

Relevance of specific IgE antibody titer to the prevalence, severity, and persistence of asthma among 19-year-olds in northern Sweden



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Background: Although sensitization to indoor allergens is strongly associated with asthma, there are questions as to how this relates to asthma symptoms.

Objective: We sought to study the relevance of IgE antibodies to cat and dog allergens in an area in which (1) the climate discourages cockroach, fungal, and mite growth and (2) dander allergens are known to be present in schools and houses without animals.

Methods: IgE to 8 allergens was tested in 963 sera from a population-based study on 19-year-olds, and associations with asthma symptoms, diagnosis, and treatment were examined. In positive sera IgE to specific cat and dog allergens was also assayed. **Results:** IgE specific for animal dander had the highest prevalence and strongest relationship to asthma diagnosis.

Furthermore, asthma severity, as judged by the frequency of symptoms and use of treatment, was directly associated with the titer of IgE antibodies to animal dander. Among the 103 subjects who had current asthma at age 19 years, 50 had asthma before age 12 years. Among those 50, the odds ratios for asthma related to any IgE antibodies to animal dander or high-titer IgE

antibodies (≥ 17.5 IU/mL) were 9.2 (95% CI, 4.9-17) and 13 (95% CI, 6.9-25), respectively. In multivariable analysis IgE antibodies to Fel d 1 and Can f 5 were each associated with current asthma.

Conclusion: High-titer IgE antibodies to cat and dog allergens were strongly associated with the diagnosis, severity, and persistence of asthma; however, a large proportion of patients with current asthma did not live in a house with a cat or dog. (J Allergy Clin Immunol 2016;138:1582-90.)

Key words: IgE titer, IgE antibodies, mammalian allergen, asthma severity, cat ownership

Asthma in children older than 3 years of age and young adults is strongly associated with sensitization to common inhalant allergens. This sensitization can be detected by skin tests or measurement of serum IgE antibodies. Generally in epidemiology and clinical studies, results from these tests have been analyzed as positive or negative rather than as a quantitative measure of risk.¹⁻⁴ The allergens that are most strongly associated with asthma are perennial allergens, such as dust mite, cat, dog, cockroach, and *Alternaria* species.⁵⁻⁸ Evaluating the relationship between sensitization and asthma is made complex by the fact that many patients are sensitized to more than 1 source of allergen.⁹⁻¹¹ This can also make it difficult to evaluate either the effects of cat ownership or the modulating effects of specific IgG antibodies on asthma symptoms.

The northernmost province of Sweden, Norrbotten, reaches above the Arctic Circle, where the prolonged cold winters lead to dry indoor environments. As a result, houses do not become contaminated with dust mites.¹²⁻¹⁴ In addition, the climate is inhospitable to cockroaches, ticks, and fungi, such as *Alternaria* species. In keeping with the low levels of exposure, children raised in Norrbotten do not become allergic to many of the allergens that are strongly correlated with asthma in other climates.¹³⁻¹⁶ Following a large population of children through their primary and secondary school years, we have reported that sensitization identified either by a positive skin test result or by the presence of measureable IgE antibodies to cat and dog allergens was a major risk factor for a physician's diagnosis of asthma at age 12 years.^{13,14} In addition, in keeping with other studies, we demonstrated that the presence of an animal in the home was not associated with increased prevalence or titer of IgE antibodies to animal allergens.¹⁴

The subjects in this cohort ($n = 3430$) were followed to age 19 years. Serum was collected from a representative sample of the cohort ($n = 963$). We report here the results of serum IgE antibody assays to a range of inhalant allergens. In addition, we carried out studies on IgE antibodies to components of cat and dog allergen

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extract, as well as assays of IgG and IgG₄ antibodies to the major cat allergen Fel d 1. The present study was designed to investigate the hypothesis that the titers of IgE to cat- and dog-derived allergens were significantly associated with the prevalence, persistence, and severity of asthma at age 19 years. Additionally, our analysis addressed the effects of cat ownership in an environment in which most other perennial allergens are not relevant to asthma.^{14,17-21}

METHODS

Patient population

Subjects were enrolled through the research program Obstructive Lung Disease in Northern Sweden in a prospective, population-based cohort, which has been ongoing since 1996 and includes data from 3430 children (97% response rate).^{12,22} In 1996, all children in the first- and second-grade classes (age 7 and 8 years) in 3 municipalities in northern Sweden were invited to participate in a prospective study.²³ The questionnaire used was based on the International Study on Asthma and Allergies in Childhood design, with additional questions about asthma, rhinitis, and eczema, and a broad screening for potential risk factors.^{12,15} The cohort was followed by repeated questionnaires until graduation from high school at age 19 years in 2006 or 2007. At age 19 years, 2861 responded (83% of those enrolled in 1996). Both in 2006 and 2007, the follow-up included a questionnaire, lung function test, and skin prick test. In addition, in 2007, all participants in Kiruna and Lulea were invited to donate blood, and 963 participated (89% of those invited, see Table E1 in this article's Online Repository at www.jacionline.org for details of the population). The study was approved by the regional ethics committee of Umea University and the Human Investigation Committee at the University of Virginia.

ImmunoCAP IgE assays

Total and specific IgE antibody levels were measured by using either commercially available ImmunoCAP (Phadia Thermo-Fisher, Portage, Mich) or a modification of the assay with streptavidin on the solid phase.^{13,24} The assays were performed with the ImmunoCAP 250 instrument, and results were expressed as international units per milliliter, with the international units both for specific and total IgE being approximately 2.4 ng. For specific assays, the standard cut point for a positive reaction was 0.35 IU/mL. The streptavidin CAP technique was used to measure IgE antibody levels to galactose- α -1,3-galactose and the cat allergen Fel d 1, with approximately 1 μ g of biotinylated antigen added to each CAP before adding 40 μ L of serum.²⁴ Sera were tested for IgE antibodies to dust mite (*Dermatophagoides pteronyssinus*), cat dander, horse dander, both dog epithelium and dander, timothy grass, common silver birch, and *Alternaria* species, as well as with ImmunoCAPs provided by Thermo Fisher for specific allergen components of cat and dog, including the lipocalins Fel d 4, Can f 1, and Can f 2; the albumins Fel d 2 and Can f 3; and the dog prostatic kallikrein Can f 5 (see Table E2 in this article's Online Repository at www.jacionline.org).²⁵⁻²⁸

Radioimmunoassays for IgG and IgG₄ antibodies to Fel d 1

Precipitation assays with radiolabeled Fel d 1 were carried out by using established techniques to precipitate with either goat anti-IgG specific for all IgG subclasses or monoclonal anti-IgG₄, followed by precipitation of the mAb with goat anti-mouse IgG. The details of these assays have been published previously and are presented in more detail in the Methods section in this article's Online Repository at www.jacionline.org.^{14,18,29,30}

Statistical analyses

Differences in the prevalence of specific IgE (≥ 0.35 and ≥ 17.5 IU/mL) and pet ownership markers between groups were evaluated by using univariable analysis with χ^2 or Fisher exact tests, where appropriate, and also presented as

odds ratios with 95% CIs. The outcome variables used were physician-diagnosed asthma, wheeze, and use of asthma medication. A multivariable binary logistic regression was used to analyze the relationship of multiple specific IgE sensitivities to a physician's diagnosis of asthma. Statistical analyses were performed with Stata/IC 11 (StataCorp, College Station, Tex) and GraphPad Prism 6 (GraphPad Software, La Jolla, Calif) software and visualized with R version 3.0 and GraphPad Prism 6 software.

RESULTS

Relevance of IgE antibody titers to prevalence, severity, and persistence of asthma

The prevalence of positive (≥ 0.35 IU/mL) or high-titer IgE antibodies (≥ 17.5 IU/mL) to 9 allergens was analyzed in relation to a physician's diagnosis of asthma at age 19 years (Table I). By using univariable (ie, unadjusted) odds ratios, high titers of IgE to mammalian allergens and also to birch pollen were strongly associated with asthma ($P < .001$). The results for cat, dog, and horse showed extensive collinearity, and because of this, we carried out logistic regression analysis for cat and dog allergens separately or for any mammal in relation to the pollens (Table II and see Table E7 in this article's Online Repository at www.jacionline.org). The results are highly significant for dog or cat dander or mammalian allergens, with consistently higher odds ratios for high-titer IgE antibodies. For the 3 allergens with the strongest associations with asthma, we also analyzed the effect of IgE antibodies as a continuous variable (Fig 1). Those results show a strong relationship for either cat or dog dander and a weaker but still highly significant relationship for birch pollen, as well as a negative result for dust mite. In keeping with the results at age 11 years, only a few sera were positive for IgE to dust mite or *Alternaria* species (Table I and Fig 1).^{14,15} The relationship between the titer of IgE antibodies to animal dander and the severity of disease was also analyzed in relation to either frequency of symptoms (Fig 2, A) or use of treatment (Fig 2, B). The results show a strong association between the titer of IgE antibodies and either symptoms or treatment requirement at age 19 years. Similar results were seen with sensitization to cat or dog alone (see Fig E1 in this article's Online Repository at www.jacionline.org).

Overall, 79 (54%) of the subjects who reported a physician's diagnosis of asthma at age 19 years had positive results to 1 or more of the mammalian allergens tested. However, a surprisingly large number ($n = 45$) had negative results to all the allergens tested. We have previously reported in the whole cohort that some of the students who received a diagnosis of asthma between age 11 and 19 years had transient episodes only.¹² To investigate this further, we divided the subjects into those with persistent asthma, late-onset asthma, and never asthma (see Table E1, B, and Fig 3, A). In addition, the results were analyzed for current asthma (ie, subjects with a diagnosis of asthma who reported either use of treatment for or symptoms of asthma) in their 19th year (Fig 3, B and Table III). For the 50 subjects with current asthma who had the diagnosis before age 11 years, 84% were sensitized to at least 1 allergen, 70% had IgE antibodies to a mammalian allergen, and 40% had high-titer IgE antibodies to a mammalian allergen; odds ratios compared with subjects who never had an asthma diagnosis were 9.7 (95% CI, 4.5-21), 9.2 (95% CI, 4.9-17), and 13 (95% CI, 6.9-25), respectively (see Table E3 in this article's Online Repository at www.jacionline.org for details of groups).

Sera were also tested for total serum IgE levels, and the results show the expected relationship between total serum IgE levels

TABLE I. Univariable analysis of asthma based on a physician's diagnosis for different levels of IgE antibodies to inhalant allergens

Allergen	IgE titer by class in students with or without* asthma†			Odds ratios for asthma (based on physician's diagnosis)		
	Negative	Class 1-3	Class 4-6	Any IgE antibody, >0.35 IU/mL (≥class 1)	IgE antibody 0.36-17.5 IU/mL (class 1-3)	IgE antibody >17.5 IU/mL (class 4-6)
Cat dander	80/664	46/119	23/31	3.8 (2.6-5.5)‡	3.2 (2.1-4.8)‡	4.6 (2.6-8.2)‡
Dog dander	83/689	45/115	21/10	4.4 (3.0-6.4)‡	3.2 (2.1-4.9)‡	13.2 (6.1-28.7)‡
Dog epithelium	116/763	26/46	7/5	4.3 (2.6-6.9)‡	3.7 (2.2-6.2)‡	8.0 (2.5-25.5)‡
Horse	101/720	35/81	13/13	3.6 (2.4-5.5)‡	3.1 (2.0-4.8)‡	5.9 (2.7-13.0)‡
Any mammal	70/646	45/128	34/40	4.3 (3.0-6.2)‡	3.2 (2.1-4.9)‡	5.7 (3.5-9.4)‡
Dust mite	137/751	12/63	0/0	1.0 (0.5-2.0), <i>P</i> = .88	1.0 (0.5-2.0), <i>P</i> = .88	—
<i>Alternaria</i> species	145/803	4/11	0/0	2.0 (0.6-6.4), <i>P</i> = .27	2.0 (0.6-6.4), <i>P</i> = .27	—
Birch tree	89/661	40/107	20/46	2.9 (2.0-4.2)‡	2.8 (1.8-4.2)‡	2.6 (1.5-4.5)‡
Timothy grass	97/647	37/115	15/52	2.1 (1.4-3.0)‡	2.1 (1.4-3.3)‡	1.6 (0.9-3.0), <i>P</i> = .10

*Numbers before and after the forward slash indicate students with and without asthma, respectively.

†As indicated by a physician's diagnosis of asthma.

‡*P* < .001.**TABLE II.** Multivariable binary logistic regression of the relationship of a physician's diagnosis of asthma to IgE antibodies to cat dander, grass pollen, and birch pollen (A); dog dander, grass pollen, and birch pollen (B); any mammal and both pollens (C); and any mammal and any pollen (D)

	Any positive result (>0.35 IU/mL)	High titer (>17.5 IU/mL)
A.		
Cat dander	3.0 (1.9-4.7)†	3.9 (2.2-7.1)†
Grass pollen	0.93 (0.57-1.5)	1.2 (0.61-2.3)
Birch pollen	1.7 (1.0-2.9)*	1.8 (0.99-3.4)
B.		
Dog dander	3.5 (2.2-5.6)†	11.4 (5.2-25.1)†
Grass pollen	0.98 (0.60-1.6)	1.2 (0.59-2.3)
Birch pollen	1.5 (0.89-2.5)	1.8 (0.95-3.4)
C.		
Any mammal	3.7 (2.4-5.8)†	5.1 (3.0-8.6)†
Grass pollen	0.91 (0.56-1.5)	1.1 (0.56-2.1)
Birch pollen	1.4 (0.86-2.4)	1.6 (0.85-3.0)
D.		
Any mammal	3.8 (2.4-5.8)†	4.9 (2.9-8.1)†
Any pollen	1.3 (0.83-2.0)	1.8 (1.1-3.0)*

**P* < .05.†*P* < .001.

and allergic asthma (see Table E4 in this article's Online Repository at www.jacionline.org). The geometric mean total IgE level for subjects with negative IgE antibody results was low (18.1 IU/mL), and this value was not significantly different among those with negative IgE antibody results and a diagnosis of asthma. Among the subjects who had negative serum specific IgE antibody assay results, there were a few (*n* = 17/576 [2.9%]) who had total serum IgE levels of 200 IU/mL or greater. These sera were assayed for a wider range of allergens, but no significant positive results were identified.

Relevance of cat, dog, or both in the home

In this cohort 279 subjects reported having a cat at home, 506 had a dog, and 176 had both, and 354 homes contained neither animal. Cat ownership had a modest negative effect on the prevalence of IgE antibodies to cat (*P* < .05) for IgE levels of 0.35 IU/mL or greater (see Table E5 in this article's Online Repository

at www.jacionline.org). By contrast, reported dog ownership had no significant effect on IgE antibodies to dog. Among the subjects with current asthma who were sensitized to cat or dog (*n* = 51), 50% were living in a home with no animals. Of the 46 cat-sensitized subjects, 39 (85%) were living in a home without a cat, and 22 (48%) reported no animals at home.

By using established techniques, IgG antibodies to Fel d 1 were assayed in all 963 sera. Positive results (≥150 U/mL) were analyzed as high titer (≥500 U/mL) and low titer (150-500 U/mL).¹⁸ Cat ownership was associated with a high prevalence of both high- and low-titer IgG antibodies (*P* < .001), as well as a modest decrease in IgE antibody levels (Fig 4).³¹ Surprisingly, the presence of IgG antibodies showed no significant effect on symptoms of asthma when analyzed relative to different titers of IgE antibodies (see Fig E2, A, in this article's Online Repository at www.jacionline.org). When the titers of IgG antibodies were analyzed relative to those of subjects requiring often or daily treatment, there was a lower prevalence in those with high-titer IgG antibodies, although the effect was not significant (*P* = .12; see Fig E2, B). The sera that were positive for IgG to Fel d 1 were also assayed for IgG₄ antibodies (see Fig E3 in this article's Online Repository at www.jacionline.org). Those results correlated with IgG to Fel d 1 (*r* = 0.40, *P* < .001) and, in keeping with this, showed a strong association with cat ownership. IgG₄ antibodies were also not a significant predictor of symptoms and were equally present in sera with or without IgE antibodies to cat (see Fig E3).

Component analysis for IgE specific for cat and dog allergens

Over the last few years, several allergens derived from cat or dog have become available to assay specific IgE antibodies (see Table E2 and www.allergen.org). Where sufficient serum was available, subjects with positive cat and dog results were assayed for relevant components. The results were first evaluated on a matrix of intercorrelations for their correlation with IgE to other components and dander extracts (Table IV). These results show correlations as high as 0.90 for Fel d 1 and cat or 0.87 for Can f 1 and dog or as low as 0.03 for Can f 5 and cat. The results for IgE-specific components were also evaluated for their relationship to asthma. Strong associations were found for

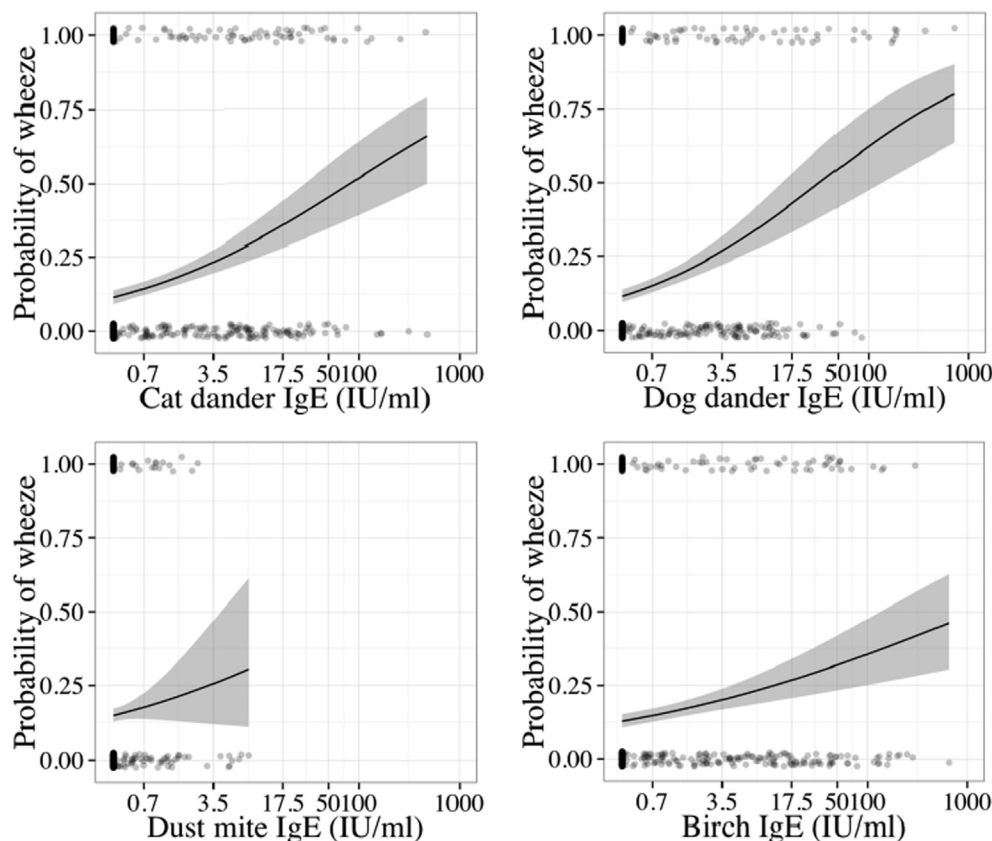


FIG 1. Probability of wheeze related to the titer of IgE antibodies specific for cat dander, dog dander, dust mite, or birch pollen. Unadjusted logistic regression lines are depicted, with 95% CIs in gray. $P < .001$, $P < .001$, $P = .17$, and $P < .001$ for cat dander, dog dander, dust mite, and birch pollen, respectively.

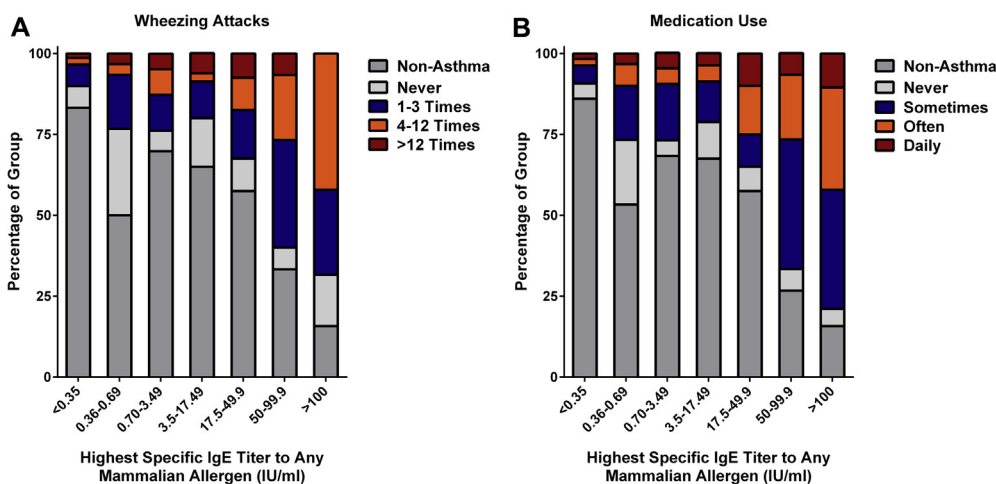


FIG 2. Relationship between IgE antibodies to any mammal and asthma severity assessed by frequency of wheezing attacks per year (**A**) or medication use (**B**). The number of subjects in each of the 7 groups shown was as follows: 716 for negative results and 30, 63, 80, 40, 15, and 19 for each of the groups from 0.35 to 100 IU/mL. By using the χ^2 test for trend, the P value was less than .001 for wheezing attacks or medication use.

Can f 1, Can f 2, and Can f 5, as well as for Fel d 1 and Fel d 4 (Table V). The 3 components with the strongest relationship to asthma were Can f 1, Can f 5, and Fel d 1. Strikingly, Fel d 1 and Can f 5 showed little to no correlation with each other. By

using multivariable analysis, the odds ratios for these 2 allergens indicated that they had a strong independent association with asthma: 4.8 (95% CI, 2.4-9.4) for Fel d 1 and 7.7 (95% CI, 2.2-27) for Can f 5 (Table VI).

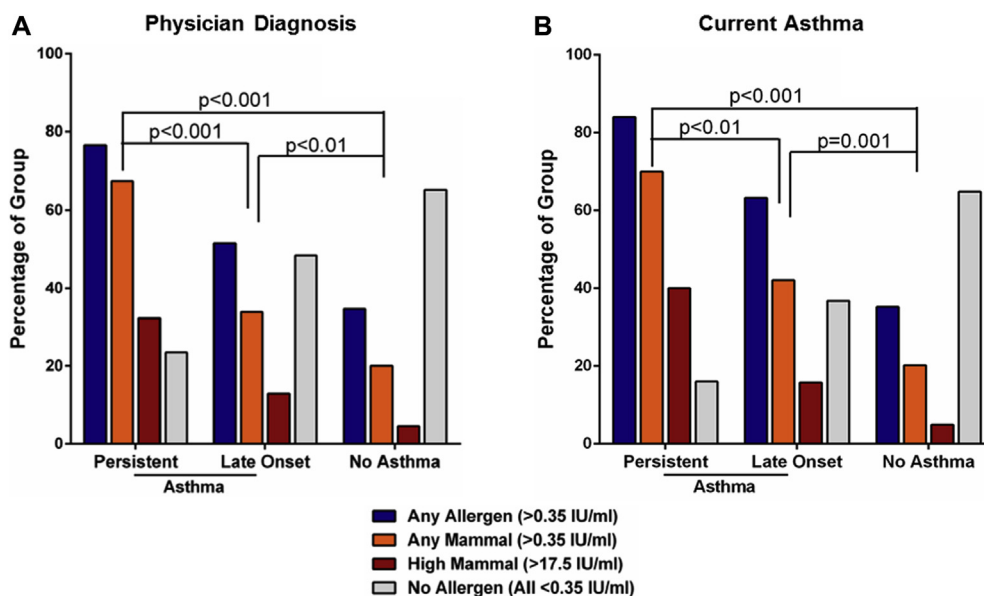


FIG 3. A, Relationship between sensitization and asthma diagnosis among patients with persistent asthma (n = 68), late-onset asthma (n = 63), and no reported asthma (n = 672). B, The same analysis for patients with current asthma, which was persistent (n = 50) or late onset (n = 38), or no reported asthma (n = 672). For each group, the prevalence of sensitization is shown for any allergen (≥ 0.35 IU/mL), any mammalian allergen, high-titer mammalian allergen (≥ 17.5 IU/mL), or no sensitization.

TABLE III. Prevalence and effect of IgE antibody titer among subject with persistent or late-onset current asthma in relation to reported medication use

Medication use	Never/sometimes			Often/daily			Total	Female sex (%)
IgE sensitivity	No.	Class 1-3	Class 4-6	N	Class 1-3	Class 4-6		
Persistent current asthma (n = 50)								
None	5	0	0	3	0	0	8*	50
Mammal†	17	10	7	20	7	13	37*	54
Nonmammal only	4	1	3	1	1	0	5	20
Late-onset current asthma (n = 38)								
None	7	0	0	7	0	0	14*	79
Mammal†	10	8	2	6	2	4	16*	56
Nonmammal only	4	4	0	4	2	2	8	38

*Prevalence of nonallergic subjects: The ratio of nonallergic subjects to subjects with IgE to any mammalian allergen for persistent current asthma was 8:37, and that for late-onset current asthma was 14:16 ($P < .01$). The ratio of nonallergic subjects to subjects with IgE to any allergen for persistent current asthma was 8:42, and that for late-onset current asthma was 14:24 ($P = .05$).

†Effect of titer of IgE antibodies on severity: The ratio of subjects with low-titer (class 1-3) to high-titer (class 4-6) IgE to mammalian allergen among subjects reporting no medication use and some use of medication was 18:9, whereas the ratio for those reporting frequent or daily medication use was 9:17 ($P < .05$). The ratio of subjects with low-titer (class 1-3) to high-titer (class 4-6) IgE to any allergen among subjects reporting no medication use and some medication use is 23:12, whereas the ratio for those reporting frequent or daily medication use is 12:19 ($P < .05$).

DISCUSSION

There are populations of children and young adults living in westernized or post-hygiene societies where the allergen sensitization associated with asthma is dominated by dust mite, cockroach, *Alternaria* species, or, as in the present cohort, animal dander.^{2,4,6-8,18} In each of these populations, the specificity of the sensitization associated with asthma correlates with the known presence of the relevant allergen in the community. However, the simple view that exposure in the child's home can predict sensitization is no longer tenable.³² To further understand the relationship between sensitization and asthma, we studied IgE antibodies in sera from 963 19-year-old subjects who were part of a long-term population-based cohort living in an area in which

mite, cockroach, and *Alternaria* species are not relevant. We report here that:

1. the titer of IgE antibodies to cat and dog allergens was an important risk factor for both the prevalence and severity of asthma;
2. current cat owners have both lower prevalence of IgE antibodies and higher titers and prevalence of IgG antibodies to Fel d 1;
3. sensitization to the specific proteins Fel d 1, Fel d 4, Can f 1, Can f 2, and Can f 5 was strongly associated with asthma, and in multivariable analysis Fel d 1 and Can f 5 showed strong independent relationships to asthma;
4. sensitization to mammalian dander allergens showed the strongest association to asthma that had been diagnosed

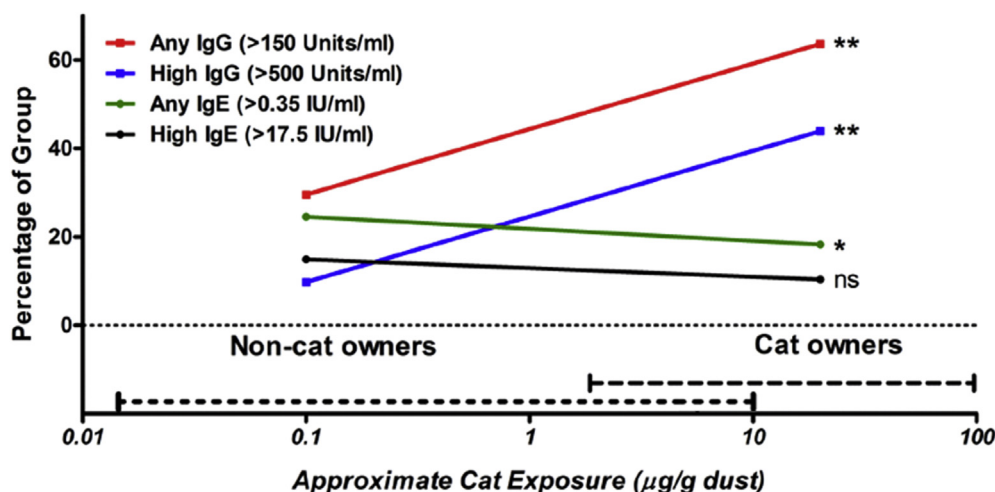


FIG 4. Relationship between IgG specific for Fel d 1 and cat ownership. Both low-titer (150-500 U/mL) and high-titer (>500 U/mL) IgE were significantly high among cat owners ($n = 279$) (** $P < .01$). By contrast, any IgE to cat dander was less common among cat owners (* $P < .05$). The approximate range of cat allergen exposure is shown for cat owners and non-cat owners ($n = 684$).³¹

TABLE IV. A matrix of intercorrelations (with 95% CIs) that was calculated from a cross-tabulation of serum IgE variables, including specific IgE antibodies to cat and dog dander and the representative allergen components and that shows the degree of correlation between the serum IgE variables

	Dog dander	Can f 1	Can f 2	Can f 3	Can f 5	Fel d 1	Fel d 2	Fel d 4	Cat dander
Dog dander	1.00	—	—	—	—	—	—	—	—
Can f 1	0.80 (0.74-0.85)	1.00	—	—	—	—	—	—	—
Can f 2	0.86 (0.82-0.89)	0.87 (0.83-0.90)	1.00	—	—	—	—	—	—
Can f 3	0.31	0.29	0.26	1.00	—	—	—	—	—
Can f 5	0.57 (0.47-0.68)	0.45	0.48	0.15	1.00	—	—	—	—
Fel d 1	0.15	0.15	0.06	0.22	0.05	1.00	—	—	—
Fel d 2	0.08	0.12	0.06	0.76 (0.69-0.81)	0.02	0.26	1.00	—	—
Fel d 4	0.20	0.37	0.17	0.23	0.05	0.33	0.19	1.00	—
Cat dander	0.12	0.15	0.03	0.33	0.02	0.94 (0.92-0.95)	0.46	0.40	1.00

Boldface indicates statistical significance.

before age 12 years and for subjects still symptomatic at age 19 years; and

5. a large proportion of the cases given a diagnosis for the first time between age 12 and 19 years were not sensitized to any allergen.

After the original report from Hesselmar et al¹⁷ in 1998 that children raised in a house with a cat were less likely to be allergic to cats, there have been extensive publications related to this phenomenon.^{33,34} Many reports have confirmed the original observation but with significant differences between the effects of cat and dog ownership.^{18,20,35} Several studies have not found a protective effect of cat ownership or have implied that the observed results could be explained by allergic families choosing not to own animals.^{36,37} Two meta-analyses on the effects of pet ownership came to slightly different conclusions, but neither found evidence that cat ownership would increase the risk of cat sensitization or asthma.^{33,34} It is well established that cat allergen is present in schools, as well as in homes without a cat.^{31,38,39} Moreover, recent evidence suggests that the quantity of allergen in homes without a cat or in schools is a function of the proportion of homes with an animal in the community.^{32,39,40}

Interestingly, if some allergic families choose not to own a cat, this would only cause an increase in sensitization among families without a cat if their children were still just as likely to become sensitized to cat allergens. In previous studies of the same cohort, at age 12 years, we found that 80% of children with cat allergy had never lived in a house with a cat³¹ and that new onset of allergic sensitization was not related to having a cat at home.⁴¹ In the present study 39 (85%) of 46 cat-sensitized subjects with current asthma were not living in a house with a cat, and 22 of them had neither a cat nor dog at home. The implication is clearly that sufficient exposure to induce symptoms is occurring in homes without a cat, in schools, or in other public places. Equally, this suggests that cat or dog sensitization should be considered relevant in patients, even if they do not have an animal at home.

Several long-term cohorts studying asthma have found that a large proportion of cases had the disease early in life.⁴² In addition, it is generally found that allergic sensitization is an important factor favoring persistence of the condition.²² On the other hand, there are cases that present in the teenage years, and there is also good evidence for an increase in the proportion of female cases at this age.^{12,43} In at least 1 study the cases that presented around

TABLE V. IgE antibodies to cat- and dog-related components: Univariable analysis of asthma based on current asthma for different levels of IgE antibodies to allergen components of cat and dog dander

Allergen	IgE titer by class in students with current/ no* asthma			Odds ratios for asthma (based on current asthma)	
	Negative	Class 1-3	Class 4-6	Any IgE antibody >0.35 IU/mL (≥class 1)	IgE antibody >17.5 IU/mL (class 4-6)
Fel d 1	51/677	33/104	19/29	5.2 (3.4-8.0) [‡]	8.7 (4.6-17) ^{‡§}
Fel d 2	89/785	6/12	2/2	5.0 (2.1-12) ^{‡§}	8.8 (1.2-63) [§]
Fel d 4	75/746	19/48	5/4	4.6 (2.7-7.9) [‡]	12 (3.3-47) ^{‡§}
Fel d 5w	41/99	0/1	0/0	—	—
Can f 1	75/770	12/31	12/5	6.8 (3.9-12) [‡]	25 (8.5-72) ^{‡§}
Can f 2	85/787	7/18	6/1	6.3 (3.0-13) ^{‡§}	55 (6.5-461) ^{‡§}
Can f 3	89/787	3/9	5/4	5.9 (2.3-15) ^{‡§}	15 (3.5-63) ^{‡§}
Can f 5	68/741	23/61	8/4	5.2 (3.2-8.5) [‡]	21 (6.4-74) ^{‡§}

*Numbers before and after the forward slash indicate students with current asthma and without asthma at age 19 years (ie, no current asthma), respectively.

[†]*P* < .01.

[‡]*P* < .001.

[§]Statistical analysis of odds ratios performed with the Fisher exact test.

TABLE VI. IgE antibodies to cat- and dog-related components: Multivariable binary logistic regression of the relationship of current asthma to IgE antibodies to Fel d 1 and Can f 1 (A), Fel d 1 and Can f 2 (B), and Fel d 1 and Can f 5 (C)

	Any positive result (>0.35 IU/mL)	High titer (>17.5 IU/mL)
A.		
Fel d 1	3.3 (2.0-5.6) [‡]	3.2 (1.5-7.0) [†]
Can f 1	2.7 (1.4-5.2) [†]	11 (3.2-35) [‡]
B.		
Fel d 1	4.0 (2.5-6.5) [‡]	4.8 (2.4-9.5) [‡]
Can f 2	2.4 (1.1-5.3)*	24 (2.6-225) [†]
C.		
Fel d 1	3.3 (1.9-5.6) [‡]	4.8 (2.4-9.4) [‡]
Can f 5	2.2 (1.2-4.0) [†]	7.7 (2.2-27) [‡]

**P* < .05.

[†]*P* < .01.

[‡]*P* < .001.

puberty were less allergic.⁴⁴ In our cohort, despite a significant increase in the number of cases between 12 and 19 years of age, there was only a modest change in the ratio of female to male cases. The 63 patients with a diagnosis of asthma at age 19 years but who did not have such a diagnosis at age 12 years had a strikingly lower prevalence of sensitization than those with persistent asthma. This was particularly clear for those who were no longer symptomatic at age 19 years: 16 (64%) of 25 had no sensitization (Table III).

When it first became possible to monitor exposure to dust mite allergens, it was generally assumed that the child's exposure was primarily in their own home.^{7,45} Several developments over the last 15 years have shed doubt on the simple relationship. First, it is clear that the highest exposure to cat or dog allergens (ie, an animal in the house) is not associated with higher prevalence of sensitization or with higher titers of IgE antibodies. Second, with increased awareness of the relevance of mite allergen, some European countries have had a decrease in the range of mite exposure levels. Third, an important mite avoidance study in Manchester, United Kingdom, found that despite careful avoidance measures in the children's homes, they still became sensitized to mite.⁴⁶ What matters here is that the subjects in the present study did not become sensitized to mite allergens. The logical explanation for this result is that the children can

become sensitized to perennial allergens from exposure to both mite and cat allergens outside their own house. The contrast between Manchester, United Kingdom, and Norrbotten is that in Norrbotten none of the schools or other houses in the community would have mite allergens.^{14,22}

In the original criteria for assessing evidence for the causality of dust exposure in a lung disease, a dose-response relationship between exposure and the disease was an important factor.^{9,47} However, those criteria were written about inorganic dusts in which individual sensitization was not considered relevant. It is now clear that the relationship between individual exposure and sensitization is too complex to use the subject's home exposure as a surrogate for overall exposure. Furthermore, it is increasingly likely that the presence of an animal, particularly an outdoor dog, can further decrease the risk of sensitization in the child.^{48,49} Thus we consider that sensitization has to be the primary characteristic used to examine the relationship between allergens and asthma.

Using stepwise logistic regression analyses, we further examined the relevance of IgE antibodies to components and extracts as risk factors for different asthma outcomes (see Table E7). The results were strikingly different by using the older dog epithelium assay (e2) compared with dog dander (e5). We believe this result confirms our view that IgE responses to different mammals are collinear and that the real conclusion is that the asthma risk in Norrbotten is dominated by IgE antibodies to mammalian allergens (Table II). In particular, this relates to the role of high-titer IgE antibodies to mammalian allergens and the risk of current persistent asthma.

There are several limitations to the present study. First, we do not have details on animal ownership from birth, and we did not sample all the houses in this cohort. However, it is increasingly clear that measurements of allergen in dust from a subject's home alone cannot be taken as an adequate model of exposure.

Second, there have been significant changes in the extracts used for *in vitro* testing of sensitization over the period of this study. Indeed, the dog dander assay (e5) produced twice as many positive results as the earlier dog epithelium assay (e2, Table I).

Third, there are more component assays available today than there were as recently as 5 years ago. Nonetheless, neither the individual component assays nor the microchip assays can provide a complete analysis of sensitization to the extract. However, a large population-based cohort with a high participation rate and longitudinal study design contributes to

the validity of the results. Furthermore, the diagnosis of asthma in the present cohort has been validated and shown to have high specificity!⁵⁰

In conclusion, the presence of a cat or dog in the house was not a significant predictor of sensitization or the risk of asthma in a geographic area in which animal dander dominated the sensitization to perennial allergens. Nonetheless, IgE antibodies, particularly high-titer IgE antibodies, were strongly associated with the prevalence, severity, and persistence of asthma. Among the patients with asthma who received a diagnosis before age 12 years and were still symptomatic at age 19 years, high-titer IgE antibodies to cat or dog allergen were associated with asthma, with an odds ratio of 13 (95% CI, 6.9-25). Furthermore, 85% of the subjects in this group did not have a cat at home, and 48% had neither a cat nor a dog. These results are in keeping with a model in which cat and dog allergens are present throughout the community at levels sufficient to contribute to both sensitization and asthma symptoms. Equally, the results strongly support a direct role for IgE antibodies in asthma morbidity.

Key messages

- In a community in which cat- and dog-derived allergens are the dominant perennial allergens because of the climate, high-titer IgE antibodies to dander allergens are strongly associated with the prevalence, severity, and persistence of asthma.
- In many cases asthma diagnosis after age 12 years was no longer causing symptoms at age 19 years. In addition, many of these late-onset cases were not sensitized and had low total IgE levels.
- A large majority of the cat-sensitized subjects with current asthma did not live in a home with a cat, and 48% had no cat or dog in the house. This observation is in keeping with the fact that animal dander allergens are present throughout the community, including schools and homes without a cat.

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