

# Role of current and childhood exposure to cat and atopic sensitization

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**Background:** Clinical and population studies have shown that exposure and sensitization to allergens derived from furred pets, particularly cats, represent an important risk factor of allergic respiratory disease and also a significant risk factor for asthma.

**Objective:** In the framework of the multicenter European Community Respiratory Health Survey an analysis of the association of current and childhood exposure to cat with atopic sensitization to cat was conducted.

**Methods:** This study included cross-sectional data from 35 centers representing 16 countries. Altogether, 18,097 subjects were included, of whom 13,509 (75%) provided a blood sample for the measurement of specific IgE. Exposure data and data for potential confounders were extracted from an interviewer-led questionnaire.

**Results:** The prevalence of sensitization to cat (serum specific IgE >0.35 kU/L) was 9%. Among those who did not report allergic symptoms in the presence of pets or house dust, those who owned cats were significantly more likely to be sensitized to cats than were those who did not (odds ratio [95% confidence interval] 1.57 [1.20-2.06]). Childhood exposure to pets including cats was associated with lower sensitization to cats in adulthood, particularly among those with a positive family history of atopy (odds ratio [95% confidence interval] 0.68 [0.51-0.93]). Positive correlations were found between the community prevalence of cat and the prevalences of sensitization to cat, respiratory symptoms, physician-diagnosed asthma, and current asthma medication.

**Conclusions:** Current cat ownership represents a significant risk for sensitization to cat if cats are allowed indoors. Our results support the hypothesis that childhood exposure to pets, including cats, might modulate immunologic mechanisms and reduce sensitization to cat in adulthood. The significant corre-

lation found between the community prevalence of cat ownership and community prevalence of specific sensitization to cat represents the first documentation of such a relationship. (*J Allergy Clin Immunol* 1999;104:941-7.)

**Key words:** Atopy, sensitization, cat allergen, allergy prevention, risk factors, childhood

Clinical and population studies have shown that exposure and sensitization to allergens derived from furred pets, particularly cats, represent an important risk factor of allergic respiratory disease and also a significant risk factor for asthma.<sup>1-3</sup> It is estimated that throughout the Western world between 60% and 70% of households have pets, especially families with children.<sup>2</sup> Because cat allergen can also be detected in public places and homes without current pet occupation, the majority of the population may be at risk for sensitization.<sup>4</sup>

In the framework of the European Community Respiratory Health Survey (ECRHS), we conducted an analysis of childhood and current exposure factors that might be associated with sensitization to cat.

## METHODS

The method of the cross-sectional ECRHS has been fully described elsewhere.<sup>5-7</sup>

This analysis includes data from 35 centers representing 16 countries. Altogether, 18,097 subjects were included, of whom 13,509 (75%) provided a blood sample.<sup>5</sup>

Data analysis was performed for specific IgE cutoff levels of >0.35 kU/L (CAP [Pharmacia & Upjohn] class 1) and >0.70 kU/L (CAP class 2), yielding similar results. We present results for a cut-off value of >0.35 kU/L, unless stated otherwise.

Because those who have symptoms on exposure to an allergen may avoid exposure, the relationship between allergen exposure and sensitization that is derived from cross-sectional studies may be difficult to interpret. Information was available on respiratory symptoms (cough, wheeze, chest tightness, shortness of breath, stuffy nose, watering eyes) in the presence of animals (eg, cats, dogs, horses), feathers (eg, pillows) or house dust (dust mite), and we used this to stratify the population in 2 groups: (1) subjects reporting respiratory symptoms if exposed to pets/feathers/house dust who might avoid keeping cats and (2) subjects without respiratory symptoms when exposed to pets/feathers/house dust who were unlikely to avoid keeping cats as pets. Logistic regression models were used to assess the effects of the exposure variables on serum-specific IgE to cat. Multiple linear regression was used to assess the associations between community prevalence of cat and age/sex-standardized community prevalence of specific sensitization to cat or symptoms (physician-diagnosed asthma, current asthma medication, respiratory symptoms

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Supported by grants of Novartis Foundation, Swiss Academy of Medical Sciences (H-P. R.) and by a senior scientist fellowship (No. 32048922.96) of the Swiss National Science Foundation (N. K.).

Received for publication Dec 28, 1998; revised July 19, 1999; accepted for publication July 21, 1999.

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**TABLE I.** Characteristics of ECRHS study population (total number of subjects 13,509, 35 centers from 16 countries)

Variable	No current cat ownership (n = 10,594 [78.4%])	Current cat ownership (n = 2915 [21.6%])	Total (n = 13,509 [100%])
Male (%)			
Age (%)	51.1	46.9*	50.2
20-<25 y	14.6	13.7*	14.4
≥25-<35 y	41.0	36.6*	40.0
≥35-44 y	44.5	49.7*	45.6
Respiratory symptoms to pets/house dust (%)†	35.6	39.8*	36.5
Sensitization to cat IgE (%)			
>0.35 kU/L	8.7	9.9	9.0
>0.70 kU/L	6.6	7.4	6.7
Family history of atopy	30.4	31.9	30.8
Mother asthma (%)	6.0	6.5	6.1
Father asthma (%)	6.1	5.4	5.9
Mother allergy (%)	18.4	21.5*	19.1
Father allergy (%)	13.7	14.5*	13.9
Childhood pet ownership			
Cat keeping	42.5	64.8*	47.3
Dog keeping	46.7	54.5*	48.4
Rabbit keeping	24.0	31.0*	25.5
Horse keeping	10.0	12.0*	10.4
Cat, dog, rabbit, or horse	66.5	81.2*	69.7

\* $P < .05$  when comparing with no current cat ownership (chi-square test).

†Respiratory symptoms to pets/house dust include cough, wheeze, chest tightness, shortness of breath, stuffy nose, watering eyes.

#### Abbreviations used

CI: Confidence interval  
ECRHS: European Community Respiratory Health Survey  
OR: Odds ratio

in the presence of animals). Community prevalences were transformed to the logit scale before regressing them against community-level covariates. This was in keeping with the assumptions of normality and homoscedasticity of residuals and also led to a slight improvement of fit compared with the regression models for untransformed prevalence data. Number of siblings was categorized as 0, 1, 2, 3, and 4 or more. Family history of atopy was defined as one or more of asthma or allergy in at least one parent or sibling as reported by the participants.<sup>8</sup> In logistic regression analysis, adjustments were made for age, sex, smoking habits, current occupation, study center, family size, bedroom sharing in childhood, family history of atopy, and respiratory infection before age 5 years. The relevance of these factors with respect to atopic sensitization has been shown previously in the ECRHS population.<sup>9</sup> Potential heterogeneity between centers in the effect of exposure was studied by meta-analysis according to DerSimonian and Laird.<sup>10</sup> Because of reduced power, which resulted from stratification by each center, adjustments were made only for age, sex, and smoking habits (former smokers pooled with smokers), and stratification was performed by respiratory symptoms (cough, wheeze, chest tightness, shortness of breath) in the presence of animals. Data for Grenoble, Huelva, and Galdakao could not be analyzed because of reduced power as a result of stratification. All analyses were carried out with the statistical software Stata.<sup>11</sup>

## RESULTS

### Sociodemographic characteristics of the ECRHS study population

The distribution of sociodemographic factors is listed in Table I. Potential confounding factors with significant

associations to exposure are shown and have been used for adjustments in logistic regression models.

### Distribution of prevalences of cat ownership and respiratory symptoms in relation to cat-specific IgE across 35 ECRHS centers

For each of the 35 ECRHS centers, prevalences of keeping cats are listed together with age/sex standardized prevalences of cat-specific IgE and respiratory symptoms in the presence of pets/house dust (Table II). Prevalences of asthma and asthma medication have been published previously.<sup>7</sup>

### Current exposure to cat and specific sensitization to cat

A significant positive association between current cat ownership and specific sensitization was found in subjects reporting no respiratory symptoms to pet/house dust for the crude odds ratio (OR) as well as for the adjusted OR (Table III). Meta-analyses of this association across 33 centers revealed similarity of the effect estimates with the results in Table III and no significant heterogeneity ( $P = .53$ ). No such association could be found in subjects with respiratory symptoms to pet/house dust, suggesting selective avoidance of pets because of health problems related to pets (Table III).

Sensitization to cat may follow a gradient across different levels of exposure. Keeping cats at home indoors (high exposure) was significantly related to specific sensitization to cat in subjects reporting no respiratory symptoms to pet/house dust (Table III). Keeping cats outside only (low exposure) was not significantly associated with specific sensitization to cat (Table III).

**TABLE II.** Study centers in relation to prevalence of cat ownership and prevalences of sensitization to cat (specific IgE) or respiratory symptoms (N = 13,509)

Country	Center	No.	Prevalence of cat ownership (%)	Prevalence of specific IgE to cat (%)*	Prevalence of respiratory symptoms (%)†
Iceland	Reykjavik	516	12.5	7.5	24.9
Norway	Bergen	749	15.3	7.8	28.1
Sweden	Goteborg	569	15.7	13.2	32.5
	Umea	411	20.1	14.1	35.3
	Uppsala	521	22.8	14.3	35.8
Netherlands	Bergen-op-zoom	417	22.8	5.8	27.5
	Geleen	355	15.0	10.3	34.6
	Groningen	351	29.9	10.1	33.8
Belgium	Antwerp city	265	25.1	9.5	49.0
	Antwerp south	325	22.8	9.4	44.0
Germany	Erfurt	716	8.0	8.1	21.2
	Hamburg	772	19.1	11.5	35.0
Switzerland	Basel	563	20.1	14.4	39.4
France	Bordeaux	512	21.3	10.1	51.0
	Grenoble	430	16.5	8.0	50.5
	Montpellier	359	21.3	8.9	41.5
	Paris	554	17.2	9.5	42.7
United Kingdom	Caerphilly	318	23.8	8.9	39.3
	Cambridge	187	24.2	13.1	49.0
	Ipswich	358	30.9	11.7	30.0
	Norwich	359	32.8	10.0	45.9
Ireland	Dublin	230	11.1	7.6	39.4
Italy	Pavia	249	29.4	4.7	20.6
	Turin	175	14.9	6.0	41.8
	Verona	332	18.8	4.9	41.1
	Albacete	392	5.3	2.7	23.3
Spain	Barcelona	175	9.2	14.0	10.2
	Galdakao	355	11.1	2.9	9.2
	Huelva	215	3.7	2.9	32.5
	Oviedo	243	9.9	4.2	22.4
	Christchurch	266	59.3	13.5	50.7
New Zealand	Hawkes Bay	141	68.6	8.6	56.3
	Wellington	297	52.7	7.5	55.4
	Melbourne	520	35.0	10.5	54.1
United States	Portland	312	45.2	13.1	50.1

\*Age/sex standardized prevalence (<0.35 kU/L).

†Age/sex standardized prevalence of respiratory symptoms (cough, wheeze, chest tightness, shortness of breath, stuffy nose, watering eyes) in the presence of pets/feathers/house dust.

### Childhood exposure to cat and specific sensitization to cat

A tendency for a negative association between cat keeping in childhood and specific sensitization in adulthood was found in the unstratified data set as well as in subjects without respiratory symptoms to pet/house dust (Table IV). Stratification by current respiratory symptoms to pet/house dust was used to assess a possible health selection bias as mentioned earlier.

Stratification by positive or negative family history of atopy was performed to evaluate the influence of this risk factor on the association between childhood exposure to cat and adult sensitization to cat (Table IV). Subjects reporting a family history of atopy were less likely

to have specific IgE against cat as adults, if they had had a cat in childhood (Table IV). Meta-analyses of this association across 33 centers revealed similarity of the effect estimates with the results in Table IV, and no significant heterogeneity ( $P = .75$ ). Because antigenic cross-reactivity among different pets has been demonstrated, it was of interest to study the influence of childhood keeping of cat and other animals on the current specific sensitization to cat.

Sensitization to cat in adulthood was significantly negatively associated with childhood exposure to cat and one or more other animal species (Table IV). After stratification, this association remained significant in subjects reporting no respiratory symptoms to pet/house dust as well as in subjects with a family history of atopy.

**TABLE III.** Associations between cat specific IgE (>0.35 kU/L) and current cat ownership among subjects with and without respiratory symptoms to pet/house dust (family history of atopy including one or more of asthma or allergy in at least one parent or sibling)

Type of current cat ownership	Total sample	Respiratory symptoms to pet/house dust	
		No	Yes
Cat ownership*	1.14 (1.00-1.32)	1.45 (1.13-1.86)	0.93 (0.78-1.11)
N (cat owners/total)	2,915/13,507†	1,754/8,572†	1,161/4,935†
Cat ownership‡	1.13 (0.96-1.32)	1.57 (1.20-2.06)	1.00 (0.83-1.21)
N (cat owners/total)	2,903/13,426†	1,739/8,476†	1,155/4,912†
Cat allowed indoors‡	1.14 (0.97-1.34)	1.63 (1.23-2.17)	1.00 (0.82-1.23)
N (cat owners/total)	2,559/13,426†	1,540/8,476†	1,013/4,912†
Cat stay outdoors only‡	0.82 (0.49-1.38)	0.88 (0.32-2.46)	0.79 (0.43-1.45)
N (cat owners/total)	254/13,426†	148/8,476†	106/4,912†

\*OR (95% confidence interval [CI]): crude.

†Total N reduced because of missing information in covariates.

‡OR (95% CI) adjusted for age, sex, smoking, occupation, study center, family size, bedroom sharing, respiratory infection before age 5 years, family history of atopy, and childhood pets.

**TABLE IV.** Associations between cat-specific IgE (>0.35 kU/L) and childhood exposure to cat among subjects in different subgroups (family history of atopy including one or more of asthma or allergy in at least one parent or sibling)

	Childhood exposure to cat* (OR [95% CI])†	Childhood exposure to cat and one or more other pet species: dog, rabbit, horse‡ (OR [95% CI])†
Unstratified data (n = 13,426)	0.94 (0.82-1.08)	0.83 (0.67-1.02)
Stratification by		
A: Respiratory symptoms to pet house dust:		
No (n = 8,476)	0.87 (0.68-1.13)	0.65 (0.45-0.93)
Yes (n = 4,912)	0.96 (0.81-1.14)	0.95 (0.73-1.24)
B: Family history of atopy:		
No (n = 7,666)	1.11 (0.92-1.36)	0.92 (0.69-1.23)
Yes (n = 5,692)	0.77 (0.63-0.94)	0.73 (0.53-0.99)

\*Reference group: no cat in childhood.

†Estimated by logistic regression adjusted for age, sex, smoking, occupation, study center, family size, bedroom sharing, respiratory infection before age 5, family history of atopy, current pet ownership.

‡Reference group: none of the above.

### Community prevalence of cats in relation to sensitization to cat (specific IgE), respiratory symptoms, physician-diagnosed asthma, and current asthma medication

Regression analysis involving all 35 centers was used to investigate the association between the community prevalence of cat in relation to the age/sex standardized prevalence of specific sensitization to cat. Sensitization to cat by community exposure to cat may be most relevant for subjects not keeping cats because subjects keep-

ing cats are already exposed to significant levels of cat allergens. Therefore community prevalence of sensitization to cat was calculated excluding cat owners and regressed against the community prevalence of cats. An increase in the community prevalence of keeping cats of 10% was associated with an estimated increase of community prevalence of cat-specific IgE of 13% (>0.35 kU/L), OR 1.13 (1.0-1.29), or of 19% (>0.70 kU/L), OR 1.19 (1.05-1.36), respectively.

The community prevalence of sensitization to cat (subjects without cat ownership were included) was regressed against the community prevalence of respiratory symptoms in the presence of pets/house dust, physician-diagnosed asthma, and current asthma medication. Significant positive associations were found (Table V). These relationships were strengthened by use of 0.70 kU/L as the cutoff value for a positive test result.

Positive associations were also found between the community prevalence of cat and the community prevalence of respiratory symptoms, physician-diagnosed asthma, and current asthma medication (subjects without cat ownership were included) (Fig 1).

### DISCUSSION

Domestic animals represent one of the most important sources of indoor air allergens.<sup>12,13</sup> The current study focuses on sensitization to cat (specific IgE), which was shown to be an important risk factor for the development of asthma.<sup>3</sup> Sensitization to cat allergen was found to be increased 1.6-fold among current cat owners without respiratory symptoms to pet/house dust. These results confirm current opinion about the allergenicity of cat epithelium.<sup>2,12,14,15</sup> In contrast, no such association could be demonstrated among subjects with respiratory symptoms to pet/house dust.

These results suggest that selective avoidance and removal of cat might lead to distortions of cross-sectional associations between current cat ownership and sensitization to cat. Respiratory symptoms (chronic cough,

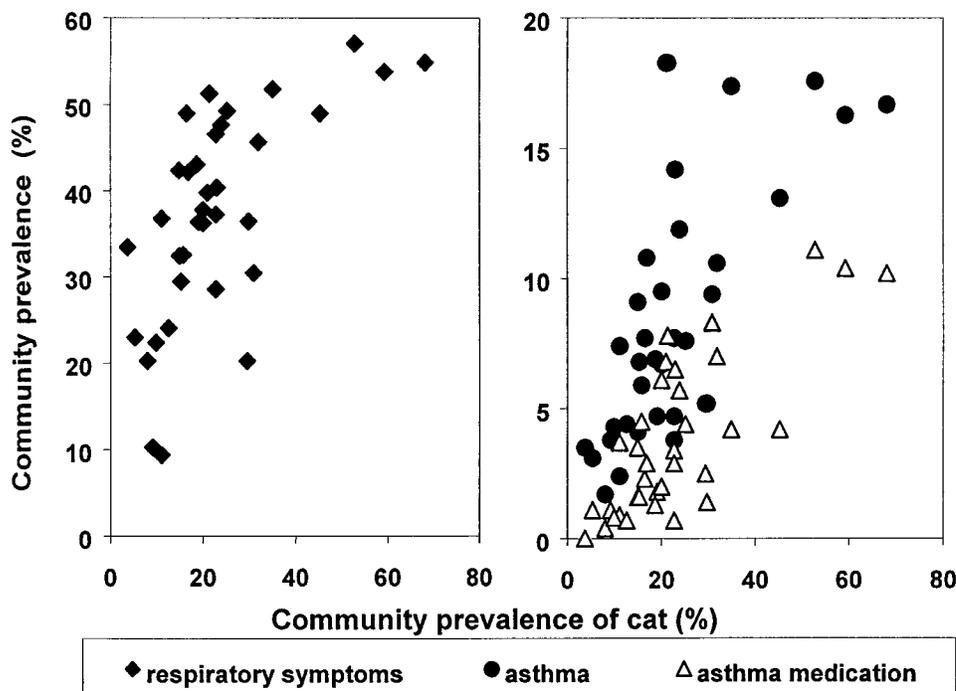


FIG 1. Community prevalence of cat in relation to community prevalence (age/sex standardized prevalences including subjects without cat ownership) of respiratory symptoms (respiratory symptoms in the presence of pets/feathers/house dust), physician-diagnosed asthma, and current asthma medication.

TABLE V. Associations between community prevalence of cat specific IgE and community prevalence of respiratory symptoms, physician-diagnosed asthma, and current asthma medication across 35 centers\*

Community prevalence of symptoms	Community prevalence of specific IgE to cat†	
	>0.35 kU/L (OR [95% CI])‡	>0.70 kU/L (OR [95% CI])‡
Respiratory symptoms in the presence of pets/house dust†	1.73 (1.01-2.49)	2.78 (1.60-4.84)
Physician-diagnosed asthma†	1.94 (1.08-3.49)	2.49 (1.29-4.82)
Current asthma medication†	2.33 (1.01-5.35)	2.87 (1.11-7.40)

\*Only subjects without cat ownership were included.

†Age/sex standardized prevalence.

‡OR for 10% increase in community prevalence of specific IgE to cat.

chronic wheeze) were identified as major reasons for pet avoidance or removal in a study addressing the question of health selection bias, supporting the validity of our approach.<sup>1</sup>

Measures to limit exposure to pets in individuals with sensitivity to pets would include keeping the pet outside and not allowing the pet into the bedroom.<sup>16</sup> Our results demonstrate a significant risk of sensitization to cats when they are allowed indoors. To allow the cat into the bedroom did not further increase the risk of sensitization (not shown). This could be explained by marked dispersal of cat antigens.<sup>17</sup>

Interestingly, keeping cats outside was not associated with a higher risk of sensitization to cats, suggesting that this type of cat ownership may reduce the exposure to cat allergens. Munir et al<sup>4</sup> have shown that allergen levels from homes without cats were 100 to 1000 times lower than those found in homes with cats. It has been suggested that exposure to pet antigens during early life may

increase the risk for development of subsequent sensitization in adolescence.<sup>18</sup> In our study, however, childhood exposure to cats was associated with a significant decrease in sensitization to cats in adulthood, particularly among those with a positive family history of atopy.

A cross-sectional study has potential biases. Assessment of exposure to cats and other animals was based on individual recall, which might be biased. A health selection bias could weaken or possibly invert the dose-response relationship between childhood exposure to cat and specific sensitization to cat, although it should be noted that the compliance of men who had been diagnosed as being allergic to cats or dogs and advised by their physicians to remove their pets was only 21% and the majority of subjects with asthma who had been advised to get rid of domestic animals because of allergic symptoms or immediate skin reactivity reintroduced a domestic animal into their environment in subsequent years.<sup>13,19</sup>

We have dealt with possible pet avoidance by stratifying the analysis according to either current respiratory symptoms in the presence of pets/house dust or according to family history of atopy. No significant differences in the prevalence of cat keeping in childhood were found between subjects with or without a family history of atopy, indicating no general tendency to renounce cat ownership among subjects with a family history of atopy.

Despite these limitations of the cross-sectional design, plausible immunologic explanations for our findings exist. Immune responses, which underlie the expression of atopy in adulthood, are believed to be initiated in infancy and childhood.<sup>20</sup> High-dose exposure to pet allergens through close contact with pets during the first years of childhood may induce deviation of immune responses toward the  $T_H1$  cytokine phenotype. Antigen dose has been implicated as an important factor in the  $T_H1$ - $T_H2$  decision.<sup>21,22</sup> In addition, pet ownership during childhood may result in increased microbiologic exposure through animal bites and scratches, flea bites, or other modes of transmission.<sup>23-25</sup> Cat and dog bites and scratches have been shown to frequently contain a complex microbiologic mix including *Toxoplasma* or *Bartonella henselae*.<sup>26-28</sup> These infections might enhance  $IFN-\gamma$  production and  $T_H1$  immunity, with particular relevance for children with a family history of atopy shown to have defective neonatal  $IFN-\gamma$  production.<sup>29,30</sup> In line with our results, childhood exposure to pets was found to be associated with a lower frequency of allergic rhinitis in schoolchildren with a parental history of allergy.<sup>31</sup>

To what extent childhood exposure to multiple animal species is associated with a rural lifestyle or poor hygiene in childhood could not be examined because of lack of childhood sociodemographic information.<sup>32,33</sup>

Numerous attempts have been made to prevent atopic disorders by interventions of allergen avoidance in childhood. Interestingly, in prospective studies the initial benefit of cat and dog avoidance regarding atopic sensitization has diminished or disappeared entirely during long-term follow-up, and there has been no protection against asthma and allergic rhinitis resulting from avoidance measures, including the removal of pets.<sup>18,34-38</sup> IgE antibodies to food and environmental antigens are detected during the first years of life but are subsequently down-regulated.<sup>39-41</sup> These results stress the need for long-term surveillance of the kinetics of specific IgE to inhalant allergens and of asthma and allergic diseases in prospective studies. New primary prevention strategies have been proposed and are based on the induction of immune deviation toward a  $T_H1$ -type immune response to inhalant allergens (eg, by administering allergen and a suitable adjuvant in a vaccination program).<sup>42,43</sup> This view was supported by recent studies that suggest that a search for factors that enhance the induction of tolerance would be more worthwhile than concentration on factors that increase sensitization.<sup>30,44</sup>

Because significant levels of cat antigens can be detected in public places and in homes where cats have never been kept, the majority of the population may be at

risk of exposure.<sup>17</sup> The significant correlation found between the community prevalence of cat and the community prevalence of specific sensitization to cat among subjects not owning a cat is consistent with the fact that it is common to find subjects allergic to cat who have never lived with a cat.<sup>4,45</sup> Persons exposed to cats might bring cat allergens into homes and public places on their clothing. This possibility is supported by recent studies showing that the total amount of cat allergen in classrooms and day nurseries was related to the number of teachers and children keeping cats at home.<sup>46</sup> The positive associations found between the community prevalence of cat and the community prevalence of specific sensitization to cat, respiratory symptoms, physician-diagnosed asthma, and current asthma medication are in line with other evidence demonstrating the importance of cat allergens with respect to the development, exacerbation, and severity of atopic diseases.<sup>3,15,35,47,48</sup> In line with our results, the prevalence of skin tests for cat antigens correlated positively with the prevalence of asthma and allergic diseases in 3 Chinese cities.<sup>8</sup>

Recent studies, taking selection mechanisms behind pet keeping into consideration, support our findings that pet exposure during childhood was associated with a lower prevalence of specific IgE on skin prick test as well as with a lower prevalence of allergic rhinitis and asthma in school children (Roost, unpublished results from the Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution).<sup>31</sup>

Long-term prospective studies avoiding recall biases and improving exposure assessment would be needed to confirm our findings, to evaluate the clinical relevance, and to be able to decide about sound public health strategies.

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