Controversial role of pets in the development of atopy in children

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Background: Exposure to environmental allergens originating from different sources has been implicated in the sensitization to the respective allergens and development of atopic diseases. Keeping domestic animals is associated with exposure to relevant allergens but there are controversial data whether this exposure promotes or protects from the development of atopy.

Data sources: We herein reviewed the literature regarding the available data for the exposure to pets (cats and/or dogs) and the development of atopy. For this purpose, we searched the PubMed database.

Results: This review attempts to answer the following questions that arise from the daily practice and the relevant studies, which are: a) is pet keeping associated with sensitization? b) is there an association between keeping pets and the development of asthma, allergic rhinitis and eczema, and, c) what is the underlying mechanism of any possible protective association? Despite the fact that several studies and meta-analyses have been conducted to explore the role of pets in the development of atopy, there are still conflicting pieces of evidence. It seems that there are different effects depending on the type of pets, the time and duration of exposure, and the genetic background of the individual.

Conclusion: Further appropriately designed birth cohort studies are needed to explore whether exposure to relevant allergens from pets promotes or protects from the development of atopy.


Key words: allergic rhinitis asthma; atopic dermatitis; atopy; pet keeping

Introduction

Exposure to environmental allergens has been implicated in the sensitization to the respective allergens and development of atopic diseases, such as allergic rhinitis, asthma and atopic dermatitis. In particular, keeping domestic animals is associated with exposure to relevant allergens and therefore it is speculated that it may contribute to the development of atopy or may aggravate the symptoms of atopic subjects. However, there are also data deriving mainly from epidemiological studies, indicating that exposure to pets in early childhood may be a protective factor for the development of atopy. As there are controversial data from different studies investigating a possible association of atopy with exposure to pets, meta-analyses have been conducted in order to clarify this issue.

The questions that arised from this everyday practice and the respective studies are as follows: a) is keeping pets associated with sensitization? b) is there an association between pet keeping and the development of asthma, allergic rhinitis and eczema? c) what is the underlying mechanism of any possible protective association?

This review attempts to answer the abovementioned questions, based on relevant studies and meta-analyses, in order to clarify which questions are adequately answered and which need further investigation.

Is keeping cats or dogs associated with sensitization?

Cats and dogs are the most common domestic animals. Their main allergens are Felis domesticus allergen 1 and Felis domesticus allergen 4 (Fel d 1 and Fel d 4) for cats and Canis familiaris allergen 1 and Canis familiaris allergen 4.
allergen 2 (Can f 1 and Can f 2) for dogs. They are disseminated by small particles, which remain in the air and adhere to surfaces and clothes. These properties result in widespread dissemination of the allergens, even in workplaces where there are no pets, i.e. in schools, where they are carried via clothes of children who keep a pet at home. This is important in areas where pet keeping at home is a very common practice.

Table 1. Cat and/or dog ownership and the risk of sensitization to the corresponding allergens (chronological order)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design, age, number</th>
<th>Type of pet</th>
<th>Outcome measure</th>
<th>Association between exposure and sensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munir AK</td>
<td>Birth cohort, 100 children at birth with a family history of allergy. Follow up at 6 and 18 months and in 86 children at 5 years</td>
<td>Dog</td>
<td>Skin prick test</td>
<td>89% who were exposed to cat or dog allergens levels of 8 μg/gm of dust or greater were not sensitized to these allergens.</td>
</tr>
<tr>
<td>Lindfors A</td>
<td>Cohort, 189 children, 1-4 years old. Follow up at 2, 7 and 12 years</td>
<td>Cat</td>
<td>Specific serum IgE</td>
<td>No relationship was found between exposure to dogs and corresponding sensitization. Reported exposure to cats was associated with corresponding sensitization.</td>
</tr>
<tr>
<td>Roost HP</td>
<td>Cross sectional, 18 097 adults, 13 509 provided blood sample</td>
<td>Cat</td>
<td>Serum specific IgE</td>
<td>A tendency for a negative association between having a cat in childhood and specific sensitization in adulthood was found. However, a significant positive association between cat ownership and specific sensitization was found in subjects reporting no respiratory symptoms to pet/house dust. Furthermore, in this study, it was estimated that a 10% increase in the community prevalence of keeping cats was associated with a 13% estimated increase in community prevalence of cat-specific IgE.</td>
</tr>
<tr>
<td>Hesselmar B</td>
<td>Representative sample of 412 children aged 7 years who were followed up at the age of 12-13 years</td>
<td>Dog</td>
<td>Skin prick test</td>
<td>A lower prevalence of positive skin prick test to cats at 12-13 years of age was seen in children exposed to a cat during their first year of life. However, no difference was observed when the analysis was performed after excluding the children whose parents had decided against keeping a pet during early childhood because of allergies in the family. There was no association between sensitization to dogs and dog ownership during the first year of life.</td>
</tr>
<tr>
<td>Arshad SH</td>
<td>Birth cohort, follow up at 1, 2 and 4 years, 1456 children were recruited and 981 followed up at 4 years</td>
<td>Dog</td>
<td>Skin prick test</td>
<td>No difference in sensitization to dogs or cats was seen in households with or without dogs or cats, respectively.</td>
</tr>
<tr>
<td>Melén E</td>
<td>Follow up of a previous cohort of 193 children, between 1 and 4 years of age, who were referred to a pediatric allergy clinic</td>
<td>Dog</td>
<td>Skin prick test</td>
<td>Exposure to a cat was associated with an increased risk of sensitization to cats. Exposure to a dog only during the first two years of life, but not later, tended to increase the risk of sensitization to dogs (odds ratio =3.03, 95% confidence interval=0.63-14.5).</td>
</tr>
<tr>
<td>Custovic A</td>
<td>Prospective, prenatally randomised cohort study</td>
<td>Dog</td>
<td>Skin prick test</td>
<td>Cat ownership was significantly associated with sensitization to cats. Dog ownership was not associated with sensitization to either cats or dogs.</td>
</tr>
<tr>
<td>Ritz BR</td>
<td>Cohort, 1893 children 5-14 years</td>
<td>Cat</td>
<td>Serum specific IgE</td>
<td>Ownership of a cat did not predispose to sensitization to cats. However, positivity for cat-specific IgE was dependent on the percentage of classmates or schoolmates who reported regular cat contact.</td>
</tr>
<tr>
<td>Owaby DR</td>
<td>Birth cohort, 835 were recruited. Exposure to a cat or dog was recorded during the first year of life, 474 completed follow up at 6-7 years</td>
<td>Dog</td>
<td>Serum specific IgE</td>
<td>Exposure to a dog decreased the risk for sensitization to dogs. No association was found with exposure to cat.</td>
</tr>
<tr>
<td>Brussee JE</td>
<td>Birth cohort, evaluation of allergen exposure at 3 months and follow up at 4 years, 4146 children</td>
<td>Dog</td>
<td>Specific IgE to cats, dogs</td>
<td>Dog allergen exposure did not influence the risk of sensitization to dogs, whereas cat allergen exposure increased the risk of sensitization to cats.</td>
</tr>
<tr>
<td>Perzanowski MS</td>
<td>Birth cohort, 725 children were recruited and repeated questionnaires were administered at the ages of 1, 2, 3 and 5 years</td>
<td>Cat</td>
<td>Serum specific IgE at the ages of 2, 3 and 5 years</td>
<td>Cat ownership was a significant risk factor for the development of anti-cat IgE at the age of 2 years but not at 3-5 years of age.</td>
</tr>
<tr>
<td>Mandhane P</td>
<td>Birth cohort of 1037 subjects. Cat and dog ownership were recorded at birth and at the ages of 3, 5, 7 and 9 years</td>
<td>Dog</td>
<td>Skin prick test at the age of 13 years</td>
<td>Ownership of either pet alone was not associated with the development of positive skin prick tests to inhalant allergens. However, a reduced risk of atopy was observed among children who had both a cat and a dog at home at the age of 9 years.</td>
</tr>
<tr>
<td>Wegienka G</td>
<td>Birth cohort, 835 children. Exposure to pets at home was recorded every year until the age of 6 years, 566 persons were followed up at 18 years</td>
<td>Dog</td>
<td>Serum specific IgE</td>
<td>Males exposed to a dog during the first year of life had half the risk of being sensitized to dogs. An indoor cat during the first year of life decreased the risk of the corresponding sensitization irrespective of gender.</td>
</tr>
<tr>
<td>Lodge CJ</td>
<td>Birth cohort, 620 infants. Information about keeping a dog or cat was given at birth. Follow up at 2, 7 and 12 years of age</td>
<td>Dog</td>
<td>Skin prick test</td>
<td>No clear relationship was found between pet ownership and sensitization.</td>
</tr>
</tbody>
</table>
Several studies have been conducted investigating the relationship between exposure to dogs and sensitization to the corresponding allergens, using either skin tests or levels of serum specific-immunoglobulin IgE (Table 1). Most studies concluded that there is no correlation between the two. On the contrary, a limited number of studies suggested a lower risk of sensitization to dog allergens at the age of 7 years among children whose family used to keep a dog, particularly during infancy. It was also recently shown that among males, those with a domestic dog in the first year of life had half the risk of being sensitized to dogs at the age of 18 years compared with those who did not have an indoor dog in the first year.

However, results of exposure to cats are conflicting. This inconsistency can be justified, to some extent, by the fact that many studies have been conducted to explore sensitization to cats compared with dogs. At least six studies failed to prove increased sensitization to cats in people who were living with a cat. Some studies have shown a reduced risk of sensitization to cats among people who owned one as a pet. A recent study showed half the risk of being sensitized to cats at 18 years of age among teens keeping an indoor cat in the first year of life.

On the other hand, studies suggested an increased risk of sensitization to cats among owners. Furthermore, the European Community Respiratory Health Survey (ECRHS) showed that the sensitization rate to cats among non-cat owners was higher in countries with higher rates of cat ownership. There was an increased risk of sensitization to cats among non-cat-owning school children who attended a school class with cat owners.

A significant point underlined by Ownby et al. was that exposure to two or more cats or dogs during the first year of life was associated with reduced incidence of allergic sensitization to other allergens at the age of six to seven years. In a population, however, where at least one parent had an atopic history, only exposure to a dog during the first year of life was associated with the reduced risk of allergic sensitization to foods and air-borne allergens at the age of one year.

In 2005, a critical review that studied the development of allergic sensitization in relation to pet keeping concluded that the results for cats are quite inconsistent. It seems, however, that there is no association between sensitization and dog keeping, whereas a protective role of dog ownership cannot be ruled out. A recent pooled analysis from 11 European birth cohorts showed that dog ownership during the first two years of life reduced the odds of sensitization to more than one aeroallergen at the age of six to ten years [odds ratio (OR)=0.45-0.65]. For cat ownership there was a similar trend that was not statistically significant.

Further studies from different countries may clarify the situation, if data regarding outdoor or indoor pet keeping are taken into account as well as pet avoidance behaviour and the age and duration of exposure to cats.

It is obvious that the issue of sensitization in relation to cat ownership has not been resolved. It seems, however, that dog ownership in childhood may either be irrelevant or even protective against sensitization to dogs and/or other aeroallergens, whereas it has not been clarified how cat ownership contributes (as a risk or protective factor) to sensitization to cats and other aeroallergens in the future.

**Table 2. Cat or dog ownership and their impact on asthma severity (chronological order)**

<table>
<thead>
<tr>
<th>Study (authors, y)</th>
<th>Design, age, number</th>
<th>Type of pet</th>
<th>Outcome measure</th>
<th>Association between exposure and asthma severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaschke P, 1999</td>
<td>Cross sectional, 129 adult asthmatics sensitized to cats or dogs</td>
<td>Dog Cat</td>
<td>Skin prick test, eosinophils, specific IgE, bronchial metacholine challenge, peak flow, questionnaires for symptoms</td>
<td>Cat or dog ownership aggravated symptoms and biomarkers of airway inflammation in asthmatics sensitized to cats or dogs.</td>
</tr>
<tr>
<td>Langley SJ, 2003</td>
<td>A random sample of 311 asthmatic subjects between 10 and 42 years of age</td>
<td>Dog Cat</td>
<td>FEV1%, eNO, PD20</td>
<td>Greater asthma severity in subjects who were sensitized and exposed to cats.</td>
</tr>
<tr>
<td>Gent JF, 2009</td>
<td>Cohort of 454 asthmatic children aged 4 to 12 years who were followed up for 1 year</td>
<td>Dog Cat</td>
<td>Level of household allergens measured at the time of study enrollment, allergen-specific IgE, and asthma severity</td>
<td>Higher pet allergen levels were associated with greater asthma severity, but only for those sensitized [cat odds ratio (OR)=2.41, 95% confidence interval (CI)=1.19-4.89; dog OR=2.06, 95% CI=1.01-4.22].</td>
</tr>
</tbody>
</table>

FEV1%, forced expiratory volume in 1 second, percent predicted; eNO: exhaled nitric oxide; PD20: provocation dose to cause 20% decrease in FEV1.

Is there an association between keeping pets and the development of asthma, allergic rhinitis and eczema?

Pet ownership by asthmatic individuals already sensitized to cat or dog allergens aggravates the severity...
of asthma, as documented by the frequency of symptoms, use of medicines, reduced respiratory function and increased bronchial hyperactivity in asthmatic children and adults (Table 2).

However, a different field of research is whether pet ownership predisposes to the development of asthma or wheezing. It has been proven that people experiencing symptoms of asthma tend to eliminate pets from the home in order to control the symptoms of their diseases. This tendency of asthmatic people may cover a correlation between the occurrence of asthma and pets. A decade ago, a meta-analysis from Apelberg et al, including studies containing data on exposure to pets (cats and/or dogs or other furry pets, before the onset of asthma), concluded that early exposure to pets increases the risk of asthma and wheezing in children over six years old. They also reached the conclusion of a lower risk of wheezing by exposed children under the age of 6 years old. They also reached the conclusion of a lower risk of wheezing by exposed children under the age of 6 years old.

Table 3. Cat or dog ownership and the risk of atopic diseases (chronological order)

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<tr>
<th>Study (authors, y)</th>
<th>Design, age, number</th>
<th>Type of pet</th>
<th>Outcome measure</th>
<th>Association between exposure and atopic diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hesselmar B, 1999</td>
<td>Representative sample of 412 children aged 7 years who were followed up at the age of 12-13 years</td>
<td>Cat, Dog</td>
<td>Atopy-related conditions assessed by questionnaire at 4 years of age</td>
<td>Analysis was performed for any pet irrespective of type. Pet keeping was associated with a lower prevalence of allergic rhinitis at 7 years of age and a lower prevalence of asthma at 13 years of age.</td>
</tr>
<tr>
<td>Remes ST, 2001</td>
<td>Birth cohort, 1246 infants were enrolled and followed up at the ages of 2, 3, 6, 11 and 13 years</td>
<td>Dog, Cat</td>
<td>Time of first report of frequent wheezing</td>
<td>Ownership of ≥1 dogs at birth was inversely associated with the development of frequent wheeze compared to those not having indoor dogs. This inverse association was confined to children without parental asthma. Cat ownership was not significantly associated with the risk of frequent wheezing.</td>
</tr>
<tr>
<td>Nafstad P, 2001</td>
<td>Birth cohort, 2531 who were followed up until the age of 4 years</td>
<td>Dog, Cat, Other</td>
<td>Atopy related disorders</td>
<td>Analysis showed that exposure to any pet at home reduced the risk of allergic rhinitis but this association was lost when the analysis was performed for dogs or cats separately. Additionally, exposure to any pet reduced the risk of eczema up to the age of 6 months and this observation was confirmed when the analysis was performed for cats or dogs separately.</td>
</tr>
<tr>
<td>Celedón JC, 2002</td>
<td>Birth cohort, 448 infants who were periodically followed up until the age of 5 years</td>
<td>Dog, Cat</td>
<td>Questionnaires about respiratory symptoms</td>
<td>No association was observed between wheezing and exposure to dogs. An inverse association was found between exposure to a cat and wheezing in the first 5 years of life and a significant interaction between exposure to a cat and maternal history of asthma.</td>
</tr>
<tr>
<td>Zheng T, 2002</td>
<td>Case-control study, 403 asthmatic children and 806 controls</td>
<td>Dog, Cat</td>
<td>Risk factors for asthma diagnosis</td>
<td>An increased risk of childhood asthma was found for those having both a dog and a cat as pets.</td>
</tr>
<tr>
<td>Hölscher H, 2002</td>
<td>Cross sectional survey, 5360 children of school age</td>
<td>Cat, Dog</td>
<td>Atopy related disorders assessed by questionnaire</td>
<td>The lifetime prevalence of asthma, hay fever and eczema was inversely associated with exposure to dogs in the first year of life. No clear relationship was identified for exposure to cats.</td>
</tr>
<tr>
<td>Zirngibl A, 2002</td>
<td>Birth cohort, 4578 children who were followed up at 1 and 2 years of age</td>
<td>Dog, Cat</td>
<td>Doctors diagnosed disease by questionnaire</td>
<td>Dog ownership was inversely associated with the risk of atopic dermatitis whereas exposure to cats was not associated with the risk of atopic dermatitis.</td>
</tr>
<tr>
<td>Nafstad P, 2001</td>
<td>Birth cohort, 2531 who were followed up until the age of 4 years</td>
<td>Dog, Cat, Other</td>
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<td>Analysis showed that exposure to any pet at home reduced the risk of allergic rhinitis but this association was lost when the analysis was performed for dogs or cats separately. Additionally, exposure to any pet reduced the risk of eczema up to the age of 6 months and this observation was confirmed when the analysis was performed for cats or dogs separately.</td>
</tr>
<tr>
<td>Svanæs C, 2003</td>
<td>Random population sample of 13 932 adult participants</td>
<td>Dog, Cat</td>
<td>Questionnaire on respiratory symptoms, serum specific IgE</td>
<td>Keeping cats in childhood was associated with asthma only among atopic subjects. Dogs, whether owned in childhood or adulthood, were associated with asthma among non-atopic subjects.</td>
</tr>
<tr>
<td>Oberle D, 2003</td>
<td>Cross sectional study, 8216 children aged 5-7 years</td>
<td>Dog, Cat, Other</td>
<td>Questions about asthma, rhinitis and eczema</td>
<td>Significant inverse associations were only found between exposure to cats and asthma when a cat was kept at home from the first year of life and it was allowed in the child's bedroom. Exposure to dogs was unrelated to the prevalence of asthma and hay fever.</td>
</tr>
<tr>
<td>Polk S, 2004</td>
<td>Cohort study, 1289 infants who were followed up until 4 years of age</td>
<td>Cat, Dog</td>
<td>Questionnaires about wheezing</td>
<td>Fel d 1 significantly increased the risk of wheezing in 3- and 4-year-olds in comparison to 1-year-olds. Multivariate analysis revealed an interaction between Fel d 1 and maternal asthma among children who wheezed in year 4.</td>
</tr>
<tr>
<td>Phipatanakul W, 2004</td>
<td>Birth cohort, 498 children with a family history of allergy or asthma. Data were collected by periodic interviews through the first year of life</td>
<td>Dog, Cat</td>
<td>Development of eczema</td>
<td>A dog at home reduced the risk for development of eczema.</td>
</tr>
<tr>
<td>Biagini Myers JM, 2010</td>
<td>Birth cohort, 762 infants with at least an atopic father periodically examined until the age of 3 years</td>
<td>Dog, Cat</td>
<td>Information on eczema development</td>
<td>Exposure to dogs decreased the risk of developing eczema at the 1, 2 and 3 years of age, especially for children carrying the CD14-159C/T CC genotype. No association with cat exposure was found.</td>
</tr>
<tr>
<td>Apelbacher C, 2011</td>
<td>Cross sectional, 17 641 children 0-17 years old</td>
<td>Dog, Furry pets</td>
<td>Information on every physician-diagnosed eczema episode</td>
<td>Keeping a dog was inversely associated with eczema development whereas no association was found when ownership of any kind of pets was included in the analysis.</td>
</tr>
</tbody>
</table>
age of six years, which may be interpreted as the result of the possibility of avoidance of maintaining domestic animals in families with an allergic history. However, it is impossible to extract conclusions for cats and dogs separately on the basis of this systematic review.

A more recent meta-analysis concluded that exposure to dogs slightly increases the risk of asthma [OR=1.14, 95% confidence interval (CI)=1.01-1.29], while exposure to cats has a mild protective role (OR=0.79, 95% CI=0.68-0.93). A protective role of exposure to pets as a whole was also identified, regardless of their nature, for the manifestation of allergic rhinitis (OR=0.79, 95% CI=0.68-0.93). However, the previously mentioned pooled analysis of 11 birth cohorts found no association between dog or cat ownership during the first two years of life and asthma or allergic rhinitis at school age.

The results of the different studies are summarized in Table 3. An interesting comment was made by the ECRHS. This survey showed that among those who do not keep cats, while living in communities where cat ownership is common, there is no increased asthma risk. But for individuals who lived in areas with low public exposure to cats, cat ownership was associated with an increased risk of asthma.

In some studies, a family history of atopy seems to affect the association between exposure to pets and asthma. Exposure to cats reduces the risk of wheezing in children aged one to five years of age without a maternal atopic history, but increases the risk of wheezing in children aged three to five years with a positive maternal history of atopy. Moreover, no association was found between dog ownership and wheezing development in toddlers, irrespective of the family history of atopy. Accordingly, the Asthma Multicenter Infants Cohort Study found an interaction between amounts of the Fel d 1 in household dust, maternal asthma, and the occurrence of wheezing at four years of age [relative risk (RR)=2.77, 95% CI=1.19-6.46]. The Tucson study also followed 1246 children from birth until the age of 13 years and concluded that only the presence of a dog as a pet was associated with a reduced risk of wheezing at the age of 13 years, and that there was no family history of asthma. All these studies converge on the conclusion that inheritance is likely to alter the effect of keeping pets with respect to the development of wheezing.

An interesting study from Beijing, where the incidence of asthma is lower than that in Western countries, pointed out that simultaneous ownership of a cat and a dog increased the risk of asthma in children aged 6 to 10 years old (OR=1.5, 95% CI=1.0-2.3). Similar effect was not observed in families that had only a dog or a cat. This statement makes it likely that increased intensity of exposure to allergens by the simultaneous maintenance of a cat or a dog proliferates the risk of wheezing. However, these findings were in total contrast to those from a recent study from New Zealand, the results of which showed that the simultaneous maintenance of a cat or a dog during childhood protects against the onset of atopy at the age of 13 years, while maintaining only a cat or a dog was not protective.

On the other hand, Remes et al underscored the low risk of wheezing in children with continual exposure to dogs. Conversely, removal of the dog by the age of 3 or 6 years led to an increased chance of wheezing. The protective role of the continual presence of pets from birth until the age of 5 to 7 years against the development of wheezing in childhood has also been shown by Oberle et al who included all pets (cats, dogs, rabbits, guinea pigs, hamsters). When they analysed the impact of each type of domestic animals, they found that only continuous exposure to a cat entering a child's bedroom was associated with a reduced risk of wheezing. From these studies, it is likely that a possible protective role of domestic animals depends on early and constant exposure to them.

There were also studies, mostly birth cohorts, which investigated the impact of pets in more than one atopic disorder. In Norway, monitoring of children from birth until the age of 4 years showed that the inclusion of any pet from birth reduced the risk of allergic rhinitis at the age of 4 years and atopic dermatitis for the first 6 months of life. In Sweden, keeping pets from birth is associated with a lower incidence of allergic rhinitis at the age of 7 to 8 years (5.9% vs. 9.5%, P=0.016) and a lower frequency of asthma (3.3% vs. 10%, P<0.001) in children at the age of 12 to 13 years. In Germany, school-aged children with continuous contact with a dog, but not with a cat, during the first year of life was associated with a reduction in allergic rhinitis (OR=0.61, 95% CI=0.39-0.95), eczema (OR=0.76, 95% CI=0.61-0.94) and sensitization to pollen (OR=0.56, 95% CI=0.38-0.80).

Several studies have shown an association between early exposure to pets and a reduced frequency of atopic dermatitis. In Germany, Zirngibl et al found that keeping any domestic animal, especially a dog, was linked to a lower likelihood of developing atopic dermatitis during the first two years of life.

A recent meta-analysis showed that the inclusion of a cat or a dog or any furry pet was associated with a lower risk of atopic dermatitis (OR=0.76, 0.62, 0.79, respectively). However, it also commented on the fact that the studies did not contain information about avoidance behaviour.

One of the latest birth cohort studies, exploring interactions between genetic and environmental factors
that influence the risk of eczema, was published by Biagini Myers et al.\(^{[43]}\) The CCAAPS study, after examining 762 high-risk children, assumed that specific genotypes and early food allergens favour the occurrence of eczema, whereas early dog ownership could work in an inverse way.

The largest cross-sectional population study\(^{[44]}\) from Germany (17 641 children, from birth until 17 years old) determined factors that increase the risk of eczema. Among them, familial allergies (especially a history of eczema), breastfeeding, jaundice and perinatal infection as well as foreign nationality, male gender, and high socioeconomic status act in a positive way, but to a minor extent. Pet keeping was not significantly related to eczema.

Further birth cohort and cross sectional studies are needed to investigate the role of dogs and cats in development of wheezing in relation to its phenotype (transient or late onset), the period of first exposure to a pet, the duration of exposure, the family history of atopy and the possibility of avoidance behavior, as randomized control studies are not a plausible model for this investigation.

It seems that the role of pet ownership for the development of atopic symptoms is not consistent between different studies. There is evidence supporting that dogs may play either an indifferent or a protective role, whereas there are major inconsistencies in the results for pet cats.

### What is the underlying mechanism of any protective association?

Data\(^{[45]}\) support the idea that chronic exposure to high concentrations of cat allergens can promote a modified T-helper 2 (Th-2) response. This response consists of a reduction in specific IgE immunoglobulins and an increase in specific IgG immunoglobulins, especially IgG4. This modified response suggested a form of immunological tolerance, although no protective action of IgG4 has been proven against the onset of atopic disease.\(^{[45-48]}\)

The existence of domestic pets, rural conditions, gas heating and breast-feeding also seem to tilt the balance between T-helper 1 (Th-1) and Th-2 dependent immune-responses toward the Th-1 side.\(^{[44]}\) Duramad et al.\(^{[49]}\) found that exposure to pets and breast-feeding from birth increases the Th1 response using interferon-γ and interleukin-4 as markers of Th-1 and Th-2 responses, respectively.

Many surveys have investigated the interaction between polymorphisms of CD14, TLR 4, CARD 4 and atopy after exposure to microbial molecules. Bottema et al.\(^{[50]}\) after mingling findings from three Dutch cohort studies, detected important roles for interleukin-13 and CD14 polymorphisms, as well as exposure to environmental factors (smoking and animals), in the onset of allergic diseases by measuring IgE (total and specific) at certain ages. Eder et al.\(^{[51]}\) also found that the C allele of CD14/-260 was associated with higher values of total IgE and specific IgE to aeroallergens in children with exposure to pets, whereas the opposite association was found in children with exposure to stable animals. The investigators assumed that children in contact with pets were exposed to microbial products different from those to which children in contact with stable animals were exposed. The genotype at CD14 locus also seems to play a role in the development of atopic dermatitis in infancy,\(^{[52]}\) as infants with the genotype -159TT were less likely to develop atopic dermatitis if they kept a dog at home.

Bisgaard et al.\(^{[53]}\) using findings from two birth cohort studies in Denmark and the United Kingdom, demonstrated that children with deficient filaggrin function were more prone to develop eczema after contacting with a cat. The mechanism explaining this observation remains to be clarified.

It seems that although pet ownership as a contributing factor to the development of atopic symptoms is easily explicable through exposure to allergens, its possible protective role is not fully understood. Possibly, the type of the role of pet ownership in the development of atopy depends on genetic predisposition, which is, to some extent, reflected in the family's atopic history.

### Conclusions

The role of cats or dogs in the development of atopic disorders needs further investigation in terms of the type of atopy, the genetic profile of the individual, the species of pet, and the period and duration of exposure to a pet. There are insufficient data to support either avoiding domestic pet ownership in order to prevent atopy, especially in non-atopic families, or beginning pet ownership in order to reduce the risk of atopy development.

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