

Contribution of dust mite and cat specific IgE to total IgE: Relevance to asthma prevalence

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Background: The prevalence of asthma is strikingly different in some Westernized countries: ~20% in New Zealand and ~8% in northern Sweden.

Objective: We investigated differences in total IgE and in the prevalence of wheezing related to the observation that high exposure to dust mite allergens induces high titers of IgE antibodies.

Methods: Two age-matched, population-based cohorts—1155 children in New Zealand (224 sera) and 3431 children (797 sera) in the Norrbotten area of Sweden—were studied. Sera were assayed for total IgE and specific IgE antibodies to relevant allergens.

Results: The mean total IgE among wheezing children was higher in New Zealand than Sweden (218 IU/mL vs 65.2 IU/mL; $P < .001$). In addition, the prevalence of high titer specific IgE antibody (≥ 50 IU/mL) was greater among the wheezing children in New Zealand compared with Sweden (35.7% vs 13.0%; $P < .001$). Specific IgE antibody to mite in New Zealand was significantly related to high total IgE (≥ 200 IU/mL; $r = 0.47$; $P < .001$), whereas the IgE antibody response to cat allergens did not make a significant contribution to high total IgE in either country.

Conclusion: The quantity of IgE antibody produced to dust mite provides a possible explanation for the higher total IgE levels found in children in New Zealand and may help to explain the differences in prevalence and severity of asthma between these 2 countries.

Clinical implications: Specific IgE antibody responses to dust mite and cat allergens may contribute differently to total serum IgE and to the prevalence of allergic disease. (*J Allergy Clin Immunol* 2007;119:359-65.)

Key words: Epidemiology, asthma, aeroallergens

Despite progressive increases in reported wheezing and in children requiring treatment for asthma, there are major differences in the prevalence of this disease in different countries.^{1,2} Higher values (ie, ~20%) have consistently been reported from the United Kingdom, Australia, and New Zealand as well as from inner cities of the United States.¹ By contrast, the reported prevalence of symptoms for Albania (3%), Greece (4%), and Scandinavia (6% to 8%) is much lower.¹ Clearly, understanding the reasons why this disease is less common in some countries would be of great importance.

In almost all studies, patients with asthma have total serum IgE levels that are elevated compared with both controls and patients with hay fever.³⁻⁶ Furthermore, there is a strong association between acute episodes of asthma measured by emergency department visits or hospital admissions and elevation of total IgE (IgE ≥ 200 IU/mL).⁷⁻¹⁰ By contrast, cutoff values for IgE that consistently distinguish between allergic and nonallergic individuals have been difficult to define.¹¹ The IgE isotype is unique in that only a relatively small range of foreign antigens give rise to IgE antibodies, and indeed a large proportion of the population has negative immediate hypersensitivity skin tests and undetectable specific IgE antibodies.¹² In addition, in most individuals, levels of circulating serum IgE are very low, that is, <100 IU/mL (where 1 IU = 2.4 ng IgE).^{13,14} Given these low levels of total IgE and limitations on the number of different specific IgE antibody responses, it is not surprising that the IgE response to one allergen source can represent a significant proportion of the total.¹⁵ In theory, allergen exposure could increase total IgE directly through increased specific IgE antibody or by having a nonspecific enhancing effect on the production of IgE.

Recent epidemiologic studies have shown at least 2 major differences between the IgE antibody responses to the allergens of dust mite on the one hand and cat on the other. Children raised with high exposure to dust mite allergen have both a high prevalence of IgE antibodies (as high as 35%) and high titers of IgE antibodies to mite allergens.^{16,17} In contrast, multiple studies have shown

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Abbreviations used

ISAAC: International Study of Asthma and Allergies in
Childhood
OR: Odds ratio

that IgE antibodies to cat allergens are less common among children raised in a house with a cat.¹⁸⁻²¹ Titers of IgE antibody to cat have also been shown to be significantly lower than those to dust mite.^{16,17} In some studies, the prevalence of asthma among children living with a cat is also decreased.^{18,19} On the basis of these findings, we proposed the hypothesis that specific IgE antibody to different allergens could differentially influence both the quantity of total IgE and the prevalence of wheezing in a community. To investigate this hypothesis, we have compared total serum IgE and specific IgE antibodies among children participating in population-based cohort studies in two countries, Sweden and New Zealand, where both allergen exposure and the prevalence of asthma are markedly different.^{16,22}

METHODS**Populations studied and allergen exposure**

Serum samples obtained from 2 cohorts of children were included in the analysis. From northern Sweden, a prospective, population-based cohort ongoing since 1996 with questionnaire data from 3431 children (97% response rate) was investigated.²³ In 2000, serum samples and questionnaire data were obtained from a random sample of those children living in the towns of Luleå and Kiruna ($n = 797$).²² From New Zealand, 112 wheezing and 112 nonwheezing children were randomly selected from an International Study of Asthma and Allergies in Childhood (ISAAC) population study of 1155 children in Hastings and Havelock (86% response rate), using a nested case control design.¹⁶ Both studies used an ISAAC-based questionnaire for parental assessment of wheezing at the same time the serum samples were collected at age 10 to 12 years. The study was approved by the ethics committee in each locale and the Human Investigation Committee at the University of Virginia.

Allergen exposure has been reported previously from assays of dust mite and cat allergens in house dust from the homes of children included in these studies.^{16,24} Mite allergen concentrations were at least 50-fold higher in New Zealand than Sweden.^{16,24} Cats were present in 28% of the homes in Sweden and in 60% of the homes in New Zealand^{16,24} (Table I).

Assays for total and specific IgE

All serum samples were analyzed at the University of Virginia for total IgE and specific IgE antibody by using CAP FEIA (Phadia AB, Uppsala, Sweden). The panel of specific IgE antibodies measured included the indoor allergens *Dermatophagoides pteronyssinus*, cat, and dog, as well as locally relevant molds or pollens.^{21,25} The cutoff for a positive specific IgE antibody result was 0.35 IU/mL. Any sera with ≥ 80 IU IgE antibody/mL were assayed at dilutions 1:5 and 1:20 to obtain accurate values for high titer IgE antibody.²⁶

Statistical analysis

Analyses were performed to evaluate relationships among total IgE, specific IgE antibodies, and wheezing. Children were grouped as

"wheezing" or "no wheezing" according to parental response to the question, "Has your child had wheezing or whistling in the chest in the last 12 months?" The use of this question has been extensively validated against other measures of asthma, including doctor diagnosis, in each of the cohorts studied here.^{1,23} Measurements of IgE antibody were log-transformed for all analyses. Geometric mean total serum IgE measurements were compared among groups by ANOVA. The relationships between elevated serum IgE (>200 IU/mL), wheezing, and country are reported as odds ratios (ORs) with 95% CIs. Pearson correlation was used to measure the relationship between specific IgE antibody responses and total IgE. Specific IgE antibody titers were compared with total IgE in a multiple regression model for each location. For the groups with total IgE > 200 IU/mL, the Kruskal-Wallis test was used for comparison of percent contribution of specific IgE antibody titers secondary to nonnormal distribution of the values. Statistical tests were performed by using SPSS 10.1 (SPSS Inc, Chicago, Ill).

RESULTS**Relationship between wheezing and total IgE**

Population-based estimates of wheezing and serum IgE levels were compared between the cohorts of children living in northern Sweden and New Zealand. The prevalence of wheezing in the last year among 3395 children living in northern Sweden (9.4%) was significantly lower than the prevalence (21.8%) among 1155 children in the New Zealand cohort ($P < .001$; Table I). In addition, the concentration of IgE in the serum of the children with wheezing in Sweden was lower than that of wheezing children in New Zealand (geometric mean total IgE, 65.2 IU/mL and 218 IU/mL, respectively; $P < .001$; Table I). The concentration of total IgE among nonwheezing children was also significantly lower in Sweden compared with New Zealand (geometric mean titers, 27.4 IU/mL and 64.8 IU/mL, respectively; $P < .001$; Fig 1). Elevated serum IgE (≥ 200 IU/mL) was significantly associated with wheezing in both countries, OR 2.6 (1.5-4.7) in Sweden and OR 4.3 (2.4-7.7) in New Zealand. However, the prevalence of high total IgE (≥ 200 IU/mL) among wheezing children was markedly lower in Sweden (26.1%) than New Zealand (55.4%; OR 0.29 [0.15-0.55]). In keeping with previous data, the severity of wheezing symptoms, as judged by responses to questionnaires, was greater among children in New Zealand compared with those in Sweden (mean symptom scores, 5.9 and 4.9, respectively; $P < .001$).^{16,21}

Specific IgE antibody measurements

Prevalence and titer of specific IgE antibodies were analyzed among children in both countries. As previously reported, both in Sweden and New Zealand, the presence of specific IgE antibody was more common among children with wheezing (Fig 2). However, in Sweden there were few children with high titers of IgE antibody to cat, grass, birch, or dog, and only 13.0% of children with wheezing had specific IgE antibody ≥ 50 IU/mL to any allergen (Fig 2). Thus, in addition to the lower prevalence of reported wheezing in Sweden, the children who reported wheezing had lower levels of specific IgE antibodies

TABLE I. Prevalence of wheezing, total IgE values, and allergen exposure in northern Sweden and New Zealand

	Sweden	New Zealand
Total number in cohort (response rate)	3395 (97%)	1155 (86%)
Age (y)	11-12	10-11
Wheezing in last 12 months (%)	319/3395 (9.4)	252/1155 (21.8)
Serum samples (n)	797†	224‡
Wheezing in last 12 months	69 (8.7%)	112
Mean total IgE with wheezing (IU/mL)*	65.2 (44.0-96.7)	218 (157-303)
Mean total IgE without wheezing (IU/mL)	27.4 (24.5-30.7)	64.8 (48.4-86.8)
Allergen in homes (μg/g dust) ^{16,24}		
Der p 1§	<0.4	21.4 (17.4-26.5)
Fel d 1		
in homes with a cat	33 (1.8-95.0)	40.8 (31.2-53.4)
in homes without a cat	0.42 (0.2-9.4)	3.3 (2.6-4.3)

*Data are presented as geometric mean (95% CI).

†Randomly selected from the population studied.

‡Randomly selected for nested case control study.

§Mean values for mite and cat allergens based on assays of 117 homes in Sweden and 224 homes in New Zealand.

(Fig 2) and total IgE (Fig 1). Only 5% of the children in Sweden had IgE antibody to mite, and the titers were uniformly low, which was consistent with the absence of detectable mite allergen in the homes in this area of Sweden (Table I; Fig 2). In New Zealand, 36% of the wheezing children had ≥ 50 IU/mL specific IgE antibody to dust mite, and high levels of IgE antibody to grass were also common. By contrast, although about 60% of the children had a cat at home, none of the children in New Zealand had IgE antibody to cat ≥ 50 IU/mL (Fig 2).

Relationship between titers of specific IgE and total IgE

Given the range of total IgE values shown in Fig 1, it is clear that specific IgE antibody values of >50 IU/mL would compose a significant proportion of total serum IgE. To investigate this relationship further, we compared the quantitative relationships between specific IgE antibody and total IgE in the 2 countries. In New Zealand, titers of specific IgE antibody to cat, dust mite, and grass pollen were significantly and positively related to total IgE. When the contribution of specific IgE was analyzed using multiple regression, IgE antibody titers to dust mite and grass were significantly associated with total IgE ($r = 0.78$). The strongest association was seen with dust mite (standardized coefficient, 0.58; Table II). In Sweden, there was a significant association between titers of specific IgE antibody to cat, grass, and dog and total IgE. In multiple regression analysis including all specific IgE antibodies, the response to each of the allergens was significant, but the regression value ($r = 0.57$) and the apparent maximum contribution (standardized coefficient, 0.30 to grass) were lower than those observed in New Zealand (Table II).

Specific IgE antibody titers in those with high total IgE

To investigate the relationship between specific IgE antibody and high total IgE, the data were analyzed for mite and cat specific IgE antibody as a percent of the total

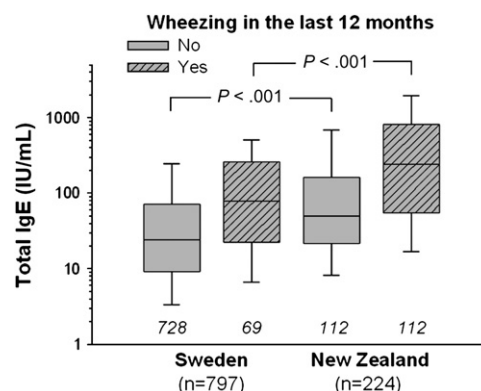


FIG 1. Total IgE levels among wheezing (shaded bars) and non-wheezing children (solid gray bars) living in northern Sweden and New Zealand (n for each group in *italics* below the plots). Titers of IgE ranging from the lower to upper quartiles are represented in boxes; whisker plots include values from the 10th to 90th percentiles. Horizontal lines show the median.

in sera with ≥ 200 IU/mL. A contribution of $>10\%$ of the total was only common for IgE antibody to mite allergens in New Zealand (Fig 3). Comparing IgE antibody to mite and total IgE, the relationship was strong and extended to sera with total IgE ≥ 1000 IU/mL ($r = 0.47$; $P < .001$; Fig 4). By contrast, the relationship between IgE antibody to cat and total IgE in sera with high IgE among the children in the Swedish cohort was not significant ($r = 0.14$; $P = .15$; Fig 4). The results suggest that IgE antibody to dust mite in the children in New Zealand makes a greater contribution to high total IgE than any of the specific IgE antibodies do among the children in Sweden. Thus, the IgE antibody responses to dust mite provide a rational explanation for the higher total IgE values in New Zealand.

DISCUSSION

It is well established that specific IgE antibody can be quantitatively high relative to the total quantity of this

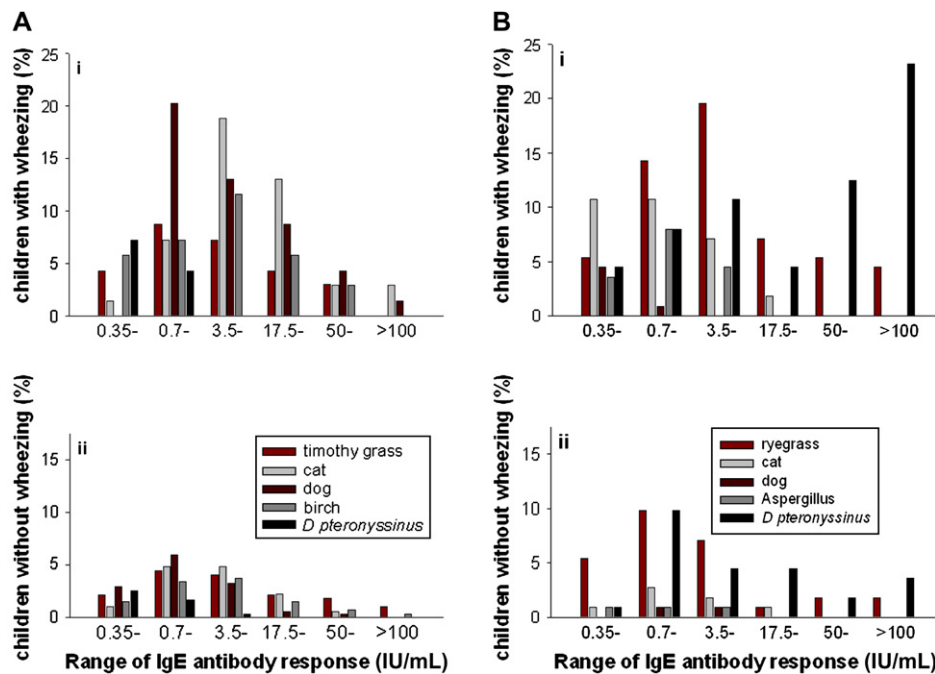


FIG 2. Specific IgE antibody titers in northern Sweden (A) and New Zealand (B). Data are the prevalence of children having a specific IgE antibody measurement in increasing ranges. Wheezing and nonwheezing children in each country are shown separately in figures marked *i* and *ii*, respectively.

TABLE II. Associations between specific IgE antibody titers and total IgE among children living in New Zealand and northern Sweden

	New Zealand n = 224	Sweden n = 797
All allergens	R (P value)	
	0.78 (<.001)	0.57 (<.001)
Specific allergens	Standardized coefficients (P value)	
Cat	0.02 (.7)	0.24 (<.001)
Dog	−0.01 (.8)	0.16 (<.001)
Grass	0.31 (<.001)	0.30 (<.001)
Dust mite	0.58 (<.001)	0.14 (<.001)

isotype in the serum and that higher serum IgE is related to the prevalence and severity of asthma. What is shown here is that specific IgE antibody to dust mite contributes to total IgE in New Zealand whereas specific IgE antibodies to cat does not relate to total IgE in either country. The results leave no doubt that IgE antibody responses to dust mite allergens can make a significant contribution to total serum IgE.²⁷ The relatively low titers of IgE antibody to cat fit with previous data suggesting that the IgE antibody response to Fel d 1 is progressively controlled with high exposure.²⁸ The contrast between the antibody responses to dust mite and cat allergens may also be a relevant factor in understanding the differences in both prevalence and severity of asthma between the 2 countries.

The argument that dust mite IgE antibody responses contribute to total IgE is easy to justify because in many

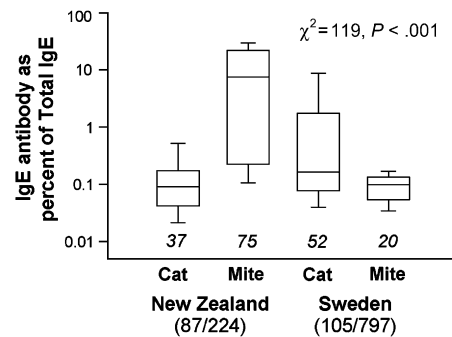


FIG 3. Specific IgE antibody to cat and dust mite as a percentage of total IgE among children with high total IgE (≥ 200 IU/mL) living in New Zealand (n = 87) and Sweden (n = 105). Number of children making a specific IgE antibody response to each allergen is given in *italics* below each plot.

cases, the quantity of specific IgE measured was 20% or 25% of the total. However, we would interpret the data shown in Fig 4, A, as suggesting that the immune response to mite in New Zealand could be an important cause of the increase in total IgE. There are 2 possible ways that a specific IgE antibody response could increase total IgE even though the measured IgE antibody explains only part of the total. Any assay for specific IgE antibody is inevitably a conservative estimate because it is dependent on the affinity of the antibody for the allergen. By contrast, the assay for total IgE uses high affinity antibodies for the isotype-specific epitopes on the heavy chain and is unlikely to underestimate total IgE. Thus, the assay may

underestimate the titer of specific IgE and thus its proportion of total IgE. Alternatively, certain allergens may have a nonspecific effect on the production of what has been called “noncognate” (or basal) IgE.²⁹ This kind of mechanism has been proposed to explain high levels of total IgE in helminth infection.³⁰ Clearly, the fact that the major allergen of dust mite is a potent enzyme could be relevant to a nonspecific effect on IgE antibody production.³¹⁻³⁴ However, there are other possible explanations for this difference in the response to cats and mites including the fact that cats are mammals (see Editorial by Platts-Mills in this issue of the Journal).

Although the two studies compared here had different designs, both used random sampling of a population with symptom surveys of the whole group. This makes it possible to estimate the prevalence of IgE and IgE antibodies among wheezing children in the community. In Sweden, the prevalence of wheezing associated with high titer specific IgE antibody (≥ 50 IU/mL) to any allergen was 1.1%, whereas in New Zealand, the estimated prevalence of wheezing associated with high titer specific IgE antibody to dust mite was 7.8%. The estimated prevalence of wheezing with a total IgE ≥ 200 IU/mL was 2.1% in Sweden and 11.6% in New Zealand. Thus, in Sweden, the number of wheezing children who were highly allergic was approximately 5-fold lower than in New Zealand. Our results help to explain why, in the ISAAC studies and European Community Respiratory Health Survey studies, asthma has been found to be more common in those English-speaking countries that are predominantly countries with high dust mite exposure.^{1,2}

There are 2 lines of evidence connecting the antibody responses observed in this study to severity of symptoms. First, elevated total serum IgE is a consistent finding among children and adults presenting acutely to the hospital with asthma.^{7,8,10,35,36} In a series of emergency department studies in children and adults, high titer specific IgE antibody is strongly associated with asthma.^{7,8,35,37} More recently, Heymann et al¹⁰ have reported that the total serum IgE of children age 3 to 18 years who were admitted to hospital was ≥ 200 IU/mL in 42 of 53 cases. There is also evidence from emergency department, hospitalization, and viral challenge studies that the effects of rhinovirus on the lower respiratory tract are largely restricted to patients with allergy who have an elevated total serum IgE.^{10,35-39} Second, worldwide studies of morbidity and mortality from wheezing have suggested that asthma is less severe in northern Sweden compared with New Zealand.^{40,41} Studies of data obtained from questionnaires have previously been validated by comparison with other indicators of asthma including bronchial hyperreactivity and physician diagnosis.^{42,43} Thus, the lower specific and total IgE levels in Sweden would be consistent with not only the lower prevalence of wheezing but also the decreased severity reported.

This study focuses on the contrast between IgE antibodies to dust mite and to cat. It was suggested several years ago that specific IgE antibody to ragweed was responsible for increases in total IgE during the ragweed

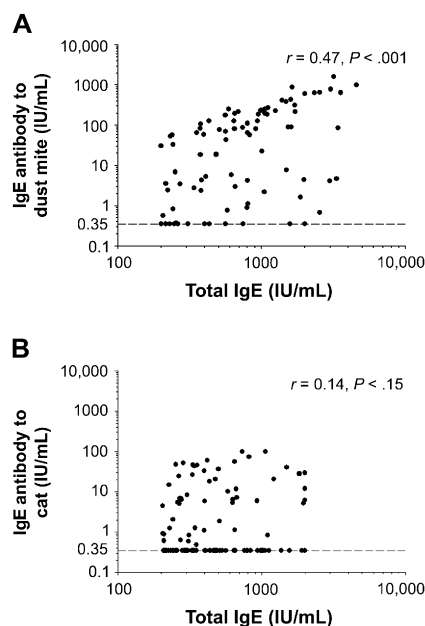


FIG 4. The relationship between specific IgE antibody and high total IgE (≥ 200 IU/mL) is shown for dust mite in New Zealand (**A**) and cat in northern Sweden (**B**).

season.¹⁵ In addition, IgE antibody to grass pollen among patients presenting with asthma during the pollen season has been found to be quantitatively high compared with total serum IgE⁴⁴ (data not shown). Among patients with asthma, levels of specific IgE antibody to some fungal allergens (eg, *Alternaria alternata*) also reach high absolute levels, although not as high as those for dust mite reported here.⁴⁵ By contrast, in Sweden, none of the 5 allergens studied were quantitatively sufficient to make an important contribution to total IgE in sera with ≥ 200 IU/mL IgE.

One of the limitations of our study is the lack of a variable that accounts for a genetic contribution to IgE levels, but there are several arguments against the importance of genetics to our results. Although there may be some subtle genetic differences between New Zealand and Sweden, the majority of the population is northern European in origin in each country. In general, northern European populations are genetically similar, and it would take a major genetic difference to explain differences in immune responses of the magnitude seen here. Further evidence can be found by examining the minority populations (accounting for $\leq 10\%$ in each country), which are dramatically different in origin. The Lapp population in the northern area of Sweden is thought to originate in central Asia. The minority group in the area of New Zealand that we studied is a mixture of Maoris and Pacific Islanders. There is good evidence that the minority populations in New Zealand become highly allergic to dust mites and have a high prevalence of asthma.⁴⁶ By contrast, asthma is not a common problem in the Lapp population, and there is no evidence in our cohort that this minority population was more allergic than the local

majority population.⁴⁷ Other limitations that we have considered include the use of floor dust samples rather than airborne samples to measure allergen exposure and the use of parental questionnaires to assess wheezing severity. Although floor dust samples may not be an accurate measure of exposure, they have been studied extensively to provide evidence for interstudy comparison of results. Similarly, the questionnaires used to assess symptoms of wheezing were designed for use in large studies performed at different centers and have been used to compare results throughout the world. They have been shown to be both sensitive and specific predictors of asthma. Finally, the children living in Sweden and New Zealand were enrolled by using different study models. Designing the optimal study to determine causation for allergic diseases can be a challenge. However, worldwide epidemiologic studies suggest that understanding the reasons for the differences in prevalence between countries may be as important as understanding the reasons for the increase in asthma.⁴⁸

By studying populations of children raised in 2 countries with dramatically different allergen exposure, an effect has been demonstrated that could not be observed within a single country. The results show that IgE antibody to mite is very common and can make a major contribution to total serum IgE, even in sera with ≥ 200 IU/mL. In turn, this provides a possible explanation for the association between asthma and total IgE and the high prevalence of wheezing in New Zealand. The relatively low levels of IgE and IgE antibodies in Sweden reflect the fact that high exposure to cat allergen does not induce high titer IgE antibodies. Thus, specific IgE antibodies in Sweden appear to make little contribution to high total serum IgE. Taken together, the results provide a possible explanation for the higher prevalence and severity of asthma in New Zealand and underscore the value of further study of epidemiologic relationships using worldwide collaborations.

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