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Using a physician panel to estimate food allergy prevalence in a longitudinal birth cohort

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The incidence of immunoglobulin E-mediated food allergy (IgE-FA) has increased in the US and Europe, likely due to a complex interplay between biologic, genetic and environmental factors.^{1–4} The estimated prevalence (95% Confidence Interval) of allergy to milk, egg, and peanut among US 0–2 year olds is 2.0% (1.6–2.4), 1.0% (0.7, 1.3), and 1.4% (1.1–1.8), respectively.⁵ Determining the prevalence of IgE-FA status for epidemiologic studies is challenging.⁶ Self-report may result in overestimates due to the inability of respondents to distinguish food intolerance from IgE-FA.^{7, 8} The double-blind placebo controlled food challenge (DBPCFC), while a gold standard for diagnosis of IgE-FA, is seldom feasible for large, epidemiologic studies. It is costly in terms of materials and staff and there is risk to the patient.^{9–11} The use of predictive decision points for specific IgE (sp-IgE) and skin prick tests (SPT) that predict clinical reactivity with > 95% certainty also have limitations and do not incorporate patient symptoms.^{12, 13} Even using sp-IgE as an outcome in research is problematic, since only 40% of persons who are sensitized to food allergens will respond to a DBPCFC.¹⁴ The challenge for advancing epidemiologic investigations in IgE-FA is to combine physician expertise with clinical assessments, medical history and

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self-report of symptoms. We describe the process of establishing a physician panel to systematically review data from infants enrolled in a birth cohort. Physicians then classified them according to the presence of IgE-FA.

The Wayne County Health, Environment & Atopy/Asthma Longitudinal Study (WHEALS) is a large, unselected, birth cohort. Methods are described in earlier publications.¹⁵ Briefly, pregnant women, aged 21-45 years, treated by HFHS physicians, were recruited from 9/2003 - 11/2007 to participate in the study along with their infants. Data available includes total serum IgE measured in infant cord blood; total and sp-IgE measured in infant blood obtained during home visits at ages 1, 6, and 12 months of age; SPT conducted at infant age 24 months, and parent interviews conducted at infant age 24 months (e.g., family medical history, coincidental diagnoses such as atopic dermatitis, etc.) and 36 months (gastrointestinal symptoms, onset and duration of reactions to food, etc.). A review of the infant's medical record supplemented clinical and interview data. All study protocols were approved by the Henry Ford Health System IRB.

Sp-IgE measurements were measured using the Pharmacia UniCAP system (Waltham, MA). Food sensitization was defined as sp-IgE > 0.35 IU/ml. A positive SPT (conducted using a Duotip-test® device, Decatur, IL) was defined as having a wheal diameter ≥ 3 mm than the saline control.

We established a physician panel of two board-certified allergists. For efficiency, infant data was forwarded to the panel only if 1 of the following criteria were met for milk, egg, or peanut allergens: (1) ≥ 1 sp-IgE ≥ 0.35 IU/ml; (2) a positive SPT; or (3) parental report of infant symptoms potentially related to food allergy *plus* at least one specific IgE ≥ 0.10 IU/ml. Infant data was presented to the panel in a standardized, web-based format. To enhance standardization in classifying infants as to the presence of IgE-FA, physicians were asked to combine professional experience with investigator-developed protocols based on the Guidelines for the Diagnosis and Management of Food Allergy in the United States.^{7, 16} A third allergist independently reviewed and ruled on discordant decisions.

Of 1258 infants enrolled, 590 (46.9%) had data sufficient for inclusion in the analysis (mean maternal age=29.8 (sd=5.2); 52.9% male infants, 63.2% Black/African-American infants). Cohort mothers included in the analysis were more likely to be married, and have higher education and income levels than those not included. Of the 590 infants, the panel reviewed data for 280 (47.5%), of which 82.1% had sp-IgE >0.35IU/ml to egg, milk or peanut; 10.7% had ≥ 1 positive SPT; and 7.1% had FA-related symptoms *plus* ≥ 1 sp-IgE ≥ 0.10 IU/ml.

Among 558 infants with sp-IgE results for all three food allergens, the overall prevalence of IgE-FA (*Highly Likely* + *Likely*) was 41/558 or 7.3% (5.2-9.5), and was 1.6% (0.6-2.6), 5.5% (3.6-7.3), and 4.3% (2.6-6.0), and for milk, egg, and peanut, respectively. By comparison, prevalence of sensitization to milk, egg and peanut was 31.6%, 24.5%, and 11.6%, respectively. The percentage meeting PD cut-points for milk, egg, and peanut, respectively, was 0.5%, 2.3%, and 1.2%.

The κ for overall agreement between panelists was 0.72 (0.65, 0.79) with discordance occurring in 6.4% of the decisions rendered. On average, panelists reviewed data for one infant in 1.7 minutes. At \$80/hour (\$2.26/chart), overall cost was < \$2000.

DISCUSSION

Systematic, cost-efficient approaches are needed to classify individuals with IgE-FA for epidemiologic research. Physician panel review has been used for other disease outcomes, such as asthma, with strong results.¹⁷ IgE sensitization and PD points represent extremes when estimating the prevalence of IgE-FA in a given population. Use of sp-IgE only as a marker of IgE-FA will overestimate the prevalence, whereas the use of IgE 95%PD points provides conservative estimates.^{7, 12} Panel review allowed incorporation of patient symptoms into the classification of IgE-FA, offering more specificity than using sensitization alone, and more sensitivity than using established 95% PD points alone.

Limitations of our study include missing data and significant differences between those included and those not included in the analysis. We acknowledge that prevalence estimates may have been different with a larger sample of participants with sufficient data for analysis.

We emphasize that results should not be viewed as a means of obtaining a *diagnosis* of IgE-FA, but represent a robust approach to classifying individual IgE-FA status for epidemiologic studies, as opposed to using sensitization or SPT metrics alone. Although some would suggest that validation of our results with a DBPCFC is a next step, we believe this would advocate for using this method as a clinical tool, which is not our intent.

In summary, epidemiologic studies provide valuable information regarding food allergy incidence, prevalence, and risk. Using a physician panel is a systematic and low cost method of classifying infants in a birth cohort as to the presence of IgE-FA.

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Abbreviations used

DBPCFC	Double-blind placebo-controlled food challenge
ETS	Environmental tobacco smoke
FA	Food allergy
HFHS	Henry Ford Health System
IgE-FA	Immunoglobulin E mediated food allergy
OR	Odds ratio
PD	Predictive decision

Sp-IgE	Allergen-specific immunoglobulin E
WHEALS	Wayne County Health, Environment & Atopy and Asthma Longitudinal Study

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Estimated prevalence of food allergy as determined by allergist panel and sensitization to egg, milk or peanut, along with IgE predictive decision points¹⁷ for each food allergen, restricted to infants with measures of sp-IgE

Table 1

	Milk (N=566)		Egg (N=567)		Peanut (N=560)		Any ² (N=558)	
	n	(%)	n	(%)	n	(%)	n	(%)
IgE-mediated food allergy ³	9	(1.6)	31	(5.5)	24	(4.3)	41	(7.3)
IgE >0.10 IU/ml	264	(46.6)	208	(36.7)	93	(16.6)	308	(55.2)
IgE 0.35 IU/ml	179	(31.6)	139	(24.5)	65	(11.6)	220	(39.4)
IgE 95% predictive decision cut-point ³	3	(0.5)	13	(2.3)	7	(1.2)	19	(3.4)

¹ Number with sp-IgE measures for this food allergen; includes n=24, n=23, and n=30 infants with missing sp-IgE data for milk, egg, and peanut, respectively.

² Denominator is persons with sp-IgE measures for all three food allergen; excludes n=32 infants missing at least 1 food sp-IgE (590-32=558);

³ As determined by physician panel and combines Highly Likely and Likely.