

High Allergen Exposure as a Risk Factor for Asthma and Allergic Disease

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Abstract

The association between pet ownership in childhood and subsequent asthma and sensitization is very controversial. Intriguing, but contradictory, reports have caused considerable uncertainty in parents who wish to avoid asthma and allergic disease in their children. This article argues that high allergen exposure is a risk factor for asthma and allergic disease. It describes dispersal of pet allergens in society and critically assesses epidemiological studies regarding how early exposure to pet allergens affects subsequent immunoglobulin E-sensitization and allergic diseases. Additionally, this article evaluates the effects of allergen exposure in already sensitized subjects with asthma. Cat and dog allergens are ubiquitous in society and may induce sensitization and allergic symptoms in predisposed individuals, regardless of pet ownership. This, in combination with selection mechanisms for pet ownership in families with a history of allergic diseases, makes it difficult to study associations between early exposure to pets and subsequent allergic disease. Nevertheless, exposure to pet allergens worsens asthma in already sensitized children. Thus, it is clear that clinicians should advise sensitized asthmatics that avoidance of exposure to indoor allergens is an important element in the treatment of allergic disease.

Index Entries

Allergens; allergy and immunology; animals; asthma; cats; child; dogs; prevention.

Introduction

People have had pets and farm animals since time immemorial. We have been dependent on cows for milk, hens for eggs, horses for transportation, dogs for protection and company, cats for chasing rodents, and rodents for...well, something. Archeological findings demonstrate that our ancestors died of violent acts, infectious diseases, and rickets, but we know very little about whether they suffered from asthma and allergies.

We do know that allergies and asthma have increased in prevalence over recent decades, and currently, at least one in three children suffers from asthma, hay fever, or dermatitis (1). Although genetic predisposition to asthma is well-recognized, genetic factors alone cannot explain the increase in the prevalence of asthma during the past 20 yr. The role of environmental factors in asthma and sensitization is further supported by the large differences in the prevalence of allergic diseases in different countries and between groups with similar ethnic backgrounds living in the same country (1–3). Apart from changes in exposure to microorganisms (4), possible environmental determinants include changes in lifestyle and altered indoor climate, which, in turn, may increase the exposure to indoor allergens.

Every day, pediatricians, general practitioners and allergologists observe that individuals with asthma or hay fever find their condition worsens after contact with furred pets or pollen. Simultaneously, studies report contradictory results regarding whether early exposure to pets increases or decreases the risk of childhood asthma. From a public health perspective, this makes it difficult to determine what advice one should give to patients, as well as to parents who wish to prevent asthma and allergic diseases in their children (5,6).

Aim

This article argues that high allergen exposure is a risk factor for asthma and allergic

diseases. However, because the issue is controversial and not straightforward, I have chosen to ask a single question and to answer it from two angles, with the focus on different situations:

- Situation 1. A newborn child with allergic parents.
- Situation 2. A child without pets at home who reacts with asthma and rhinoconjunctivitis to cats and dogs in friends' houses.

Should families keep or remove the cat or dog they already have, and if they do not have one, should they get one? The focus here is on pet allergens, and the effects of house dust mite (HDM) allergen are mentioned only briefly.

Epidemiological Studies

Epidemiological studies can assess relationships between exposure and disease in human populations. To calculate risk associations, it is very important that exposure and outcomes are clear and specific (7). For example, pet exposure can be estimated through reported pet ownership, pet contact, or by measuring pet allergen at home. Outcomes can be assessed through reported symptoms, diagnoses, or medication. Measures of association, such as odds ratio, are the preferred way of expressing results of dichotomous outcomes (e.g., sick vs healthy). Confidence intervals around these measures indicate the precision of these results. The odds ratio and confidence interval reveal the strength, direction, and plausible range of an effect, as well as the likelihood of chance to occur (8). Attributable or etiological fraction denotes the proportion of a disease that is attributable to a certain risk factor in a population. Effect modification is a type of interaction between variables, where the strength of association between exposure and outcome is influenced by a third variable—for example, genetic predisposition. Data regarding exposure and outcome can be collected prospectively or retrospectively.

Cross-sectional studies can examine the presence or absence of exposure and disease at a certain time. Because both exposure and outcome are ascertained simultaneously, the temporal relationship between the two might be unclear. Data regarding exposure may also be collected in retrospect, but the data may then be subject to recall bias.

Cohort studies proceed in a logical sequence, from exposure to outcome. An exposed and an unexposed group are followed prospectively to determine outcomes. If the exposed group develops a higher prevalence or incidence of the outcome than the unexposed group, then the exposure is associated with an increased risk.

Case-control studies begin with an outcome and look for exposure retrospectively. Nested case-control studies are performed within a cohort study.

Randomized, controlled trials are the gold standard of epidemiological research. Participants are assigned exposures purely by chance. They are then followed prospectively, as in cohort studies. This reduces the likelihood of bias in determination of outcomes.

To evaluate whether a study measures what it was designed to measure (internal validity), potential *bias* must be considered. Bias in epidemiological research denotes deviation from the truth (9). There are three general categories of bias.

1. Selection bias: the exposed and unexposed groups differ in some important aspect, aside from the exposure. Participation bias is one type of selection bias.
2. Information bias: information about outcome is obtained in different ways for exposed than for unexposed individuals. Differential information bias, such as recall bias in cross-sectional studies, may increase or decrease the estimated risk, depending on the direction of the bias; nondifferential information bias tends to obscure real difference.
3. Confounding: the results can be accounted for by the presence of a factor that is associated with both exposure and outcome

but that is not directly involved in the causal pathways. Confounding can be controlled for through restriction, matching, stratification, or with multivariate techniques.

Different types of bias or misclassification of exposure or disease may distort or obscure true risk associations. For example, families who have a pet and want to keep it might report wheezing less often than those without a pet, and families with an atopic constitution might choose not to report their pet ownership if the primary prevention program advises them not to keep pets. Therefore, critical interpretation of epidemiological studies is essential for the formulation of proper prevention programs (10).

Allergen Dispersal and Exposure

Dispersal

Cat and dog allergens are ubiquitous and have been found in dust samples from many different environments: schools, day care centers, hotels, cinemas, pubs, buses, trains, hospitals, department stores, and homes without cats (11–16). Cat allergen is carried in clothing (17–19), and accumulation of cat allergen in environments without cats has been shown to correlate with the number of visitors who either have a cat at home or who are in regular contact with a cat (14,16). However, to a large extent, cat and dog allergens are airborne, and the allergen levels in the air do not always correlate with those in dust (20–23). Airborne allergen levels provide a more accurate estimate of the level of personal allergen exposure in a low-exposure environment, so long as adequate sampling methods and assays are used. In a study in which airborne cat allergen was collected with personal samplers from children attending classes with many (>25%) or few (<10%) cat owners and from homes with or without cats, the median airborne cat allergen concentration in classrooms was significantly higher than that found in the homes of non-cat-

owners, and there was a fivefold difference in the median levels of airborne cat allergen between classes with many and few cat owners. Non-cat-owners in classes with many cat owners had higher levels of cat allergen in their mattresses at home than did non-cat-owners in classes with few cat owners, and allergen levels in the clothes of non-cat-owners increased after a school day (24). This indicates that allergen is spread through clothing from homes with cats to public places, where the allergen then disperses in the air and contaminates the clothes of individuals without cats.

Consequently, it is difficult to remain unexposed to cat and dog allergens. Even if families do not keep pets indoors, their children will be indirectly exposed to the allergens either in public places or at home, where allergens are equally likely to come from the clothes of visiting pet owners and other family members. The levels of cat and dog allergens in pet-free homes where relatives or friends have cats or dogs have been shown to be significantly higher than those found in pet-free homes without any reported cat or dog contact but are lower than those found in homes with a cat or dog (25). On the other hand, HDM allergens are carried on larger particles, and only a small proportion is believed to be directly respirable, which makes it easier to estimate exposure (26).

Exposure

The prevalence of cat and dog ownership differs somewhat among countries. Approximately 20% of Swedish households have cats, and 16% have dogs (27,28). In the United Kingdom, pet ownership is more common: about one-third of all homes have a cat, and one-quarter of all homes have a dog (28,29). More than half of the population of Atlanta, GA reported cat or dog ownership (30). In urban Ghana, the proportion of cat and dog owners is comparable to that in the United Kingdom, but because the pets are often kept outside, allergen levels in many homes with pets are lower than those in homes without pets in the

United Kingdom (31). This indicates that similar proportions of pet ownership in different countries do not equate to similar levels of exposure to allergen and that actual measurement of cat (Fel d 1) and dog (Can f 1) allergen is essential to estimate individual exposure.

It has been suggested that children with a family history of allergic diseases are born into a low-risk environment, and it has been shown that families in which the mother is allergic not only tend to keep fewer cats (32) but also tend to have lower levels of cat and HDM—but not dog—allergens in mattress dust samples (33,34). We can only speculate as to whether this is because of preventive measures or because the index child or a sibling had developed symptoms of allergic disease.

Health Effects

Associations Between Allergen Exposure, Sensitization, and Asthma

The case for a causal relationship between allergen levels, sensitization, and asthma would best be supported by evidence for a dose-response relationship between exposure and symptoms. Many population-based studies have confirmed a strong association between asthma and sensitization to indoor allergens (2,35–38). The sensitizing allergen varies; HDM is the major allergen in many parts of the world, whereas cockroaches are common sources of allergen in larger cities in the United States; the mold *Alternaria* is a common allergen in the deserts of Australia and the United States; and cats and dogs are common sources of allergen in Scandinavia (39–42). This may reflect that an individual with asthma is susceptible to sensitization to the most prevalent perennial allergens in the environment, rather than indicating an increased risk of asthma when an individual is exposed to these specific allergens. Therefore, the evidence for a causal relationship between allergens and asthma in a general population depends on epidemiological findings showing a strong association between spe-

cific immunoglobulin E (IgE) and asthma in children who already have the disease.

The causal relationship between allergen exposure and subsequent sensitization or asthma is controversial. In 1998, a review of the literature suggested increased risk of sensitization in childhood after early exposure to pets (43), whereas another review found little consistent association between allergen exposure and asthma prevalence (44). A recent meta-analysis concluded that pet exposure increased the risk of wheezing in older children (45), and more recent studies have added conflicting data regarding the relationship between pet exposure and sensitization or asthma in children, adolescents, and adults.

Importantly, it must be recognized that asthma and sensitization do not necessarily occur hand-in-hand. Many of the recent studies have measured associations between early allergen exposure and asthma, whereas others have used general sensitization or even allergen-specific sensitization as outcome variables. Clearly, these associations are not directly comparable, and this may be one reason for the disparate results. Age may also be a factor: young children may not yet have developed IgE antibodies to inhalant allergens; therefore, their asthma may not be combined with sensitization and may not be classified as allergic.

In an attempt to summarize the literature on associations between early allergen exposure and subsequent sensitization or asthma, Table 1 presents the most often cited works. Other exposures, such as environmental tobacco smoke, breastfeeding, gender, and heredity for allergic disease, may act as confounders or effect modifiers in the causal relationship (46–48), but these have not been included in the table. Some of the studies are reviewed in the following sections.

Early Allergen Exposure, Subsequent IgE Sensitization, and Symptoms

Sporik et al. (49) presented the key study linking allergen exposure in infancy to the subse-

quent development of asthma. They reported a weak dose–response relationship between early exposure to HDM and specific mite sensitization ($p = 0.06$), as well as associations between early allergen exposure and asthma at age 11 yr in a small cohort of 67 children (49). In the large German birth cohort study (the Multicenter Allergy Study), a dose–response relationship between exposure to cat allergen at home and sensitization to cat at age 3 yr was observed (50), but there was no relationship between early indoor allergen exposure and the prevalence of asthma, wheeze, or bronchial hyperreactivity (BHR) at age 7 yr (51), implying that sensitization and asthma may be determined by independent factors.

Initially, exposure to an allergen was believed to be a prerequisite for sensitization to that allergen, although there seemed to be a genetically determined propensity for sensitization. Threshold levels for allergen exposure leading to sensitization and to exacerbations of symptoms were previously suggested to be 1 and 8 μg for cat, respectively, and 2 and 10 μg for dog, respectively (52,53). The strong association between sensitization and asthma was interpreted as a causal relationship between exposure and disease. However, a few years ago these findings were challenged by suggestions from cross-sectional studies that early pet ownership might reduce the risk of subsequent sensitization and allergic disease (54,55). Recently, a multitude of prospective studies implied similar results. In the Tucson birth cohort study of 1246 children, dog exposure in early life was shown to prevent the development of asthma-like symptoms up to age 11 yr—at least in low-risk children with no family history of asthma—but had no influence on the development of allergic sensitization (56). In a birth cohort of 474 children (43% lost to follow-up), Ownby et al. found that early exposure to two or more dogs or cats in the first year of life was negatively associated with subsequent allergic sensitization to multiple allergens during childhood (30). One birth cohort study of

Table 1
Studies on Early Exposure to Cat or Dog and Subsequent IgE Sensitization or Asthma

Author	Study design	Age; No.	Exposure	Outcome	Result	Comment
Wahn MAS, Germany, 1997 (50)	Prospective birth cohort	0–3 yr; 1314 (67%) (499 high-risk)	Allergens cat, mite 6, 18 mo questionnaire 1, 3, 6 mo; 1, 2, 3 yr	Sp-IgE mite, cat 1, 2, 3 yr	Dose–response allergen exposure—sensitization	Atopic family history enhances dose–response
Lau MAS, Germany, 2000 (51)	Prospective birth cohort	0–7 yr; 1314 (71%) (49%)	Allergens cat, mite 6, 18 mo, 5 yr questionnaire 1, 3, 6 mo; 1, 2, 3, 7 yr	Doctor-diagnosed asthma; BHR Sp-IgE mite, cat SPT	No association allergen exposure—asthma, BHR Positive association atopy—asthma, BHR No association pet ownership—atopy	Low levels of cat allergen <50% of asthma cases attributed to atopy
Tariq, United Kingdom, 1998 (125)	Prospective birth cohort	0–4 yr; 1456 (84%) (67%)	Cat or dog ownership			
Nafstad, Norway, 2001 (126)	Prospective birth cohort	0–4 yr; 3754 (67%)	Cat and dog ownership at birth	Atopic eczema, rhinitis, asthma	Negative association pet ownership—atopic eczema 0–6 mo Negative association pet ownership—rhinitis 4 yr, weak—asthma 4 yr	Selection bias?
Remes, United States, 2001 (56)	Prospective birth cohort	0–13 yr; 1246 (86%) (~50%)	Cat and dog ownership at birth	Wheezing Total S-IgE or SPT 9 mo, 6 yr, 11 yr	Negative association early dog exposure—wheezing No association early dog exposure—atopy	Parental asthma: no association early dog exposure—wheezing
Ownby, United States, 2002 (30)	Prospective birth cohort	0–6 yr; 835 (57%)	Number of cats or dogs at home in the first year	SPT, Sp-IgE cat, dog, mite, pollen	Negative association ≥ two dogs or cats in childhood—atopy	Association more obvious in boys than girls
Celedon, United States, 2002 (57)	Prospective birth cohort	0–5 yr; 448 (90%)	Cat allergen Fel d 1 >8 µg/g of dust at age 2 mo	Wheezing Total S-IgE	No maternal asthma: negative association cat exposure—wheezing Maternal asthma: positive association cat exposure—wheeze, increase w/age	87.4% of those exposed to a cat in early life still exposed to a cat Baseline IgE value differs
Almqvist, Sweden 2003 (25,34)	Prospective birth cohort	0–4 yr; 4098 (91%) (70%)	Cat or dog contact at birth; none, indirect or direct (dust samples and questionnaires)	Wheezing Sp-IgE cat, dog, and other airborne allergens	Positive association any cat exposure—cat sensitization No association any dog exposure—dog sensitization Negative association cat or dog ownership—sensitization other airborne allergens	Selection of cat and dog ownership, and cat allergen levels, based on parental history of allergic disease.

Table 1 (continued)

Author	Study design	Age; No.	Exposure	Outcome	Result	Comment
Perzanowski, Sweden, 2002 (58)	Prospective cohort from 7 yr	7–8 yr, 10–11 yr; 3431 (63%)	Cat or dog ever in the house; data on exposure before 1996 collected retrospectively	Doctor-diagnosed asthma SPT	Negative association ever cat—atopy if parental allergy Negative association ever cat—asthma prevalence if parental asthma	Inverse associations only in children with family history—distorted? Selection of pet ownership?
McConnell, United States, 2002 (127)	Prospective cohort from 9 yr	9–16 yr; 3535	Cat and dog ownership	Wheezing, asthma	Positive association dog ownership—wheeze	32% of new asthma cases attributable to pets
Jaakkola, Finland, 2002 (128)	Case-control	21–63 yr; 521 cases, 932 controls	Furred pets currently and in the past	Incident asthma	Positive association pet in the past and asthma Negative association pet currently and asthma	Explained by selective avoidance
Hesselmar, Sweden, 1999 (54)	Cross-sectional	7–9 yr, 12–13 yr; 412	Cat or dog ownership	SPT, asthma, allergic rhinitis	Negative association pet ownership—rhinitis 7–9 yr—asthma 12–13 yr Negative association cat ownership—SPT 12–13 yr	Similar results without children whose parents had decided against pet keeping
Hesselmar, Sweden, 2003 (59)	Cross-sectional	12–13 yr 412 (98%) (75%)	Early or current cat or dog ownership	SPT, S-IgE, S-IgG1, S-IgG4, asthma, rhinitis, eczema	No association pet ownership—atopic disease; Positive association high-dose allergen—IgG4	Supports a modified Th2 response
Roost, ECRHS, 1999 (55)	Cross-sectional	20–44 yr; 18,097 (75%)	Cat exposure early in childhood	Sp-IgE cat	Negative association early cat exposure—atopy Positive correlation community prevalence of cat—atopy negative association early dog exposure—adult atopy	Negative association seen in particular among those with family history of atopy—distorted study result? Adjusted for atopic family history
Svanes, ECRHS, 1999 (129)	Cross-sectional	20–44 yr; 18,530 (75%)	Dog ownership in childhood	Sp-IgE grass, mite, cat, <i>Cladosporium</i>		
Svanes, ECRHS, 2003 (28)	Cross-sectional	20–44 yr; 18,530 (75%)	Childhood and current cat, dog and bird ownership	Adult asthma and hay fever	Positive association childhood cat—asthma if atopic. Positive association dog—asthma if nonatopic Negative association dog—hay fever	Cat effect especially if low community cat prevalence

Table 1 (continued)

Author	Study design	Age; No.	Exposure	Outcome	Result	Comment
Bråbäck, Sweden, 2001 (130)	Cross-sectional	10–11 yr; 2108 (84%) (74%)	Current or former pet ownership	SPT, wheeze, rhinitis	Negative association—cat ownership—atopy (if no family history) and rhinitis	Higher prevalence of sensitization in northern vs southern Sweden, related to number of pets
Brunekreef, Holland, 1992 (123)	Cross-sectional	6–12 yr; 3344 (73%)	Pet ownership current and past	Respiratory symptoms	Severity of respiratory symptom (spt): pets currently, 0 past: no spt pets currently and past: mild spt never had pets moderate spt past pets, no currently: sev spt	Explained by selection; pet avoidance in allergic individuals
Anyo, Holland, 2002 (66)	Cross-sectional	7–12 yr; 2729 (65%) (48%)	Cat and dog ownership never, in the past and currently	SPT, S-IgE, hay fever, asthma	Negative association current pet ownership—atopy and hayfever Positive association past pet ownership—asthma	Explained by selection and pet avoidance Inverse relation early pet exposure—pollen sensitization
Lanphear, United States, 2001 (131)	Cross-sectional	<6 yr; 8257	Dog ownership	Doctor-diagnosed asthma	Positive association dog ownership—asthma	Positive association pet avoidance—asthma; OR = 24
Platts-Mills, United States, 2001 (37)	Cross-sectional	12–14 yr; 226	Cat allergen Fel d 1 at home	SPT, S-IgE, IgG, IgG4; asthma defined as symptomatic BHR	Positive association levels of Fel d 1—IgG4 Positive association atopy—asthma	Modified Th2 response; high IgG4 in children exp to high levels cat allergen

No., number of children who were involved in the study; (%), response rate on questionnaires; (%), response rate on SPT or blood samples; SPT, skin prick test; Sp-IgE, specific serum-IgE antibodies; S-IgE, total serum-IgE; atopy, positive SPT, S-IgE, or Sp-IgE; ECRHS, European Community Respiratory Health Survey.

448 children suggested an increased risk of asthma after cat exposure in children whose mothers had asthma; simultaneously, this study showed a decreased risk of asthma after cat exposure in children whose mothers did not have asthma (57). This could be attributed to cat exposure of already sensitized children who are at risk of asthma, because 88% of the children still held cats. Another prospective cohort starting at age 7 yr with retrospectively collected information on cat exposure showed a decreased risk of asthma at age 10 yr—especially in children who were exposed to cats who also had a family history of asthma. This may be caused by information bias in a cohort where children with allergic heredity did not keep pets as often as those without allergic heredity, but other mechanisms must be considered (58).

Nevertheless, it is difficult to explain why these studies demonstrate such incongruent results. Various immunological mechanisms have been implied, and selection effects must be considered. A modified T-helper (Th)2-response with a bell-shaped or flat dose-response curve and increased immunoglobulin G4 among children exposed to high levels of cat allergen was suggested to explain the reason that having cats in the house can decrease the risk of sensitization or the reason that children living in a house with “moderate” levels of cat allergen (4–20 $\mu\text{g/g}$ of dust) are more likely to become allergic to cats than those exposed to more than 20 $\mu\text{g/g}$ of dust (37,58,59). Another possibility is suggested by the observation that children in rural areas have a reduced risk of asthma and atopy: environmental exposure to endotoxin may downregulate the immune response (60,61). It has also been suggested that the window of opportunity during which environmental influences can affect the development of childhood asthma is restricted to the prenatal or early postnatal period (62–65), and the timing of exposure in terms of early and current pet ownership may distort study results. There may also be a “pecking order” of aller-

gens, so that exposure to HDM more readily sensitizes than cat and dog exposure, which in turn tends to reduce sensitization to pollen and grass allergens (25,30,66,67). Although dog allergy has been recognized as a clinical problem, cat allergy has received far more scientific interest. Presumably, the behavior of domestic cats also has an impact on the distribution of the allergen. Cats are more likely than dogs to wander around the house and sit on furniture, such as beds and chairs (68). Common epitopes and some degree of crossreactivity between cat and dog allergens has been discussed, but the data are inconsistent (69–71).

Some studies have implied that it is possible to become sensitized to cat through indirect cat exposure. The most intriguing evidence comes from the island of Tristan da Cunha, where cats were exterminated in 1974 to eliminate toxoplasmosis (71). Positive skin test reaction to cat was present in six individuals (12.8%) born more than 1 yr after the cats were eliminated. Of these six children, two had attended school outside the island and might have become sensitized there, but the remaining four children (one of whom was born in 1983) must have become sensitized either from allergen that remained in the homes or from allergen brought in on visitors' clothes. Similarly, a high prevalence of cat sensitization has been demonstrated asthmatic Japanese children living without cats (70). In an area of Italy where approx 16% of all households had cats, cat sensitization was three times more frequent in children who never had a cat at home than in children living with cats, suggesting that exposure in public places is more important than exposure in the home (72). In the European Community Respiratory Health Survey, a significant correlation between the prevalence of cat ownership in the community and the prevalence of specific sensitization to cat was observed in adults (55) along with more asthma in sensitized adults who grew up with cats in areas with a low prevalence of cats in the community (28). Studies have also suggested

that indirect cat exposure at school may result in sensitization (42) and asthma (73).

Therefore, it is possible that a true association can be assessed by combining direct and indirect exposure—that is, any exposure—and using children unexposed to cat allergen as the reference group. This was done in a recent report from a prospective birth cohort study, where any cat contact—either direct or indirect—was associated with increased risk of cat sensitization (25). These children may have been directly or indirectly exposed to cat later in life, but they still had higher risk of sensitization than those without any exposure to cat at the median age 2 mo. Thus, it may be possible to come closer to the true effects of early exposure to pets by estimating total levels of personal allergen exposure over time, perhaps in a multicenter prospective study with adequate sampling methods and assays.

Concerning exposure to HDMs, ongoing randomized, controlled intervention studies in risk populations have implied that it is possible to decrease HDM allergen levels in homes by stringent environmental control and that living in a low-allergen environment reduces respiratory symptoms during the first year of life in high-risk infants (74,75), decreases the use of oral steroids at 18 mo (76), and gives lower sensitization rates at age 8 yr (77). Reports regarding whether HDM allergen avoidance is associated with an increased or decreased risk of sensitization and, more importantly, wheezing and asthma as the children grow older will be most interesting.

Allergen Exposure in Already Sensitized Subjects With Asthma

The debated causal relationship between early exposure and subsequent asthma should not be confused with the association between allergen exposure and worsening of asthma in already sensitized individuals (Table 2). Cat allergy is common among asthmatic patients in clinical populations and is also a significant

risk factor for emergency room visits caused by asthma (52,78). In a case-control study in which adults with severe asthma were matched with a mildly asthmatic group, a larger proportion of the severely asthmatic group were sensitized and exposed to indoor allergens (79). It has also been demonstrated that asthmatic individuals with pets at home have more symptoms, a higher degree of BHR, take more medication, and score higher on inflammatory parameters than asthmatic individuals without pets at home (80). Levels of exhaled nitric oxide have also been shown to be significantly higher in patients with asthma who are both sensitized and exposed to relevant allergen than in those who are sensitized but not exposed (81). Moreover, a recent study of 311 children with asthma and sensitization showed that subjects who were both sensitized and exposed to high levels of sensitizing allergen had significantly lower forced expiratory volume in 1 s percent predicted values, higher exhaled nitric oxide values, and more severe airway reactivity than subjects who were not sensitized and exposed. Both the interaction between sensitization and exposure to any allergen and the interaction between sensitization and exposure to cat allergen had significant effects on nonspecific bronchial reactivity, indicating that asthmatic subjects exposed in their homes to allergens to which they are sensitized have a more severe form of the disease (82). Additionally, in occupational settings, several studies have indicated worsening of respiratory symptoms in sensitized subjects after allergen exposure (83,84). Similarly, a correlation between allergen levels at home and severity of asthma in sensitized children has been proposed for HDM and cockroach exposure (39,85).

It has also been suggested that asthmatic children who were allergic to cats may suffer a worsening of their disease as a result of indirect exposure to cat at school after a period of nonexposure (86). Among children in classes with many cat owners, lung function expressed

Table 2

Studies on Exposure to Cat or Dog in Already IgE-Sensitized Individuals With Asthma

Author	Study design	Study population	Exposure	Outcome	Result
Gelber, United States, 1993 (52)	Case-control	114 cases with acute asthma, 114 controls	Dust samples from 186 homes analyzed for cat, HDM, cockroach allergen	S-IgE, Sp-IgE HDM, cat, pollen, cockroach	Cat and cockroach: sensitization and allergen in the house significantly associated with asthma
Plaschke, Sweden, 1999 (80)		129 asthmatics sensitized to cat or dog	Cat or dog at home (<i>n</i> = 39) No pet at home (<i>n</i> = 90)	Symptoms, steroids, SPT, PEF, Sp-IgE, eosinophil counts, BHR	Subjects with pets had more symptoms, steroids, abnormal PEF, and higher eosinophil counts and BHR than subjects without pets
Simpson, United Kingdom, 1999 (81)	Cross-sectional study	43 asthmatics with positive methacholine test, without steroid treatment	Dust samples from homes analyzed for HDM, cat and dog allergen	eNO, S-IgE, Sp-IgE HDM, cat, dog, SPT HDM, cat, dog	Levels of eNO significantly higher in sensitized asthmatic patients exposed to relevant allergen than in those unexposed
Tunncliffe, United Kingdom, 1999 (79)	Case-control study	28 cases with severe asthma, 28 controls with mild asthma	Dust samples from homes analyzed for HDM, cat, and dog allergen	SPT for HDM, cat, and dog.	Severe asthmatics sensitized and exposed to allergens significantly greater than sensitized and exposed mild asthmatics
Almqvist, 2001 (86)	Panel study	92 asthmatic children sensitized to cat and no cat at home	Classrooms with many (>18%) cat owners (<i>n</i> = 47) or few (<18%) cat owners (<i>n</i> = 45)	Weekly mean reported PEF, days with asthma symptoms, use of inhaled steroids or β -agonists, adjusting for age, sex, and fever and/or sore throat	Ninefold increased risk of exacerbated asthma among children in classes with many cat owners compared with few cat owners
Celedon, United States, 2002 (57)	Prospective birth cohort	448 children with at least one parent with a history of atopy followed from birth until 5 yr	Cat allergen Fel d 1 >8 μ g/g dust at age 2 mo	Wheezing and total S-IgE (87.4% of those exposed to a cat in early life still exposed to a cat)	No maternal asthma: negative association cat exposure—wheezing Maternal asthma: positive association cat exposure—wheeze, increase w/ age
Langley, 2003 (82)	Cross-sectional study	311 asthmatics	Dust samples analyzed for HDM, cat, and dog allergen	FEV ₁ , BHR, and eNO	Sensitized subjects exposed to high allergen levels had significantly lower FEV ₁ , higher eNO, and more severe airways reactivity than those nonsensitized and exposed

Age of the index children; No., number of children who were involved in the study; (%), response rate on questionnaires; (%), response rate on SPT or blood samples
SPT, skin prick test; Sp-IgE, specific serum-IgE antibodies; S-IgE, total serum-IgE; atopy = positive SPT, S-IgE, or Sp-IgE; FE₁, forced expiratory volume in 1 s; HDM, house dust mite; eNO, endothelial nitric oxide; BHR, bronchial hyperactivity.

as mean morning peak expiratory flow (PEF) decreased, days with asthma symptoms were more frequent, and the children reported a doubling of the average daily use of β -agonists and a 16% higher average daily dose of steroids after school start than during summer holidays. Those in classes with few cat owners reported no change. In agreement with this, low-dose allergen exposure has been shown to increase BHR and induce an inflammatory response in patients with pre-existing atopic asthma (87–91). Studies involving repeated exposure to low doses of allergen followed by a high-dose bronchial allergen challenge have indicated reduced late asthmatic response in asthmatic individuals, despite enhanced bronchial hyperresponsiveness to methacholine and elevated sputum eosinophils prior to allergen challenge (92). Similar results were observed in a study comparing repetitive low-dose antigen challenges with an equivalent single-dose allergen challenge in subjects with allergic asthma. The quantitative effects on lung function and sputum eosinophilia were similar, but repetitive low doses of antigen (as might mimic natural allergen exposure) produced an inflammatory response equivalent to the response evoked by the large single-dose challenge with a smaller total amount of antigen, suggesting priming and cumulative effects may have occurred (93). However, this is prevented with inhaled steroid treatment (94) and needs to be confirmed in larger trials.

Therefore, these studies concur that sensitized subjects with asthma suffer exacerbation of their disease when exposed to the relevant allergens, and the degree of deterioration appears to be a matter of dose. Granted, there are asthmatic patients who claim they tolerate their own pet but not the pets of others, but clinical studies to confirm the mechanisms around this are lacking. Meanwhile, the best choice for a clinician must be to advise sensitized asthmatics that avoidance of exposure to indoor allergens is an important element in the treatment of allergic disease.

Allergen Avoidance

For asthmatic individuals whose disease worsens because of direct or indirect pet contact, it is vital to avoid exposure to the allergen (secondary prevention), regardless of how early exposure to pets may affect the development of sensitization or asthma in childhood (primary prevention). Even if factors other than allergen exposure play a major part in determining which child will develop asthma, thereby proving allergen elimination inefficient as a primary prevention measure, a reduction of direct and indirect allergen exposure will remain a very important element in secondary prevention.

Several studies have shown that Fel d 1 is still present in homes where a cat has previously lived and even in houses where no cat ever lived (95,96). It is not clear whether repeated washing of cats removes allergen from the cat and leads to progressive reduction in the quantity of allergen in the home, but it appears that cats and dogs must be washed at least once a week to reduce airborne levels of Fel d 1 and Can f 1 (97–100). Vacuum cleaning appears to provoke increases in airborne Fel d 1, primarily that carried by large particles, although there is less leakage from vacuum cleaners with HEPA filters or microfilters (101,102).

The use of tannic acid or Allerpet/c to reduce allergen levels also has limited effects on cat allergen (98,103). Air cleaners have been shown to reduce levels of airborne allergen, but studies regarding their clinical usefulness have provided inconsistent results. In a double-blind, placebo-controlled trial to evaluate the effect of HEPA air cleaners on subjects with cat allergies who had a cat at home, there was no effect on disease activity, despite decreased levels of cat allergen in the homes of those with active air cleaners (104). Another research group showed a significant reduction in airway hyperresponsiveness in young asthmatic patients when air cleaners were used in living rooms and bedrooms (105). A reduction in cat aller-

gen levels without removal of the cat can be achieved by washing the cat, reducing the amount of furniture, vacuuming, and filtering the air (97). This is a rather time-consuming way to reduce allergen levels, and it is likely to be acceptable only to subjects sensitized to cats who really want to keep their cat at home. It is not feasible to suggest that families without a cat undertake stringent environmental control measures to rid their air of passively transferred allergen.

It is becoming well-known that school environments affect children with asthmatic symptoms; some schools have established allergen avoidance classrooms (106,107). However, recent data have implied that allergen avoidance measures, such as removing curtains, upholstery, and plants; replacing bookshelves with cupboards; and cleaning schools regularly, do not reduce airborne cat allergen, unless the rate of pet ownership is minimized or stringent rules about clothing are introduced (108). Many studies have emphasized clothes as an important carrier of allergen (17–19,24), and measures to reduce allergen levels in cat-free environments can easily be suggested. It is of considerable interest to look into possible intervention measures and to take steps to minimize the amount of allergen brought to school in cat owners' clothing, either by asking cat owners to wear clean clothes to school and to not cuddle with the cat in the morning or by having children change into school uniforms at school. Interesting data from a recent study show that levels of cat allergen are lower in classes that ban pet ownership or classes in which the children change into special school clothing at school than in control classes (109). It remains to be seen whether a reduction in allergen levels at school has an effect on the allergen load in homes without a cat, as well as how the health status of sensitized asthmatic children is affected.

Recently, several randomized control studies regarding HDM avoidance have been published, with somewhat differing results. In a

study of 47 children, one group managed to reduce levels of HDM allergens by encasing mattresses and pillows, and this resulted in a reduction in the use of inhaled steroids in the active group (110). However, in another study of 1122 adults with asthma, allergen-impermeable covers reduced the levels of HDM allergens at 6 mo but not at 12 mo, with no significant difference in PEF or steroid medication between active and control groups (111). Another group succeeded in reducing HDM allergen levels by using impermeable bedding covers, but this had no significant effect on clinical outcome measures among 232 adults with rhinitis (112). The reason for these differing results may be that even if it is possible to reduce allergen levels in a bedroom, there is still plenty of allergen around the house and in public places, and it is most likely that HDM-sensitized individuals are also sensitized to other indoor allergens to which they are simultaneously exposed.

If the reservoirs of allergens in homes and in public places turn out to be difficult to sufficiently eradicate to reduce indirect exposure to indoor allergen, then it is important to encourage patients not only to avoid allergens but also to comply with pharmacological therapy. Specific immunotherapy has been shown to reduce sensitivity to allergens such as cat (113,114). Primary prevention strategies based on the induction of an immune deviation toward a Th1-type immune response to inhalant allergens have been proposed—for example, by administering allergen along with a suitable adjuvant in a vaccination program (115–117).

Heredity for Allergic Diseases as Confounder and Effect Modifier

Twin studies suggested that 75% of asthma sufferers inherit the disease (118,119). There are also indications that the maternal influence is stronger than the paternal influence, perhaps because of *in utero* immunological environment and cytokine profiles at birth (38,65,120). If genetic studies turn out to be fruitful, then

they may make it possible to identify individuals who would respond to certain primary prevention measures or therapeutic intervention strategies. The more we understand about an individual's genetic background, the better placed we will be to interpret his or her susceptibility to specific exposures. This would improve our understanding of the effect of environmental exposure, because gene-environment interactions are believed to play an important role in the development of allergic disease (121,122).

A few of the studies regarding associations between pet exposure and disease briefly mention whether there is a difference in pet ownership between households with and without a family history of allergic disease. It is interesting to speculate which other factors might influence people in their decision to keep pets, thereby possibly confounding studies on associations.

Families with a history of allergic diseases may be less prone to keep pets, and many countries have primary prevention programs in which families with heredity for allergic diseases are advised not to keep pets. Meanwhile, cat allergen is ubiquitous in society and may induce sensitization in predisposed individuals, regardless of pet ownership. Children with a family history of allergic disease also have a higher risk of becoming allergic themselves. Taken together, this might distort study results (34,66,123,124).

Conclusion

It is not an easy task to argue for high early allergen exposure as a risk factor for sensitization and development of asthma, considering the multitude of studies that have been published in the recent years. Because of the fact that so many studies present incongruent results—even longitudinal studies in which infants are followed from birth—it is a difficult undertaking to design primary prevention strategies and summarize them in the form of

advice. We should not advise people without heredity for allergic diseases who wish to prevent allergies and asthma in their children to get rid of their pets. Conversely, we probably should not recommend pet ownership as prophylaxis against asthma. For the child with allergic parents (*see* Situation 1), the family should look for early symptoms of allergic diseases and should be advised to remove the pet (or to not get one) if one or more of the family members react to the pet. A challenging task would be to perform a randomized control trial in which children are randomized on the basis of heredity for allergic diseases and then allocated into different arms with and without cat and dog ownership. Only in this way can we ascertain the risk of disease at age x years, and even then we will have to struggle with the issue of indirect exposure. The ethical committees would probably not approve this type of study, and meanwhile, we must fall back on single studies and meta-analyses.

On the other hand, the task of arguing that high allergen exposure constitutes a risk factor for asthma and allergic disease in already sensitized subjects is much easier. Most studies on the issue agree that subjects exposed to the relevant allergen do get worse. For the aforementioned child (*see* Situation 2) who reacts to cats and dogs in friends' houses with asthma and rhinoconjunctivitis, the best advice is to reduce the exposure to allergen and to not acquire a family pet.

In conclusion, even if much research remains to be performed before hypotheses on the effects of early allergen exposure are proved or disproved, it seems clear that allergen avoidance will reduce symptoms in sensitized children with asthma and that avoidance of exposure to indoor allergens is an important element in the treatment of allergic disease.

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