

Animal Allergens

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Animal allergen exposure in early childhood and its relationship to the development of atopic disease is a subject that has been evolving rapidly. Recently, several well-designed studies have helped elucidate previous, often conflicting findings on this topic. In addition, results from studies on farm-animal exposure have added strength to data on early dog and cat exposure. In this paper, we review several recent studies that have helped clarify the relationship between early animal-allergen exposure and childhood atopic disease.

Introduction

There has been much interest in the topic of pet exposure in early childhood and its relationship to the development of allergic disease. Much of the initial information on this topic came from retrospective cross-sectional and cohort studies [1,2]. Unfortunately, the findings from these studies were often conflicting, which resulted in significant controversy and confusion. In a review of the literature up through the mid-1990s, Ahlbom *et al.* [3] concluded that exposure to pet allergens in infancy increases the risk for allergic sensitization and recommended that families not own pets until the child is at least 2 years of age. Another review a few years later concluded that pet-allergen exposure in childhood was not consistently associated with asthma prevalence [4]. On the other side, another study reported a lower frequency of allergic rhinitis and asthma in children exposed to pets during the first year of life [2].

In recent years, however, there have been a number of well-designed, prospective studies that have evaluated the effect that early pet exposure has on the development of allergic disease and asthma. These studies have addressed the recall bias that was cited as a possible reason for the conflicting study results found in the earlier, retrospective studies. However, these studies have also not yielded completely consistent results, and the controversy continues. Some of these studies indicate that early exposure to animal allergens, especially in the first year of life, may protect against the development of

allergic disease in childhood [5••], whereas others have found that early pet exposure does not seem to influence the development of allergic sensitization [6–8]. In this article, we review the recent data on early exposure to animal allergens in regard to the development of allergic sensitization and atopic disease.

Exposure to Indoor Pets

The initial studies on the effects of early pet exposure focused mainly on exposure to cat allergen. Most of the data indicated that there is a risk for sensitization to cat at low levels of cat allergen exposure [9,10], although other studies found no association between allergen exposure and sensitization [11,12]. A study published in 2002 by Ownby *et al.* [5••] was aimed at further clarifying the relationship between exposure to cats and dogs in infancy and the development of allergy. This was a prospective birth cohort study of more than 800 infants that evaluated a number of variables, including family history, parental smoking, cord-blood immunoglobulin (Ig)E levels, and indoor allergen exposures. Follow-up interviews were conducted when the children were 3 years, 5 years, and 6 years old. At age 7 years, a clinical evaluation was performed with prick skin testing for six allergens, including dust mite, cat, dog, grass, and ragweed, as well as measurement of total IgE levels and allergen-specific IgE levels to the same six allergens evaluated by skin testing. The presence of a diagnosis of asthma requiring treatment, as well as pulmonary function tests and methacholine challenge tests, were also examined [5••].

Fifty-seven percent of the children completed the clinical evaluation and were found to be similar to the children who did not complete the study. Results on those evaluated revealed an inverse relationship between dog exposure and allergic sensitization, as measured by skin testing and dog-specific IgE levels. Any exposure to a dog was also associated with lower total serum IgE levels. Even after adjusting for confounding variables, exposure to two or more dogs resulted in a lower risk for atopy (95% confidence interval [CI], 0.14–0.72) and seroatopy (95% CI, 0.19–0.96), indicating a possible dose-response relationship between dog exposure and the development of allergy. A similar trend of a decreasing prevalence of atopy with increasing exposure to cat (no exposure to cat, exposure to 1 cat, or exposure to 2 cats) was also observed, although these results did not reach statistical significance. This same inverse relationship was also seen for sensitization to dust mite and to the

outdoor allergens that were studied. In addition, lower serum IgE concentrations, reduced methacholine responsiveness, and better lung function were demonstrated in boys, but not in girls, who were exposed to two or more dogs or cats [5••].

Platts-Mills *et al.* [13] at the University of Virginia demonstrated a bell-shaped, dose-response relationship between cat allergen exposure and cat sensitization in a cross-sectional study. They found that the lowest rates of cat sensitization occurred at the lowest and highest levels of cat allergen exposure and that moderate exposure resulted in the highest rate of sensitization. They proposed that this phenomenon may be due to a modified T-helper cell type 2 (T_H2) response in which high levels of exposure lead to the production of cat allergen-specific IgG and IgG4 antibodies rather than IgE antibodies [13].

Data on the effect of early pet ownership and indoor allergen exposure on the development of asthma in young children have also been conflicting. Large birth cohort and cross-sectional studies performed in the United States and Sweden have shown that pet ownership during infancy decreases the risk for wheeze in later childhood [6,14,15]. Several other studies, however, have shown no association between early pet exposure and the development of asthma during childhood [5••,16,17].

A birth cohort study, known as the Manchester Asthma and Allergy Study, found that the combination of specific sensitization and current allergen exposure was associated with poorer lung function in early life. Specifically, this study examined the effect that pet ownership and current exposure to dog, cat, and dust mite allergens had on lung function in children who were 3 years of age. Results from this study revealed that the children who were both sensitized to and currently exposed to high levels of the indoor allergens had worse lung function at age 3 years compared with those children who were either not sensitized, or were sensitized but not currently exposed to high levels of allergens. No difference in pulmonary function was observed in children whose families owned either a cat or dog at birth or at age 3 years [18•]. Furthermore, the study showed that a maternal or paternal history of asthma was significantly associated with worse pulmonary function in children sensitized and exposed to high levels of allergen, suggesting that a strong genetic component may predispose a child to wheeze when associated with certain environmental exposures.

In another prospective study aimed at examining whether early exposure contributes to the risk for developing allergic disease and asthma, Almquist *et al.* [19•] followed a group of more than 4000 children in Sweden from birth to 4 years of age. Data were collected on "allergic heredity," early pet exposure (pet present in the home when the child was 2 months of age), and information on asthma symptoms. At age 2 years, dust samples were evaluated for cat and dog allergen content, and at age 4 years, allergen-specific IgE levels to common inhalant allergens

and pulmonary function were tested. Results of the study revealed differences in sensitization patterns in those with early exposure to cat compared with early exposure to dog. Children exposed to cat, either directly or indirectly, were more likely to be sensitized to cat at age 4, but there was no effect on the prevalence of asthma at age 2 or 4 years. Alternatively, children with early dog exposure were slightly less likely to be sensitized to dog at age 4 years, had a lower risk for asthma, and were less likely to be sensitized to pollen at age 4 years.

Gern *et al.* [20] also addressed this question in a prospective birth cohort study of American children using data from the Childhood Origins of Asthma Study (COAST). The aim of the study was to determine the effect of early pet exposure on the immune response and subsequent development of atopic disease. Exposure to dogs in the first year of life, but not to cats, was associated with an enhanced interleukin (IL)-10 response, as well as a decrease in allergic sensitization and atopic dermatitis in the first year of life. This study suggested that early exposure to endotoxin, a powerful stimulator of IL-10 production, might alter the immune system in such a way to result in a lower risk for allergic sensitization.

Exposure to Farm Animals

In addition to these studies on cat and dog exposure, studies on early farm-animal exposure provide further information on the effect that animal exposure may have on the development of atopic disease in childhood. These studies have demonstrated a lower prevalence of asthma and allergic rhinitis in children raised on farms, compared with children raised in the same geographic area, but not on a farm [21–23]. Kilpeläinen *et al.* [24] also demonstrated decreased allergic sensitization to cat allergen in children raised on farms. It has been suggested that exposure to microbial compounds, specifically endotoxin, rather than allergen exposure, may affect the immune response in such a way to provide a protective effect against the development of asthma and allergic sensitization.

Von Mutius *et al.* [25] demonstrated that elevated endotoxin levels are not limited to the stables where livestock are kept but are also elevated in the homes of farming families. Comparison of airborne and settled dust from the homes of both farming and nonfarming families in rural Germany and Switzerland revealed significantly higher endotoxin levels in the homes of farming families, compared with the homes of nonfarming families. The study proposed that in the farming environment, endotoxin exposure may provide an important protective effect on the development of atopy in childhood.

The timing of the farm exposure, as well as the duration of exposure, seems to be important for inducing the protective effect. In a cross-sectional survey of more than 2500 children in rural Austria, Germany, and Switzerland (ALEX Study team), long-term and early-life exposure to a

farming environment was shown to provide protection against the development of asthma, hay fever, and allergic sensitization [26]. The participants in this study filled out questionnaires on symptoms of asthma, hay fever, and atopic dermatitis and had RAST testing performed for common allergens. The children were divided into groups (no exposure, low exposure, and high exposure) and were also categorized as to whether or not they drank unpasteurized farm milk in their first year of life. In general, children raised on farms had a significantly lower prevalence of asthma and hay fever than children who were not raised on farms. The frequency of eczema was not significantly different between these two groups. There was a tendency for more protection against hay fever and allergic sensitization as the amount of exposure to stables in the first year of life increased. Furthermore, those children exposed to stables or unpasteurized milk only in the first year of life had a reduced prevalence of asthma, compared with children only exposed after the first year. The lowest frequencies of asthma, hay fever, and allergic sensitization were seen in the children exposed both to stables and to unpasteurized milk during the first year of life, compared with children with both of these exposures between age 1 and 4 years [26].

Using the same rural study population, Braun-Fahrlander *et al.* [27••] demonstrated an inverse relationship between endotoxin levels collected from mattress dust samples and the occurrence of hay fever, asthma, and allergic sensitization in children from both farming and nonfarming families. The protective effect was found when exposure occurred during the first year of life, as well as when the exposure occurred in early childhood. Children who grew up in rural, nonfarming homes had mattress endotoxin levels that were similar to levels found in urban homes. This study suggested that exposure to "ubiquitous microbial products," as assessed by measuring endotoxin, may influence the development of allergies and asthma in childhood.

A study recently published in the journal *Allergy* [28•] examined the effect that contact with farm animals and pets, as well as exposure to endotoxin and cat allergen, had on the prevalence of asthma and allergies in rural children. The data were collected from the ALEX study discussed earlier [26]. Measurements of cat allergen and endotoxin in mattress dust were taken, and cat-specific IgE and IgG4 antibody levels were measured. The analysis revealed that in children who grew up on farms, current contact with dogs was associated with a reduced risk for hay fever and asthma. These two associations remained, even when controlled for indoor endotoxin levels or for current contact with farm animals. In children with exclusive cat exposure, only the risk for wheezing was reduced. IgG4 antibody levels were not increased in these children, suggesting a modified Th2 response was not responsible for the inverse relationship found between cat allergen exposure and asthma. Endotoxin levels were elevated in

homes with dogs and/or cats, a finding supported elsewhere in the literature [29,30].

Conclusions

Synthesis of the current data still does not provide a completely clear picture as to the effect that early animal exposure has on the development of allergic disease in children. However, most of the data show a trend of reduced risk for allergic disease in children exposed to animals early in life. This is most consistent for farm animal and dog exposure, and much less consistent for cats. It is not clear how much of the effect is due to the actual animal allergens or to other exposures, such as endotoxin and other microbial products that are elevated in the presence of animals. In addition, the role of genetics and family history of atopy on the protective effect of pet exposure on childhood allergic disease has not been fully elucidated. Fortunately, there are a large number of well-designed, prospective studies underway that should provide more, clear answers in the next few years.

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