correlated with environmental exposure to the specific stimulants, suggesting that postnatal exposure to inhaled allergens is important. A recent study by Finn *et al.* [14•] confirmed that early postnatal environmental exposure to inhaled allergens affects later PBMC proliferative responses in children at risk of atopy. Higher home cockroach allergen levels (and to a lesser degree house dust mite) were associated with an increased PBMC proliferative response at 2 years of age. Lymphocyte proliferation was associated with recurrent wheeze, but this does not yet prove that early cockroach allergen exposure influences the later development of specific sensitization or the full asthmatic phenotype. Furthermore, it remains unanswered whether it is early or cumulative exposure that is important.

Allergen exposure and IgE-mediated sensitization

Several studies have confirmed a simple dose–response relationship between mite allergen exposure and specific sensitization in infants and children [15,16, 17••]. Early infancy has been suggested as a critical period for primary sensitization, initially in the epidemiological studies relating atopy to the month of birth [18]. In the Poole cohort [19], household exposure to more than 2 $\mu\text{g/g}$ of Der p 1 during infancy was associated with an increased prevalence of sensitization to dust mite by 5 years of age. However, the results of the study can be interpreted in a different way: it is possible that allergen levels measured in infancy are a marker of cumulative exposure throughout childhood. The outcomes may therefore be related to cumulative exposure during childhood, rather than to exposure in early infancy.

Exposure and sensitization: are all allergens the same?

Sporik *et al.* [20•] recently reported a close relationship between the prevalence of specific allergen sensitization in children aged 12–14 years attending three schools in New Mexico and Virginia, and the domestic reservoir concentration of mite and cockroach, but not cat, allergen. This, along with the studies reporting a protective effect of cat ownership on sensitization, raises the question of whether the dose–response relationship between exposure and sensitization may be different for cat compared with mite allergen.

Pet ownership, sensitization and atopic disease

This is a major area of controversy highlighted in recent years. Different investigators have published intriguing and often conflicting data on the effect of pet ownership in early life on the subsequent development of sensitization and atopic disease. Some studies found that exposure to cats and dogs in early infancy was associated with specific IgE sensitization and allergic disease later in childhood [21]. Others, however, reported the opposite finding, i.e. a protective effect [22••].

In Sweden, the prevalence of respiratory allergy is significantly lower in children who were exposed to pets during the first year of life [22••]. Questionnaire data were supported by the finding of a lower prevalence of positive skin tests to cats in children exposed to cats during the first year of life. It can be speculated that early exposure to high levels of pet allergens could induce a form of immune tolerance. Some data have been reported for other allergens that could support this view. For example, Nilsson *et al.* [23] found that children born during the tree pollen season were less likely to develop allergic rhinitis, positive skin test or high specific IgE to tree pollen at the age of 12–15 years. In contrast, Lindfors *et al.* [24•] reported a strong positive association between the concentration of cat allergens in floor dust and sensitization both to cats and dogs. There was a strong suggestion for the synergism between different indoor environmental exposures, and the combination of exposure to environmental tobacco smoke, damp housing and a high level of Fel d 1 ($>8 \mu\text{g/g}$) resulted in a very high risk of sensitization to cats (odds ratio of 42). In a study from New Zealand [25•], there was a modest association between asthma and the presence of a cat in the home both in early life and currently (7–9 years), compared with owning a cat in just one of these times or not at all.

In a recent study from Japan [26], the prevalence of sensitization to cat dander among patients with asthma progressively increased as the patients grew older, up to the age of 16 years (? suggesting the importance of cumulative exposure). Overall, 34% of patients were sensitized to cats, but did not keep them in their homes. These patients must have been sensitized as a result of passive exposure to cat allergen in their homes or in other places. Further intriguing findings on the prevalence of sensitization to cats were reported from Tristan da Cunha [27•]. In this unique island with a high prevalence of asthma, cats were exterminated in 1974 because of toxoplasmosis, but 20% of the 282 islanders who took part in the study were skin test positive to cats in 1993 (i.e. almost 20 years after cats had been eliminated from the island).

In stage II of the European Community Respiratory Health Study, Svanes *et al.* [28] reported a strong protective effect of dog ownership in childhood on adult atopy. The finding that this effect was similar in subjects with and without parental allergy could suggest that this was not caused by the lower proportion of dog ownership in families with allergies. A further report from the same study [29••] found a significant positive association between current cat ownership and sensitization to cats in subjects without, but not in those with respiratory symptoms, suggesting selective cat avoidance in those with problems related to pets. However, an inverse association between cat ownership in childhood and sensitization to cats in adulthood was seen in all subjects, irrespective of symptoms. The majority of studies that investigated the relationship between pet ownership in early life and subsequent sensitization and atopic disease were cross-sectional and retrospective. In a prospective study, Wahn *et al.* [15] demonstrated a strong dose–response relationship between exposure to cat allergen and specific sensitization during the first 3 years of life, and to a lesser degree by the age of 7 years [17••].

How can we explain the protective effect of pet ownership seen in some studies? A recent very important study [30] suggested that many children who are exposed to a high level of cat allergen made a modified T helper type 2 response characterized by the presence of IgG4 antibody to cat proteins without becoming allergic (i.e. no IgE response), which could be regarded as a form of tolerance. The production of IgG and IgG4 antibodies without IgE may explain the reported decreased risk of asthma in children living in homes with cats. It also casts doubts on whether a simple shift in the balance of T helper type 1 and 2 responses is responsible for the increase in the prevalence of atopy and asthma.

Is it possible to explain these apparently irreconcilable differences between various studies? First, prospective studies [15] indicated that even low levels of cat allergen exposure are associated with some risk of sensitization, and that at least in early life there appears to be a dose–response relationship between exposure and sensitization. Cat allergen is ubiquitous, and exposure outside the domestic environment may lead to specific IgE responses. The recent report from the European Community Respiratory Health Study [29••] indirectly confirmed the potential importance of passive exposure, finding a significant correlation between the community prevalence of cat ownership and the community prevalence of sensitization to cats, respiratory symptoms, physician-diagnosed asthma and current asthma medication in 35 centres from 16 different countries. If cumulative exposure to allergens is important for the development of sensitization (and symptoms), then clear-cut differences regarding pet ownership are likely

to be seen only in early life. The cumulative passive exposure of non-pet owners in homes without pets and public places may induce sensitization in later childhood and adolescence, confounding the effect of pet ownership. Furthermore, those exposed to very high levels of cat allergen may initially mount an IgE response (high cumulative exposure in early life), which as a consequence of continuous high exposure may be replaced by a modified T helper type 2 response as a form of tolerance.

Allergen exposure and asthma

In a recent very important report from the German Multicentre Allergy Study [17•] mite and cat allergen exposure in early life remained strongly related to respective specific sensitization at age 3–7 years (at 7 years, this effect was stronger for mite than for cat allergen), confirming the trends observed in earlier life (i.e. at 1 and 3 years of age) [15]. These data appear to conflict with the hypothesis that high levels of cat allergen may induce a tolerant immune response. However, the levels of Fel d 1 in the Multicentre Allergy Study [17•] were remarkably low compared with those we observed in the UK. At 7 years of age, sensitization to indoor allergens was strongly associated with wheezing, doctor's diagnosis of asthma, and higher bronchial responsiveness. However, there was no dose–response relationship between allergen exposure (either early, during the first year of life, or later at the ages of 4 and 5 years) and any measure of asthma/wheeze at 7 years. This might suggest that different factors may be important in the development of atopy from those involved in the development of asthma. The authors argued that rather than indoor allergens inducing asthma, the reverse may be true, i.e. that a capacity to produce IgE responses to allergens and develop sensitization is a characteristic of asthmatic individuals. In a review on environmental predictors of allergic disease, von Mutius [31•] suggested that the mechanisms inducing asthma may not be susceptible to changes in allergen levels, and that the capacity to mount a strong IgE response to indoor allergens may be a feature of asthmatic individuals. Although this possibility cannot be discounted, the hypothesis is not supported by experience in another area, i.e. occupational asthma. Of the subjects who develop occupational asthma to high molecular weight agents, it is previously atopic individuals who are at particular risk (e.g. laboratory animal handlers are at increased risk if they are already sensitized to domestic pets). Occupational asthma does not develop without the appropriate exposure.

Has increased allergen exposure contributed to the increase in the prevalence of asthma and atopy?

Some indirect evidence exists to suggest that high exposure to mite allergens in early life may be related to

subsequent asthma. In a study from New Zealand [25•], sleeping on sheepskin in infancy (a marker of high mite allergen exposure) was positively associated with current asthma prevalence in 7–9-year-old children. Current exposure, however, was not associated with current asthma. In the USA, Sporik *et al.* [20•] reported a puzzling association between current asthma and the concentration of mite allergen among atopic children, but not among those who were specifically mite sensitized.

Although there is no direct evidence to confirm an increase in dust mite allergen exposure, the indirect evidence is compelling that this could be one among several important co-factors. For example, over the past few decades, sales of pillows using synthetic fillings have increased enormously, based on the concept that they are non-allergenic (as opposed to feather pillows). However, synthetic pillows accumulate mite allergens faster and ultimately contain approximately fivefold more Der p 1 [32] and eight to 10 times more cat and dog allergen than feather pillows [33•]. A UK study found a moderate, but significant increase by 20% in the ratio of current childhood wheezers to those who never wheezed, and an increase of 16% in the 12 month period prevalence of wheezing attacks between 1978 and 1991 [34]. The prevalence of wheeze was negatively associated with the use of feather pillows (reduction in the odds of 36% for infrequent wheeze and 61% for frequent wheeze). Furthermore, when changes in potential risk factors over time were investigated, an observed increase in the use of non-feather pillows from 44 to 67% was estimated to be large enough to explain more than half of the increase in wheeze [34]. It is tempting to speculate that the increased use of non-feather pillows has contributed to increasing allergen exposure, which could be partly responsible for the increase in the prevalence of wheezing. The association between the use of synthetic bedding and allergic rhinitis has recently been reported in a study of more than 18 000 children aged 6–9 years in Austria [35•].

Conclusion

A number of cross-sectional and prospective studies have confirmed that there is a close dose–response relationship between house dust mite allergen exposure in the home and the development of IgE-mediated sensitization. The hypothesis that allergen exposure causes asthma has been challenged, and it is possible that IgE-mediated sensitization may be regulated differently from airway inflammation and clinical manifestations of asthma. This subject has been a topic of several review articles, which have raised as many questions as they provided answers [30,36•–38•,39,40].

The relationship between allergen exposure and disease development is confounded by a number of important factors. The measures of reservoir allergen levels we use are at best surrogates of personal inhaled exposure, if only because of the huge differences in aerodynamic behaviour (e.g. mite versus pet allergens). Furthermore, in real life, populations and individuals are exposed to a mixture of several allergens, irritants and pollutants. We know very little about the impact of mixtures of allergens and their possible synergistic effect. Simultaneous exposure to high levels of more than one allergen may potentiate the effect of individual allergens, and the emphasis on exposure to individual allergens may be misleading. The dose-response relationship between allergen exposure and the risk of disease may not be linear, and may be different for different allergens (e.g. linear for mite, bell-shaped for cat). We know little about the effects of other contaminants of house dust such as endotoxin (e.g. endotoxin exposure may be protective in early life, but a risk factor later on in patients with established disease). Finally, and perhaps most likely, some as yet unidentified factor(s) has altered the population susceptibility to allergic sensitization and also end-organ responsiveness. Allergen exposure may still be the critical factor in initiating disease in an increasingly susceptible population.

Several prospective intervention studies investigating the effect of environmental control on the development of sensitization and asthma are currently being performed [41•]. Only the long-term prospective follow-up of well defined cohorts, avoiding recall bias and with an objective measure of exposure (e.g. allergen levels in dust), will provide definitive answers to the important questions on the relationship between environmental allergen exposures, sensitization and asthma, and will enable us to decide about appropriate public health strategies.

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