# Dogs, cats, and asthma: Will we ever really know the true risks and benefits?

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Early in our medical careers, many of us were told that allergies "cause" asthma. However, we probably also heard, usually from a pulmonologist, that there was no scientific evidence demonstrating a causal link between allergies and asthma. After years of study, why is the relationship between allergies and asthma still debated?[1]

An important challenge in understanding the relationship of allergic sensitization to asthma is our broadening understanding of the complex interactions among many variables, which ultimately lead to an abnormally responsive lung. Lung hyperresponsiveness appears to be the final common pathway responsible for the various symptoms we cluster together for a diagnosis of asthma. Efforts to understand the different pathophysiologic processes responsible for pulmonary hyperactivity have led to the concept of asthma phenotypes or underlying endotypes.[2] Among the recognized phenotypes, allergic asthma appears to be the most common.[3] Allergic asthma is typically defined by an observed association between asthma symptoms and exposure to an airborne allergen when IgE antibodies specific for the same allergen can be demonstrated.

However, studying the relationships between allergen exposure and asthma in human subjects is difficult. The large number of exposure, genetic, and behavior variables to be considered requires studying large numbers of participants to obtain adequate statistical power, but as the number of participants increases, the feasibility of obtaining uniform, detailed medical histories relating allergen exposures to asthma symptoms typically decreases. Allergen exposures in chambers or by means of bronchial challenge are criticized as having allergen doses substantially larger than the estimated exposures in normal environments. Even the correlation of allergen-specific IgE antibodies to asthma has become increasingly complex. Several studies have shown that simply classifying a person as atopic based on a single specific IgE test grossly oversimplifies the patterns of allergic sensitization present among subjects.[4] Others have shown that the relationships of allergen-specific IgE to allergic reactions depends on the concentrations of IgG antibodies of the same specificities.[5]

Perhaps the clearest example of allergic sensitivity causing asthma is provided by the study of occupational asthma. When nonsensitized workers begin a new job and become exposed to a new allergen, some will experience allergic sensitization and then begin to have typical asthma symptoms. Prompt removal of affected workers from the workplace will reduce symptoms and lead to resolution of asthma in some cases.[6] Again, the argument against occupational asthma proving the link between allergy and asthma focuses on the unusually high airborne concentrations of allergens typical of risky occupational settings.

To better define the relationship of allergic sensitization to asthma, a study needs a large number of participants living in normal home environments prospectively followed over many years. Ideally, the home environments would only have a potentially sensitizing level of exposure to 1 allergen.

In this issue Perzanowski et al[7] have taken advantage of a large cohort (3430 children) living in the relatively unique home environments of northern Sweden to further investigate the relationship of allergy to asthma. The cities in which the participants lived, Kiruna and Lulea, are located just above and below the Arctic Circle (currently, 66°33′46.6″N) or slightly further north than Fairbanks, Alaska. Because of the heating required during prolonged winters, there are virtually no dust mites or cockroaches, making dogs and cats the only major sources of persistent indoor allergens. The investigators found that the concurrent concentrations of cat- and dog-specific IgE antibodies were strongly related to the prevalence and severity of asthma among the participants at 19 years of age. Increasing concentrations of cat- and dog-specific IgE were associated with the increasing prevalence and severity of asthma. Interestingly, although the prevalences of sensitization to cat and dog were nearly equal, odd ratios for asthma were noticeably higher when the current dog IgE level was greater than 17.5 IU/mL than when the cat IgE level was greater than this concentration. The collinearity between cat- and dog-specific IgE antibody concentrations made it impossible to statistically answer the question of whether cat or dog IgE was more strongly related to asthma. However, multivariable analysis showed that cat- and dog-specific IgE were each more strongly related to asthma than grass or birch pollen IgE. The strong associations between the concentrations of antibodies and asthma was repeatedly seen whether the outcome was physician-diagnosed asthma, current asthma, asthma medication use, or wheezing episodes. Analysis of IgE concentrations to specific cat and dog allergen components resulted in even greater odds ratios for asthma. When the intercorrelations between IgE responses to the 4 dog and 3 cat allergen components were calculated, the greatest correlation was between Can f 3 and Fel d 2, which are both serum albumins with similar structures. Correlation between cat (Fel d 4) and dog (Can f 2) lipocalins were modest.

The results of the current study are similar to those of a previous study of the relationship of cat allergy to asthma among

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children residing in the dry, high-altitude environment of Los Alamos, New Mexico.[8] Los Alamos was chosen for study because the dry climate and elevation combined to make homes virtually free of dust mites and cockroaches. Asthma was ascertained by means of questionnaire, spirometry, and histamine challenge, and allergic sensitization was ascertained by means of skin testing. Unfortunately, dog extract was not included among the skin tests. When children (n = 16) both sensitized and exposed to high cat allergen concentrations (>10 μg Fel d 1/g dust) were compared with the 90 children without asthma, the odds ratio of cat sensitivity–associated asthma was 6.2 (95% CI, 2.2-17.6; $P < .001$). However, even for children who had always resided in the relatively dust mite– and cockroach-free environment of Los Alamos, sensitization to these perennial allergens was found in some children.

Both the current and Los Alamos studies found that cat and dog allergen concentrations were relatively high, even in homes without a resident animal. These findings are consistent with other studies showing that animal allergens are distributed to homes, schools, and public buildings in which animals are not resident by adhering to the clothing of pet owners.[9] Indeed, the current study found that of those participants with high concentrations of IgE antibodies to cat, 85% did not have a cat in the home, and 48% did not have either a cat or dog in the home.

Unfortunately, the current study in Sweden did not enroll children until they were 7 or 8 years of age. Most studies that have shown a protective effect on allergic disease risk from cat and dog exposure have shown that the protective effect depends on pet exposure during the first year of life. Some of these "pet protective" studies suggest that cats and dogs alter the home microbiome (resident populations of various bacterial, fungal, and viral organisms) and that exposure of children in the home to the microbes associated with cats and dogs reduces their risk of becoming allergic and having asthma.[10] An important but unanswered question is the source of the risk-reducing microbes associated with cats and dogs in homes. The organisms might be the animal's commensal microbes or they might be microbes from soil or other outdoor sources that adhere to the animal and are carried into and deposited in the home. If the reduced risk of allergy associated with pets is related to transport of outdoor microbes, the unique climate of northern Sweden might show dramatically different home microbial communities associated with resident cats and dogs. The low humidity of homes during long winters might also substantially affect home microbial communities. Studying the microbiomes of homes with and without cats and dogs throughout a year in northern Sweden would likely be highly revealing.

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