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"Limitations of reliance on specific IgE for epidemiologic surveillance of food allergy"

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To the editor

It is extraordinarily difficult to estimate the true prevalence of food allergy. Questionnaire based estimates tend to overestimate the real rate of food allergy, defined here as evidence of both IgE sensitization and clinical reactivity, while the gold standard, food challenge, is logistically difficult. In fact, in the extensive literature review conducted for development of the NIAID Guidelines for the Diagnosis and Management of Food Allergy, the authors could only conclude that "food allergy affects more than 1–2% but less than 10% of the population"[1].

Allergen-specific IgE offers a potential surrogate. Recently, for example, a nationally representative survey, NHANES (National Health and Nutrition Examination Survey) 2005–6, collected data on food-specific IgE. However, it is not clear how to extrapolate food-specific IgE levels to estimate prevalence of food allergy in the absence of clinical data, given that most people with low level sensitization to foods are not clinically allergic[1]. One option that has been widely used is to apply positive predictive values (PPVs) for higher levels of food-specific IgE generated from previous work[2–5]. For example, using previously reported 50% and 95% PPVs and NHANES data, one group estimated the US prevalence of food allergy to be 2.5%[3], while others applied PPVs to inner city asthmatics[5]. However, the

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only PPVs available were generated from referral pediatric allergy populations[6–8] which are very unlikely to be valid for the general population. Here we incorporate dietary data from NHANES 2005–6 to relate patterns of reported food consumption to food-specific IgE levels. In doing so, we demonstrate the marked limitations of using IgE data alone to estimate food allergy prevalence.

NHANES is a complex population-based survey of the non-institutionalized civilian U.S. population (http://www.cdc.gov/nchs/nhanes.htm). In the 2005–6 survey, specific IgE by ImmunoCap to milk, peanut, egg and shrimp was obtained on a random subsample. Here, subjects 2 years and older were included (except for shrimp, where subjects 6 and over were included) in analyses of shrimp consumption over the past 30 days, and milk, egg and peanut consumption over the past year. Subjects were considered to consume cow's milk if they reported drinking whole, 2%, 1%, nonfat or unpasteurized milk as a beverage, in their cereal or in coffee or tea; excluding rice, soy or "other" milk. Subjects were considered to eat hen's eggs if they reported eating egg, including eggs, egg whites, egg substitutes, egg salads, quiche and soufflés. Although most egg substitutes contain egg whites, sensitivity analyses were done excluding egg substitutes. Lobster, crayfish and crab were grouped with shrimp as "crustaceans". Peanut consumption could not be defined with as much certainty, and was included only as an exploratory analysis; subjects were asked if they "ate peanut butter or other nut butter", and if they ate "peanuts, walnuts, seeds or other nuts" in the past year. History of asthma attack, itchy rash, allergic reaction and problems with sneezing in the past year were by self-report. See supplemental methods for details. There were no questionnaire data specifically relating to food allergy.

According to the cutoffs used by others[3], for each food we divided subjects into groups defined by food-specific IgE: "unlikely food allergy" (food-specific IgE of 0.35–2kU/L), "probable food allergy" (food-specific IgE between 2 kU/L and 7 kU/L for egg, 15 kU/L for milk, 14kU/L for peanut and 5kU/L for shrimp) and "likely food allergy" (food-specific IgE above those levels). The percentage of subjects in each IgE category consuming the relevant food was calculated. Within each category of IgE, the percentage of subjects with specific medical symptoms was compared by category of food consumption. Survey weights, strata and sampling units were incorporated into the analyses, except for analyses of symptoms by consumption status because the numbers of people in the higher IgE categories were too small.

5459 subjects had complete data for at least one of the food frequency questions and food-specific IgE; 7106 subjects had data on shrimp recall and IgE. Subjects who had dietary data were older ($p<0.001$), and more likely to be female ($p<0.001$), higher income ($p<0.001$) and Caucasian ($p<0.001$). There were no differences by history of allergic reaction, rash, asthma attack or sneezing problems in the past year ($p>0.05$ for all).

As can be seen in Table 1, milk, egg and peanut consumption was high in all categories of food-specific IgE, although lower for peanut and shrimp in the highest categories of food-specific IgE compared to the unsensitized category ($p=0.03$ for both). In the "probable food allergy" range of food-specific IgE, where previous studies had demonstrated ~50% PPV, 94% of subjects were consuming milk, 88% were consuming egg, and 96% reported eating peanut or other nut butter or peanuts/seeds/nuts. For the population as a whole, shrimp consumption was lower, with only 46% of those without shrimp sensitization eating shrimp in the previous 30 days. Still, even for shrimp, 31% of those deemed to have "likely food allergy" by IgE (i.e. PPV 95%) reported eating shrimp in the past 30 days. Unweighted analyses of the primary outcome are included in supplementary table 7.

After stratifying for age, the same pattern was generally true, although very few subjects fell into the highest IgE categories, and so the estimates of consumption were more unstable (Tables 2 and 3). Among the "probable food allergy group", 96% of children and 94% of adults were consuming milk, 79% of children and 93% of adults egg, 93% of children and 97% of adults peanut/seeds/nuts, and 2% of children and 33% of adults shrimp. Although both the rate of food sensitization and food consumption, for some foods, varied by age, there was no evidence of interaction between age, when dichotomized as <18 or ≥18, and IgE level, except for shrimp, where consumption was more likely among adults in the "probable food allergy category" (p=0.047).

We then examined whether subjects with higher food-specific IgE who consumed the food might have had unrecognized reactions to these foods. As would be expected, those with higher food-specific IgE tended to have more allergic symptoms; however, subjects in the higher IgE categories who ate the food were no more likely to report an asthma attack, sneezing, allergic symptoms/allergy attack, or a chronic itchy rash in the previous year than those who did not consume the food, even after adjusting for age, ethnicity, gender and income (see supplemental results and tables).

From these data, it is clear that in the general US population, a large percentage of people with high food-specific IgE consume the foods to which they are sensitized, and therefore are unlikely to have true clinical allergy. Although food frequency data were not obtained specifically for allergy diagnosis, questions related to milk, egg and shrimp consumption were relatively specific and not likely to overestimate food consumption. In fact, for egg and milk, we did not include other common forms of raw and concentrated egg or milk such as custards, cheese and yogurt in our analyses because of the possibility of misclassification, and so likely underestimated real consumption. For peanut, is it is possible that the data overestimate peanut consumption as the questions mixed peanuts with other nuts and seeds, but the same general issues are likely to be relevant.

These findings suggest that PPVs derived from allergy clinic populations cannot be meaningfully applied to the general population. This is not surprising, given that (1) the PPV of any diagnostic test is a function of underlying population prevalence[9] and (2) most of the previous estimates were generated from samples with approximately 20–80% prevalence of food allergy[6–8]. Given the lack of population-based data on the relevance of IgE levels to clinical allergy, it is currently not possible to reliably estimate the true prevalence of food allergy from IgE alone. There are several reasons why high food specific IgE may not accurately predict clinical disease. One is that, for certain foods, false positive results may be related to cross-reactivity with aeroallergens; for example shrimp and cockroach IgE levels were highly correlated in this dataset [data not shown]. However, even with more specific testing IgE testing, such as component based tests, some patients will have high IgE but not be clinically allergic. This may not be a major problem for research that focuses on associations with other factors, but for prevalence estimates it severely limits the inferences that can be made from IgE. Although questionnaires tailored to food allergy may provide more specific information about intake and symptoms, we still lack validated combinations of questionnaires plus/minus laboratory tests that are applicable to the general population. We will need more accurate methods in order to fully understand the burden of food allergy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

NHANES	National Health and Nutrition Examination Survey
PPV	Positive predictive value

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Key Messages

- In the general US population, large percentages of people with elevated food-specific IgE report consuming the relevant food.
- Positive predictive values for food-specific IgE derived from allergy clinic patient populations cannot be applied reliably to population samples.

Table 1

Consumption of foods by category of specific IgE to that food*.

	Milk		Egg			Peanut		Shrimp		
IgE Category	**% each group (#)**	**Drinks milk?**	**% each group (#)**	**Eats egg?**	**Eats egg w/o egg substitute?**	**% each group (#)**	**Eats peanut butter, peanuts, seeds?†**	**% each group (#)**	**Eats shrimp?**	**Eats crustaceans?**
Not-sensitized	94.6%	92%	96.1%	93%	90%	92.9%	96%	93.9%	46%	50%
"Unlikely food allergy"	4.6%	94%	3.6%	92%	91%	4.9%	97%	4.6%	48%	51%
"Probable food allergy"	0.7%	94%	0.3%	88%	88%	1.9%	96%	0.9%	32%	34%
"Likely food allergy"	0.1%	98%	<0.1%	93%	51%	0.3%	76%	0.7%	31%	31%
All	5389	92%	5408	93%	90%	5459	96%	7106	46%	50%

*Survey weighting was used to estimate percentage of US population within each IgE Category consuming the relevant food.

†Includes peanut butter, other nut butter, peanuts, nuts and seeds.

Table 2

Consumption of foods by category of specific IgE to that food* among subjects <18.

	Milk		Egg			Peanut		Shrimp		
IgE Category	**% each group (#)**	**Drinks milk?**	**% each group (#)**	**Eats egg?**	**Eats egg w/o egg substitute?**	**% each group (#)**	**Eats peanut butter, peanuts, seeds?†**	**% each group (#)**	**Eats shrimp?**	**Eats crustaceans?**
Not-sensitized	87%	97%	93%	87%	85%	90%	95%	95%	30%	34%
“Unlikely food allergy”	12%	97%	6%	86%	84%	6%	96%	4%	34%	34%
“Probable food allergy”	1%	96%	0.5%	79%	79%	4%	93%	1%	2%	2%
“Likely food allergy”	0.01%	0%	0.09%	90%	30%	0.6%	83%	1%	11%	11%
All	2026	97%	2037	87%	85%	2058	95%	2251	30%	34%

*Survey weighting was used to estimate percentage of US population within each IgE Category consuming the relevant food.

†Includes peanut butter, other nut butter, peanuts, nuts and seeds.

Table 3

Consumption of foods by category of specific IgE to that food[*] among subjects ≥18.

	Milk		Egg			Peanut		Shrimp		
IgE Category	**% each group (#)**	**Drinks milk?**	**% each group (#)**	**Eats egg?**	**Eats egg w/o egg substitute?**	**% each group (#)**	**Eats peanut butter, peanuts, seeds?[†]**	**% each group (#)**	**Eats shrimp?**	**Eats crustaceans?**
Not-sensitized	96%	91%	97%	94%	91%	94%	96%	94%	50%	54%
"Unlikely food allergy"	3%	91%	3%	95%	94%	5%	98%	5%	48%	53%
"Probable food allergy"	1%	94%	0.2%	93%	93%	1%	97%	1%	33%	36%
"Likely food allergy"	.2%	100%	0.01%	100%	100%	0.2%	71%	1%	24%	24%
All	3363	91%	3371	94%	92%	3401	96%	4786	49%	54%

[*] Survey weighting was used to estimate percentage of US population within each IgE Category consuming the relevant food.

[†] Includes peanut butter, other nut butter, peanuts, nuts and seeds.