

Cat and dust mite sensitivity and tolerance in relation to wheezing among children raised with high exposure to both allergens

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Background: Recent evidence has suggested that high exposure to cat allergens is associated with decreased prevalence of sensitization to cat and, in some studies, decreased asthma. **Objective:** Our objective was to study antibodies to cat and mite allergens and their relationship to wheezing in a country with high exposure to both allergens.

Methods: Sera from 112 wheezing and 112 control children aged 10 to 11 years in a nested case-control study in New Zealand were assayed for specific IgE antibody, as well as IgG antibody and IgG4 antibody, to Der p 1 and Fel d 1.

Results: IgE antibody to both mite (99/224) and cat (41/224) were strongly associated with wheezing (odds ratios, 5.2 and 6.5, respectively). Children who had ever lived with a cat were less likely to have IgE antibody to cat (20/141 vs 21/83, $P < .04$); however, cat ownership had no effect on IgE antibody to mite (67/141 vs 32/83, $P = .23$). Among sensitized children, cat ownership was associated with a lower prevalence of IgE antibody to cat (28% vs 66%, $P < .001$), and this analysis remained significant after exclusion of children whose families had chosen not to own a cat. Among sensitized subjects, the mean titer of IgE antibody to cat (1.7 IU/mL) was 10-fold lower than for mite (22.1 IU/mL). A cat in the home had no significant effect on endotoxin or mite allergen in house dust, whereas cat allergen was much higher (40.8 vs 3.3 $\mu\text{g/g}$).

Conclusion: The response to these 2 allergens was distinct on the basis of the prevalence of sensitization, the titer of IgE antibody, and the effect of cat ownership. The results suggest that induction of tolerance to cat allergen is an allergen-specific phenomenon that cannot be attributed to endotoxin or family choice. The strength of the IgE antibody response to dust mite in humid climates could contribute to the increased prevalence and severity of asthma. (J Allergy Clin Immunol 2005;115:74-9.)

Key words: Asthma, cat, mite, tolerance, high exposure

Sensitization to allergens from house dust mites and domestic cats is associated with asthma.¹⁻³ The prevalence

of sensitization to house dust mite allergens (as judged on the basis of skin test or IgE antibodies) has been consistently related to the level of exposure.^{2,4} By contrast, the presence of a cat in the home has been found to be associated with a reduced prevalence of sensitization and, in some studies, a reduced risk of asthma.⁵⁻⁷ Several mechanisms have been suggested to explain these observations. First, some atopic families might choose not to own a cat, which could account for the decreased prevalence of allergy among cat owners. Alternatively, it has been suggested that sensitization to cat allergen and other allergens is nonspecifically reduced because of increased exposure to endotoxin or other bacterial products in houses with pets.⁸⁻¹⁰ Finally, a novel immune response to cats has been demonstrated in subjects living with cats in whom increased levels of IgG and IgG4 antibody to cat allergen are present without IgE antibody.^{11,12} We have proposed that this immune response represents a form of tolerance that is allergen specific.^{13,14}

New Zealand provides an ideal environment in which to explore these relationships and to determine not only whether the tolerance to cat allergen is specific for this allergen but also whether tolerance occurs with exposure to high levels of dust mite allergens. Asthma is both common and severe in New Zealand and is strongly associated with allergy to house dust mites or cats.¹⁵ In a recent study of homes in Wellington, all households had at least 2 μg of Der p 1/g dust, and 36% had levels greater than 100 $\mu\text{g/g}$.¹⁶ These concentrations are high, even by comparison with the levels measured in other temperate areas. Furthermore, 60% of children live with a cat, and even in houses without a cat, the mean levels of Fel d 1 were still significant (ie, approximately 3.2 $\mu\text{g/g}$ dust).^{17,18} The purpose of our study was (1) to determine whether there is a true difference between the response to these 2 allergens on the basis of the prevalence and titer of IgE antibody, as well as the presence of IgG and IgG4 antibody to purified allergens, and (2) to investigate how these responses relate to wheezing.

METHODS

In 2000, 1155 children (response rate, 86%) aged 10 to 11 years participated in Phase 2 of the International Study of Asthma and Allergies in Childhood in the boroughs of Hastings and Havelock North, New Zealand (population 70,000). On the basis of response to

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TABLE I. Odds ratios for wheezing related to IgE antibody, IgG antibody, and cat exposure among children in New Zealand

Risk factor	Prevalence among children with:		Univariate OR (95% CI)	Multivariate	
	Wheezing (n = 112)	No wheezing (n = 112)		Model 1, OR (95% CI)	Model 2,* OR (95% CI)
Mite IgE	71	28	5.2 † (2.9-9.2)	3.3 (1.7-6.4)	2.6 (1.2-5.3)
Cat IgE	34	7	6.5 (2.8-16)	3.1 (1.1-9.0)	2.9 (0.95-9.0)
Grass IgE	63	30	3.5 (2.0-6.1)	1.4 (0.71-2.9)	1.4 (0.68-2.9)
<i>Aspergillus</i> species IgE	18	4	5.2 (1.7-16)	1.3 (0.36-4.7)	—
Dog IgE	6	2	3.1 (0.62-16)	0.50 (0.081-3.1)	—
Total IgE (>200 IU/mL)	63	24	4.7 (2.6-8.5)	2.7 (1.3-5.8)	—
Cat ever	71	70	1.0 (0.6-1.8)	—	—
Mite (Der p 1) IgG positive‡	79	52	2.8 (1.6-4.9)	—	1.5 (0.76-2.8)
IgG positive but IgE negative	19	30	0.56 (0.29-1.1)	—	—
Cat (Fel d 1) IgG positive	51	35	1.9 (1.1-3.3)	—	1.0 (0.51-2.0)
IgG positive but IgE negative	25	32	0.72 (0.39-1.3)	—	—

OR, Odds ratio.

*In model 2 the influence of IgG antibody was included, and only sensitization to dust mite remained a significant risk factor.

†Bolding indicates ORs with significance at the .05 level.

‡IgG antibodies to mite and cat were measured using purified antigens and radioimmunoprecipitation.

the question, "Has your child had wheezing or whistling in the chest in the last 12 months," 21.8% were judged to have current wheeze. A subsample of children with (n = 112) and without (n = 112) current wheeze was randomly chosen for this nested case-control study and provided blood. Dust samples were obtained from mattresses and analyzed as described previously.^{16,18} The severity of wheezing in the last 12 months was assessed and scored by using 3 measures: the number of attacks of wheezing was scored from 1 to 4 as none (1), 1 to 3 (2), 4 to 12 (3), and greater than 12 (4); the frequency of sleep disturbance was scored from 1 to 3 as never (1), less than 1 night weekly (2), and 1 or more nights weekly (3); and the occurrence of breathlessness severe enough to limit speech was scored from 1 to 2 as no (1) and yes (2). The questionnaire also included questions on pet exposure both currently and during the first year of life, as well as the question, "Have you ever made a decision to avoid or remove cats from the house because your child had asthma or other allergic problems?" This research was approved by the Hawkes Bay Ethics Committee and the Human Investigation Committee at the University of Virginia.

Total and specific IgE antibody levels were measured with the Pharmacia CAP (Uppsala, Sweden). Specific IgE antibody levels were measured for dust mite (*Dermatophagoides pteronyssinus*), cat, rye grass, *Aspergillus fumigatus*, and dog. Values of greater than 0.35 IU/mL were considered positive. In addition, the purified allergens Der p 1, Der p 2, and Fel d 1 were biotinylated, and IgE antibodies were measured using streptavidin CAPs. IgG antibody to the purified allergens Der p 1 and Fel d 1 were assayed by means of radioimmunoprecipitation.¹⁹ Each allergen was radiolabeled with iodine 125 and then incubated with patient serum. Goat anti-human IgG was added to bind the IgG antibody-allergen complexes, and after washing, radioactivity was measured in the resulting precipitates. In the sera with detectable IgG antibodies to Der p 1 or Fel d 1 (>50 U/mL and 125 U/mL, respectively), antibodies of the IgG4 isotype were measured using an extended protocol.^{11,20} The first incubation was with monoclonal mouse anti-human IgG4, followed by goat anti-mouse IgG. A specific control curve was used to derive units for each IgG and IgG4 assay.¹¹

Univariate and multivariate logistic regression were used to determine associations between IgE and IgG antibodies and wheezing. The first model of logistic regression included only the occurrence of IgE antibody (model 1), whereas the second model included the IgE antibody results, as well as cat exposure and IgG antibody results (model 2). The relationship between exposure to pets

and antibody responses was analyzed using the χ^2 test. Patients were divided into exposure groups on the basis of the presence or absence of a pet in the home. An independent-samples *t* test was used to compare geometric mean titers of antibody between exposure groups. These analyses were performed with S-PLUS version 2000 software (Insightful, Inc, Seattle, Wash).

RESULTS

Prevalence of IgE antibody in relation to wheezing and cat ownership

The prevalence of IgE antibody to common inhaled allergens was higher among the wheezing children. Specific IgE antibody to the dust mite *D pteronyssinus* was present in 63% of the wheezing children and in 25% of the control subjects (odds ratio, 5.2; CI, 2.9-9.2). In univariate analysis specific IgE antibodies to grass, cat, and *Aspergillus* species were also associated with wheezing (Table I). In multivariate analysis, including specific IgE antibody, only mite and cat sensitization remained significant in relation to wheezing (model 1, Table I).

Of the 224 families studied, more than 60% reported keeping a cat at some time during the life of the child (cat ever group). Cat ownership ever was not associated with wheezing (Table I). Furthermore, the prevalence of IgE antibody to cat was lower among children who had ever lived in a house with a cat compared with those who had never lived with a cat (20/141 vs 21/83, *P* = .04; Fig 1, A). By contrast, cat ownership had no effect on the prevalence of IgE antibody to mites (67/141 vs 32/83, *P* = .23). Among children with IgE antibody to mite or cat (allergic group), those who had lived with a cat had a far lower prevalence of IgE antibody to cat (28% vs 66%, *P* < .001; Fig 1, B). Furthermore, when subgroups of cat ever were examined (ie, cat in the first year or cat currently), the negative effect of cat ownership on the prevalence of IgE antibody to cat was present in each group (Fig 1, B).

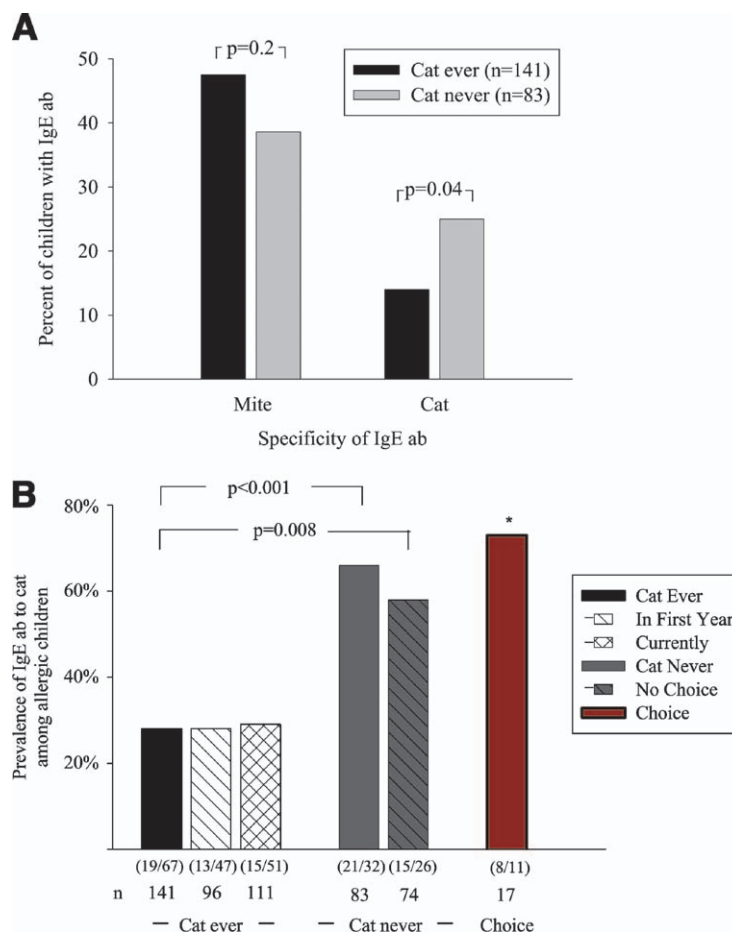


FIG 1. A, The percentage of children with IgE antibody to dust mite and cat allergens among children who had lived with a cat ever compared with children who had never lived with a cat. **B**, Prevalence of IgE antibody to cat among allergic children. Actual values are shown in parentheses under each column. Children who lived with a cat ever were examined on the basis of timing of exposure. Among families who had never lived with a cat, those who had chosen not to own a cat because of allergic symptoms were included in the choice group. The prevalence of sensitization to cat among allergic subjects in the choice group was significantly different from that seen in the group living with a cat currently (* $P = .004$).

Seventeen families in the cat never group reported choosing not to own a cat. When these families were excluded, the prevalence of sensitization to cat among allergic children without a cat remained significantly higher ($P = .008$). Among the choice group, 73% of the sensitized children had IgE antibody to cat (Fig 1, B).

Differences in IgE antibody titer among mite- and cat-sensitized subjects

The assays for IgE provide quantitative results in international units per milliliter (1 IU = 2.4 ng). In this study the titer of IgE antibody to cat (geometric mean, 1.7 IU/mL; 95% CI, 1.2-2.6) was significantly lower than that for IgE antibody to mite (22.1 IU/mL; 95% CI, 14-35; $P < .001$). This difference was seen equally among the cat ever and cat never groups and also among wheezing and nonwheezing children (Fig 2). The titers of IgE antibody seen in the cat never group could reflect low exposure; however, the results show that even the levels of cat allergen that are known to occur in homes with a cat do not

increase the titers of IgE antibody to cat (geometric mean, 1.5 IU/mL [95% CI, 0.9-2.6] vs 2.1 IU/mL [95% CI, 1.2-3.4]; $P = .4$). Assays of IgE antibody to purified major allergens were carried out on 210 sera. The mean titer for IgE antibody to Fel d 1 (3.2 IU/mL; 95% CI, 1.8-5.7) was 10-fold lower than IgE antibody to Der p 1 or Der p 2 (31.0 IU/mL [95% CI, 20-49] and 36.7 IU/mL [95% CI, 24-55], respectively; Fig 3).

IgG antibodies in relation to wheezing and cat ownership

Specific IgG antibodies were present in a large proportion of children with mite and cat allergy (Table I). Although IgG antibodies were significantly associated with wheezing in univariate analysis, when the effects of specific IgE antibodies were included in multivariate analysis, there was no evidence for an independent role for IgG antibodies (model 2, Table I). Serum IgG antibody to Fel d 1 without IgE antibody was more common among children who had lived in a house with a cat ever (48/141

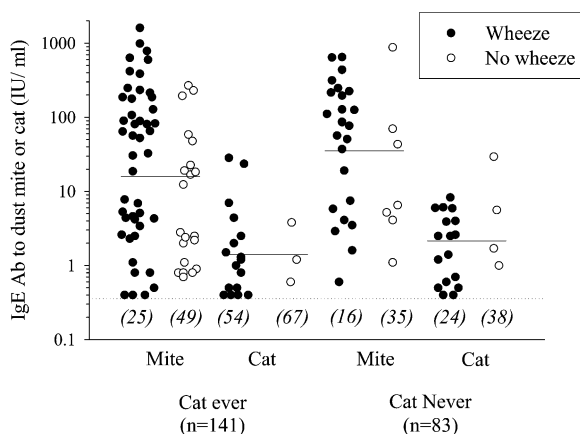


FIG 2. Titers of IgE antibody (in international units per milliliter) to dust mite and cat allergens among children who lived with a cat ever compared with children who never lived with a cat. Children with wheezing are indicated by filled circles. The geometric mean titer of IgE antibody is shown for each allergen. The number of sera negative for each allergen is indicated in parentheses below each column.

vs 9/83, $P < .001$). Antibodies of the IgG4 isotype specific for Der p 1 were detected in 42 sera; of these, 39 also contained IgE antibody to mite. By contrast, IgG4 antibodies to Fel d 1 were present in sera from 30 children, and 17 of these sera had no detectable IgE antibody to cat allergens ($P < .001$).

Endotoxin, dust mite, and cat allergens in dust from homes with or without a cat currently

Dust samples were assayed for endotoxin, as well as mite (Der p 1) and cat (Fel d 1) allergens (Table II). The mean mite levels were very high and were not significantly influenced by current cat ownership. The measured values of endotoxin, which varied over a wide range, were slightly lower in homes with a cat. The levels of Fel d 1 in homes with a cat were high (40.8 $\mu\text{g/g}$). Even in homes without a cat, the mean level of cat allergen was 3.3 $\mu\text{g/g}$.

Influence of cat ownership and allergen-specific responses on wheezing

The presence of a cat in the home ever (or currently) was not a significant predictor of wheezing. Furthermore, the prevalence of wheezing in children with IgE antibody to cat (Table 1) was equal among those with a cat (17/20) compared with that among those without a cat (17/21, Fig 2). Symptoms of wheezing were assessed by questionnaire. Forty-four children had a symptom score of 6 or greater (out of 9). Analysis of these children with persistent symptoms identified 35 of 44 as having IgE antibodies to mite (33 children) or cat (16 children). The mean titer of IgE antibody to mite in this group was increased compared with that in all mite-sensitized subjects (89.1 vs 22.1 IU/mL) and markedly enhanced compared with the mean titer of IgE antibody to cat (1.5 IU/mL). Thus both the increased prevalence of IgE antibody to mite and the higher titer of IgE antibody to mite compared with

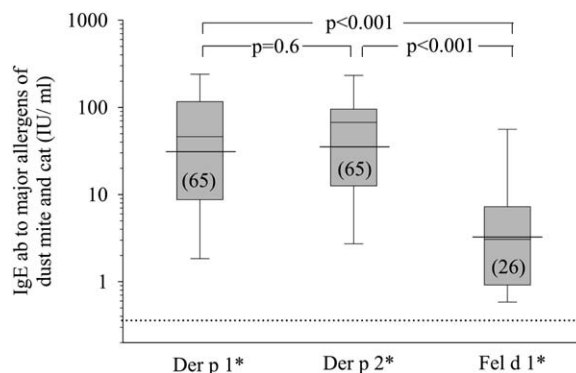


FIG 3. Titers of IgE antibody to the major allergens Der p 1, Der p 2, and Fel d 1 were measured using streptavidin CAPs. Boxes indicate values between the 25th and 75th percentiles (median shown with horizontal line). Whisker bars extend to the 10th and 90th percentiles. Results are shown for 210 children for whom sufficient serum was available.

cat were evident among children with more severe symptoms.

DISCUSSION

Previous studies showing that the presence of a cat does not increase sensitization to cats or can decrease the prevalence of IgE antibody have been open to several different interpretations. These include both the effect of family choice about pet ownership and the possible nonspecific effects of endotoxin.^{7,10,11} In the present study the differences between the responses to dust mite and cat allergens are accentuated because of high exposure to each. The high prevalence of sensitization to dust mite allergens argues strongly that the presence of a cat does not have a bystander effect on the response to dust mite. In addition, the results suggest that even the high levels of mite allergen found in New Zealand do not produce significant tolerance. Our data add a major new element in that the titer of IgE antibody to cats and to the cat allergen Fel d 1 is strikingly lower than that to mite or mite allergens; this effect was also evident in children with more severe symptoms. In fact, the titer of IgE antibody to cat was low both in the high-exposure group and among wheezing children. Overall, the data strongly suggest that IgE antibody to cat allergen is controlled and that this reflects a biologic difference between the response to mite and cat allergens.¹³

If families with an allergic history choose not to own a cat or get rid of the cat when a child becomes allergic, it could produce a spurious increase in sensitization to allergens in general among families without a cat. Our finding that mite sensitization was not affected by the presence of an animal argues against this explanation. Indeed, in this study 30 wheezing children who were allergic to mite but not to cat allergens had lived in a house with a cat. Furthermore, when we excluded the families who chose not to own a cat, the effect of a cat was still significant (Fig 1, B). Evidence has also come from studies

TABLE II. Exposure to endotoxin, as well as mite and cat allergens, in dust from 224 homes with or without a cat*

	Cat currently (n = 111)	No cat (n = 113)	Effect of cat
Endotoxin (EU/g)†	13,700 (11,100-17,000)	17,400 (14,500-20,900)	NS
Der p 1 (μg/g)‡	24.8 (20.3-30.2)	21.4 (17.4-26.5)	NS
Fel d 1 (μg/g)	40.8 (31.2-53.4)	3.3 (2.6-4.3)	P < .001

NS, Not significant.

*Samples were collected with a vacuum cleaner, sieved, and extracted.

†Endotoxin was assayed using the Limulus Amebocyte Lysate assay.

‡Der p 1 and Fel d 1 were assayed using 2-site mAb assays.

TABLE III. Classification of the major allergens associated with asthma

	Class 1	Class 2
Allergens	Mite (also cockroach)	Cat*
Size	Large particles (10-30 μm)	Smaller particles (2-15 μm)
Airborne	Only with disturbance	Continuously
Total inhaled	1-10 ng/d	0.1-0.5 μg/d
Enzymatic activity	Yes	No†
Tolerance at high dose	No evidence	Yes with animal in house

*The occupational allergens derived from rat urine and pig urine have much in common with category 2.

†The cat allergen Fel d 1 has structural and sequence homology with Clara cell secretory protein, which has a role in controlling inflammation in the lungs of mice.

in the United Kingdom and the United States, confirming a paradoxical effect of domestic animals, although very few families had chosen not to own animals.^{6,10}

When it was reported that early-life exposure to farm animals could nonspecifically reduce allergic sensitization, several authors suggested that the effects of cat ownership could also be explained by high levels of endotoxin.^{9,10} In our study 2 lines of evidence argue against a role for endotoxin. First, the influence of cat exposure was specific for sensitization to cat. Second, measured concentrations of endotoxin in floor dust were not significantly different in homes with a cat (Table II). One of the proposed mechanisms for an influence of endotoxin on allergic disease was an increase in IL-12 production, which is recognized as a cofactor for T_H1 responses. However, the evidence that nonallergic individuals make a T_H1 response to common inhalant allergens is limited. Our evidence, both from the present and previous studies, suggests that many children living with a cat make an IgG4 response to Fel d 1 without IgE antibody, which is best regarded as a modified T_H2 response.^{7,11,12}

Several recent developments might be relevant to understanding the mechanisms of cat-specific tolerance. First, elucidation of the tertiary structure of Fel d 1 has confirmed structural similarity with Clara cell secretory protein (CCSP).²¹ This molecule has potent immunomodulatory effects in mice and might have similar effects in human subjects.²² Second, studies of the *in vitro* T-cell response to peptides of Fel d 1 have identified 2 peptides at the amino terminus of chain 2 that selectively induce IL-10 and IFN-γ.^{13,14} Again, the results suggest that the

properties of the protein might be relevant to differences in the human immune response to mite and cat allergens. However, the *in vitro* T-cell studies found high IL-10 production by T cells from both tolerant and allergic subjects.^{13,23} Those findings are in keeping with our current results (ie, that the IgE antibody response to cat is controlled not only in tolerant individuals but also in individuals who are sensitized to cat allergen). This strongly suggests that the mechanism for tolerance to cat allergens is control of the T_H2 response rather than a switch to T_H1.²⁴ Interestingly, evidence from a mouse model has shown that the T_H2-induced inflammatory response to inhaled ovalbumin cannot be controlled by T_H1 cells but can be effectively controlled by cells that are genetically engineered to produce IL-10.²⁵

There are several differences between dust mites and cats that could be relevant to our observations (Table III). The obvious differences are (1) that cat allergen is airborne continuously on smaller particles, (2) that the estimated inhaled exposure per day for Fel d 1 is 10 to 100 times that which has been estimated for dust mites,²⁶ and (3) that the properties of the major allergens are very different. Dust mite group I allergens (Der p 1 and Der f 1) are potent enzymes that can cleave CD25, CD23, and CD40, as well as open up epithelial junctions.^{27,28} By contrast, Fel d 1 does not have enzyme activity and is heavily glycosylated. The combination of glycosylation and high exposure (up to 1 μg/d) makes it possible that Fel d 1 induces tolerance through the gastrointestinal tract.²⁹ The properties of allergens derived from cockroaches are similar to those of dust mites in enzymatic activity, particle behavior, and the lack of evidence for tolerance. On the other hand, horse and rat allergens might have more in common with cat allergens (Table III).³⁰

Differential tolerance to common environmental allergens might have a direct bearing on worldwide variations in asthma prevalence and severity. Studies of asthma symptom prevalence in children have found a 20-fold variation in recent wheeze and a 30-fold variation in symptoms of severe asthma in different countries.³¹ Asthma symptoms are reported most frequently in the United Kingdom, Australia, and New Zealand, where sensitization to dust mite is common and allergen exposure is high. In northern and eastern Europe, where dust mite sensitization is less common and levels of mite allergen are low, asthma is less common and less severe. In addition, high rates of asthma mortality have been consistently reported from New Zealand, Australia, and the United Kingdom, as well as

among African American subjects living in poverty in the United States.³² Thus both the highest prevalence and mortality have been associated with high exposure to dust mite allergens, cockroach allergens, or both. Our data might be relevant to understanding why the prevalence and severity of wheezing is lower in countries in which the dominant allergens are those from cats.⁷

In conclusion, among children with high exposure to cat and dust mite allergens, both the prevalence and the titer of IgE antibodies are much higher for allergens derived from dust mites. The implication is that both the development and extent of the IgE response to cat allergens is controlled, whereas the response to dust mite is not. Such fundamental differences between allergens and the response to them could influence both the prevalence and the severity of asthma. The results have implications for the advice given to patients, the interpretation of evidence about causality, and the design of strategies to treat or prevent allergic disease.

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