



The effect of pet ownership on the risk of allergic sensitisation and bronchial asthma

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Summary An increasing volume of evidence suggests that early contact of children with the allergens of furred pets (especially those produced by cats) may determine a lower risk of developing allergic sensitisation to these materials. A possible explanation of this data is that an early inhalation of high levels of the major cat allergen *Fel d 1* induces the production of IgG and IgG4 antibodies with a "protective" effect.

Other authors have shown that the prevalence of allergic sensitisation to cats, in adults, is reduced in those patients exposed to the lowest and highest levels of the allergens. On the contrary, the risk of developing sensitisation to cats is significantly higher when the patients were exposed to intermediate levels of *Fel d 1*. Moreover, epidemiological studies have demonstrated a relatively low prevalence of cat allergy (about 10%) in some countries where rates of cat ownership are high.

This data confirms the role of indirect exposure to pet allergens in inducing allergic sensitisation. Clothes of pet owners have been indicated as the carriers for the dispersal of these allergens in pet-free environments. However, it is important to point out that exposure of highly sensitised patients to relevant amounts of pet allergens (such as in a pet shows/shops) may determine a dramatic exacerbation of nasal and/or bronchial symptoms.

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Sensitisation towards pet and mite allergens

Several studies have demonstrated that changes induced by human activities in indoor environments and the so called "westernised lifestyle" are likely

to be responsible for the increasing exposure of residents to locally produced allergens or chemical agents.^{1,2} In fact, the majority of modern indoor environments contain energy saving systems (such as insulated doors and windows) which can both increase indoor temperature and humidity and decrease natural air ventilation.³ In these environmental conditions indoor allergens and chemical products cannot be adequately removed/diluted by normal air circulation and

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consequently the level of exposure of susceptible individuals may increase.^{4,5}

Allergic sensitisation to animal allergens is a common occupational hazard in occupationally exposed workers.⁶ However, increasing environmental awareness has determined an increasing prevalence of furred pet ownership, especially of cats/dogs in domestic environments of many industrialized countries and consequently it has raised the degree of exposure to the allergens produced by these creatures.⁷ For example, it has been calculated that, in Northern Europe, almost 23–34% of school children own a cat and/or a dog.⁸ In some geographical areas up to 50–70% of asthmatic children is sensitised to allergens of common domestic animals.⁹ A high prevalence of allergic sensitisation to pet allergens has also been shown in some geographical areas characterised by a hot climate and a low degree of humidity. In these climatic conditions the growth of mite and cockroach populations is not favoured and consequently the degree of exposure to these allergens is low.¹⁰

People and animals have been living in very close contact for thousands of years without any problems for people. However, it is important to emphasise that contact between people and animals is quite different when we consider ancient and recent times and, in the latter case, if we compare rural and urban areas.

In our cities, domestic animals usually live in relatively narrow environments, with insulated doors/windows, upholstered furniture, fitted carpets on which their epithelia may be easily kept. Under such circumstances, high amounts of pet allergens can be found. On the contrary, in rural areas domestic animals usually live outdoors and, consequently, the degree of indoor allergen contamination is lower. Moreover, in these areas contact between people and farm animals, including their products, is traditionally close from birth to adulthood.

Possible mechanisms for development of tolerance

Studies have consistently shown a direct relationship between exposure to mite allergens and development of specific sensitisation as well as a strong association between mite sensitisation and atopic asthma^{11–14} (Fig. 1). On the contrary, an increasing body of evidence from farming communities in Europe has shown that early contact with farm animals may determine a “protective” effect

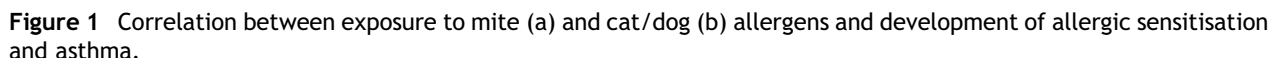
on the development of allergic sensitisation and bronchial asthma.^{15–20} It has, therefore been suggested that the protection induced by farm environment might be mediated by high exposure to bacterial endotoxins.^{21,22}

However, several recent studies have suggested that early exposure of children to allergens from common pets (cats and dogs) in domestic environments might determine a lower degree of allergic sensitisation to these proteins^{23–25} (Fig. 1). Similar results have been confirmed also in preteenage children,²⁶ and, recently De Meer et al.²⁷ demonstrated that having had a cat before 18 years of age protects against adult asthma and atopy. Children raised in a house with 2 or more dogs or cats in their first year of life have not only less allergic sensitisation to the allergens of these animals, but also less sensitisation to other common allergens.²⁸ Moreover, pet ownership in the first 2 years of life seemed to offer some protection against sensitisation to pollen.²⁹

Recently Platts-Mills et al.³⁰ confirmed that exposure to high amounts of cat allergens in children is associated to a lower risk of sensitisation to cats. On the contrary, increasing exposure to mite was associated with increased prevalence of sensitisation to mite allergens.³⁰

These findings were interpreted in terms of higher exposure to cat allergen, which can cause the production of an IgG and IgG4 antibody response without sensitisation or risk of asthma. This modified T helper-2 cell response should be regarded as a form of induced tolerance. These results were confirmed by Custovic et al.^{31,32} who analysed the relationship between current exposure to cat allergen and development of specific sensitisation to cats in a large population of adults. These findings indicate that the prevalence of sensitisation to cats was significantly decreased in patients exposed to the lowest and the highest levels of cat allergen. On the contrary, the risk of sensitisation to cats was significantly increased with medium-level exposure to *Fel d 1*.

Moreover, Custovic et al.³² have provided further evidence that the proportion of patient positive to dust mite skin tests increased as exposure to mite allergens (a linear dose/response relationship) grew higher. Similarly, studies carried out in inner-city areas demonstrated that children are more likely to become sensitised to cockroach allergens³³ or to mouse allergens³⁴ if the degree of exposure to these materials is very high. The lack of a dose/response relationship between exposure to cat allergens and development of specific sensitisation is also confirmed by data from some large epidemiological studies. It has been demonstrated



Other mechanisms for possible protective effects

It has been also demonstrated that the “protective” effect of dog exposure on the development of wheezing in children was significantly associated with a negative history of asthma³⁷ or allergic diseases³⁸ in parents. In children with negative maternal history of asthma, exposure to cat was associated with a “protective” effect on the development of wheezing.³⁹ This data suggests that the “protective effect” and the risks associated to pet ownership can only be studied among individuals without allergic heredity to avoid the bias of pet removal. Moreover, it is likely that those with atopic predisposition will develop allergic diseases any way.^{24,38} Recently, Svanes et al.⁴⁰ demonstrated that the effects of pet-keeping in childhood varied according to the type of pet, the allergic sensitisation of the individual, and the wider environmental exposure to allergen. Cats owned in childhood were associated with more asthma in sensitised adults who grew up in areas with a low community prevalence of cats. Dogs owned in childhood seemed to protect against adult allergic disease but promote non allergic asthma. In Table 1, possible reasons for “the protective effect” of pet ownership are shown.

Table 1 Possible mechanisms to explain “the protective effect” of pet ownership on the risk of allergic sensitisation.

- A modified TH2 response in children exposed to relevant amounts of cat allergen characterised by high levels of IgG/IgG4 without production of IgE.³⁰ This immune response might induce clinical tolerance.
- The lower degree of IgE production but not the high levels of IgG4 might be responsible for the induction of clinical tolerance.⁶⁶
- T-cell responses to *Fel d 1* in vitro are characterised by IL-10 production in cat allergic and cat tolerant individuals.⁶⁷ A purified peptide of *Fel d 1* induces higher levels of IFN-gamma in vitro.⁶³
- The high presence of endotoxins or other pro-inflammatory substances in domestic environments with cats/dogs (other than in farming) might determine a down-regulation of immune responses.^{22,68–70}
- Transmission of microbes causing manifest lower airways infections might possibly influence the development of the airways and the lung parenchyma.^{71,72}

Methodological considerations

It is important to underline that the observed lower risk of wheezing among exposed young children compared to unexposed ones is consistent with a protective effect but, in large epidemiological studies, it could be partially attributed to decisions made by allergic families to get rid of an animal or avoid having a cat/dog as well as to different bias attributable to methodological reasons.⁴¹ For example, an accurate assessment of pet allergen exposure is not an easy task⁴² considering that pet ownership may vary with family history of allergy and socio-economic factors.^{43,44} The assessment of pet exposure by evaluating the amounts of cat/dog allergens found in dust may be misleading since these allergens are largely airborne. A significant correlation between settled and airborne levels of pet allergens has not been found.⁴⁵ The assessment of personal exposure to pet allergens over time is also very difficult to perform.

Another possible bias in the assessment of pet allergen exposure derives from the ubiquity of pet allergens. For this reason when we identify adults/children who are not exposed to cats/dogs (because they have never owned these animals), it is crucial to distinguish between subjects with frequent contact with cats/dogs outside the home and subjects without any contact with pets and consequently exposed only to passively carried allergens.⁴² On the basis of this background Almqvist et al.³⁸ demonstrated that early exposure to cats seems to increase the risk of sensitisation to cats but not of asthma at 4 years of life. By contrast, dog ownership appears to be associated

with lowered risk of sensitisation to airborne allergens (pollens) and asthma.

The lack of a gold standard for defining bronchial asthma in childhood constitute another possible bias in large epidemiological studies where wheezing or doctor's diagnosis of asthma are usually registered. However, since the criteria used to define this disease may be very different according to research groups, results may vary accordingly.⁴⁶

The problem of the ubiquity of cat allergen and possible prevention strategies

The increasing body of evidence suggesting a possible “protective” effect of early pet ownership associated to a well demonstrated risk of becoming sensitised to pet allergens also as a consequence of indirect exposure to cats/dogs highlights the problem of the ubiquity of these materials and of the possible strategies to reduce the degree of indirect exposure.

Fel d 1 is now considered an ubiquitous allergen being found in many indoor environments where a cat has never been kept.⁴⁷ Significant amounts of *Fel d 1* have been found in dust sampled from floors, walls, upholstered furniture or from the air of private/public places such as offices, hospitals, schools, means of transport etc. without the presence of cats.^{48–53}

Recent studies have shown that cat allergens found in indoor environments without cats have been passively carried by the clothes of cat owners.^{54,55} Accumulation of cat allergens in indoor environments without cats has been demonstrated

to correlate with the number of visitors owning a cat or with those who are in regular contact with this animal.^{42,56}

We have recently shown the first case of intensive sensitisation to rabbit allergens induced by indirect exposure to these materials by clothing of rabbit owner.⁵⁷ Data on the efficacy of prevention measures to minimise exposure to allergens of domestic animals, especially of cats, is still controversial. Although the relocation of cats is usually considered the first-line measure from a clinical point of view, there is no data on the efficacy of cat removal in reducing clinical symptoms in highly sensitised patients.

Considering that many cat-sensitised patients refuse to give up their cats and the long persistence of cat allergen in indoor environments after the cat's relocation, the use of vigorous cleaning procedures according to usual protocols⁵⁸⁻⁶¹ will significantly reduce the levels of *Fel d* 1, but it is unlikely that these procedure could completely abolish cat allergen contamination.

Since several studies have consistently shown that clothes of cat owners constitute the main contributors for the dispersal of cat allergen in cat-free environments, we performed some experiments in order to evaluate the efficacy of different cleaning procedures in removing cat allergen from fabrics passively contaminated by cat contact.

We approached the problem by using a study design for comparing different cleaning systems (with or without water) on different type of clothing.

Washing determined a complete removal of *Fel d* 1 from cotton fabrics.⁶² In this experiment we used only water (without detergents) to avoid possible modification of allergenic structure. On the contrary, commercial dry cleaning removed large amounts of cat allergen from wool fabrics but did not completely abolish *Fel d* 1 contamination.⁶³ Interestingly, some control fabrics (non-exposed to cats) contained low amounts of allergen probably by passive contamination from other clothes during the dry cleaning process.

In our laboratory, another study is currently in progress to evaluate the efficacy of vacuum cleaning in removing cat allergen from contaminated cotton fabrics.

Conclusions

Problems regarding allergic sensitisation to the allergens of domestic animals constitute an important field of investigation in respiratory allergy.

In fact several questions about the modality of sensitisation (especially in the first months of life), the ubiquity of pet allergens and possible prevention strategies still remain unanswered.

On the contrary increasing animal awareness in the most industrialised countries determines an increasing furred pet ownership and consequently a higher dispersal of pet allergens also in pet-free private environments and in many public places.

To further complicate this intriguing issue, an increasing body of evidence suggests that the presence of cats/dogs at home, especially in the first months of life, may induce a "protective" effect on the development of allergic sensitisation and atopic bronchial asthma. However, further studies are necessary to confirm these data. Moreover, it is important to control for bias (information and selection bias) and confounders e.g. heredity, smoking, breast feeding, socio-economy.^{42,64}

It is important to point out that, although avoiding the contact with cats/dogs in the first months of life cannot be recommended as a primary prevention of allergy, exposure of already and highly sensitised patients to relevant amounts of pet allergens (e.g. in environments where two or more animals usually live, in pet shows/shops, etc.) may result in dramatic exacerbation of their nasal and/or bronchial symptoms.⁶⁵

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