

The natural history of persistent peanut allergy

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ARTICLE INFO

Article history:

Received for publication June 28, 2011.

Received in revised form November 27, 2011.

Accepted for publication November 28, 2011.

ABSTRACT

Background: Peanut allergy affects 1% of children, and for those with persistent disease, few data have been published on trends in peanut-specific immunoglobulin E (P-IgE) levels or the value of P-IgE in predicting reaction severity.

Objective: The primary outcome was the frequency of inadvertent peanut exposure. Secondary outcomes included clinical characteristics, trends in P-IgE, characteristics of accidental exposures, and predictors of reaction severity in patients with persistent peanut allergy.

Methods: Records of patients with persistent peanut allergy were reviewed. Other allergic conditions, P-IgE levels, and peanut exposures were documented.

Results: Seven hundred eighty-two patients were studied, 524 of them male. The median age at initial observation was 1.4 years; the median duration of follow-up was 5.3 years. Of the 782 patients, 93.1% were avoiding other foods, 70.8% had atopic dermatitis, 57.3% allergic rhinitis, and 55.8% asthma. The median initial P-IgE was 28.0 kU/L, and the median peak P-IgE was 68.1. Six hundred eighty-five exposures were seen among 455 patients: 75.9% ingestion, 13.6% contact, 4.5% airborne. 73.7% resulted in urticaria/angioedema, 22.2% lower respiratory symptoms, 21.2% gastrointestinal symptoms, and 7.7% oral erythema/pruritus. Treatment included antihistamines (33.4%), emergency department visits (16.5%), epinephrine (13.1%), corticosteroids (7.7%), albuterol (3.2%), no treatment (26.3%), and not recorded (29.6%). The rate of postdiagnosis ingestion was 4.7%/year; exposures with severe reactions, 1.6%/year; reactions treated with epinephrine, 1.1%/year. Reaction severity did not change with repeated exposure. Severe reactions were associated with higher P-IgE, but not with age, sex, or asthma.

Conclusion: In this referral population, the rates of accidental peanut exposures and severe reactions were low. There was a strong association between higher P-IgE levels and reaction severity.

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Introduction

Peanut allergy is common and is a frequent cause of severe and sometimes even fatal reactions.^{1–3} Recent studies suggest that the prevalence of peanut allergy among children is over 1% and rising.^{4–10} In the general United States population, the prevalence of self-reported peanut allergy in children was 0.4% in 1997, compared with 0.8% in 2002 and 1.4% in 2008.¹⁰ Peanut allergy was once thought to persist throughout life. However, we now know that clinical tolerance can develop in approximately 20% of children, although recurrence is also possible.^{11–14}

Several studies have examined the natural history of peanut allergy over time.^{13,15–20} Our group previously reported on this

topic but focused on the subset of children who lost their allergy.^{13,21} In those reports, we found that peanut-specific immunoglobulin E (P-IgE) levels were the best predictor of developing peanut tolerance. However, for those with persistent disease, very few published data are available on trends in P-IgE levels over time or the value of P-IgE in predicting reaction severity.^{22–25}

In this study, we examined a large cohort of children with persistent peanut allergy to better characterize this disease by describing the trends in P-IgE levels over time, the frequency and source of inadvertent peanut exposures, and the nature of these reactions, as well as potential predictors of reaction severity.

Methods

We performed a retrospective chart review of patients seen by 2 attending physicians (R.A.W. and E.C.M.) at 2 tertiary pediatric allergy clinics between 1990 and 2009. Data were extracted by 2 physician reviewers (J.A.E. and D.L.N.) between February 2008 and

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Disclosures: Authors have nothing to disclose.

Funding Sources: Supported by The Eudowood Foundation.

July 2009. Seven hundred eighty-two patients were included with persistent peanut allergy, defined as (1) objective symptoms within 2 hours of a known peanut exposure, either in the community or during an oral food challenge, with supporting diagnostic testing (peanut skin prick test [SPT] with a wheal larger than 3 mm, or peanut-specific IgE [P-IgE] greater than 0.35 kU/L), and without known tolerance to peanut, or (2) a P-IgE greater than 14 kU/L without known tolerance to peanut. In patients without a known reaction to peanut, P-IgE was measured as part of an evaluation for other food allergies, or because of a sibling with peanut allergy. Patients were provided with detailed verbal and written education regarding strict peanut avoidance, including the avoidance of peanut oil and products with precautionary labeling, as well as written action plans for treatment of reactions. This information was reinforced at all follow-up visits. Food challenges to assess the development of peanut tolerance were offered to patients if their P-IgE declined to less than 5 kU/L and they had not had a recent reaction. The specific data collected included age, sex, current avoidance of other foods, history of reaction to other legumes (including lentil, chickpea, green pea, green bean, and other bean), history of other atopic diseases, all peanut exposures (including food source, route of exposure, symptoms, and treatment), results of P-IgE levels and SPT, results of oral peanut challenges, and dates of the first and last visit. This study was approved by the Johns Hopkins Institutional Review Board with a waiver of consent.

The diagnoses of asthma, eczema, and allergic rhinitis were made by the attending physicians. Information about specific food avoidance and peanut exposures was obtained at every visit. Patients with peanut allergy followed in these clinics typically have food-specific IgE levels checked annually using the Phadia ImmunoCAP System (Phadia, Uppsala, Sweden), at least until the long-term prognosis is established. The P-IgE levels measured by methods other than the ImmunoCAP System were not included.

The age at first observation was defined as the age at the first clinic visit, first reaction to peanut, first diagnostic test for peanut allergy, or first food challenge to peanut, whichever came first. Follow-up time was defined as the time between the age at first observation and the last point of contact with the patient. Patients were considered lost to follow-up if their last clinic visit was greater than 3 years before the time of chart review.

The primary outcome of interest was the frequency of inadvertent peanut exposure. Secondary outcomes of interest included trends in P-IgE levels, the route and source of peanut exposures, the symptoms and treatment received with each exposure, and predictors of reaction severity.

The P-IgE levels were recorded as less than 0.35 kU/L, greater than 100 kU/L, or, if between these 2 values, the specific value was recorded. For statistical analyses, P-IgE levels less than 0.35 kU/L were assigned a value of 0.18 kU/L, and levels greater than 100 kU/L a value of 101 kU/L. The P-IgE level obtained at the youngest age was considered the initial P-IgE level. When analyzed as predictors of reaction severity, initial and peak P-IgE levels were stratified into 4 categories: P-IgE $\geq$ 100 kU/L and 3 evenly distributed groups for P-IgE < 100 kU/L.

Peanut exposures were defined as either prediagnosis or post-diagnosis if they occurred after peanut avoidance was prescribed. Reactions to peanut exposures were defined as severe if they resulted in: (1) cardiovascular symptoms, (2) lower respiratory symptoms, or (3) symptoms from 3 or more systems (cardiovascular, lower respiratory, upper respiratory, skin [urticaria, angioedema, eczema], gastrointestinal, or oral). Reactions were defined as mild if they resulted in symptoms from 2 or fewer systems and did not include lower respiratory or cardiovascular symptoms.

Because not all patients had a known peanut exposure, patients were categorized as those with a clear history of a reaction and those without a history of reaction but with a P-IgE greater than 14

Table 1
Patient characteristics

Patient characteristics	All subjects (n = 782)	Positive history (n = 486)	No history of reaction (n = 296)
Male (%)	524 (67.0)	313 (64.4)	211 (71.3)
Female (%)	258 (33.0)	173 (35.6)	85 (28.7)
Age at 1 st observation (yrs) [Median (range)]	1.4 (0–16.0)	1.5 (0–16.0)	1.3 (0.2–14.2)
Follow-up time (yrs) [Median (range)]	5.3 (0–19.6)	5.6 (0–19.5)	4.4 (0–19.6)
Lost to follow-up (%)	205 (26.2)	142 (29.2)	63 (21.3)
Age at 1 st positive P-IgE or P-SPT (yrs) [Median (range)]	2.1 (0.2–16.4)	2.9 (0.3–16.4)	1.4 (0.2–14.2)
Initial P-IgE kU/L [Median (IQR)]	28.0 (6.0–99.0)	20.7 (3.8–87.1)	36.3 (15.1–>100)
Peak P-IgE kU/L [Median (IQR)]	68.1 (18.3–>100)	43.9 (8.8–>100)	92.0 (34.5–>100)
Peanut challenge (%)	76 (9.7) ^a	76 (15.6)	0 (0)
Other food allergies (%)			
Avoiding other foods	728 (93.1)	435 (89.5)	293 (99.0)
Avoiding food other than tree nuts	514 (65.7)	242 (49.8)	272 (91.9)
Tree nuts	685 (87.6)	409 (84.2)	276 (93.2)
Milk	279 (35.7)	88 (18.1)	191 (64.5)
Soy	103 (13.2)	30 (6.2)	73 (24.7)
Egg	309 (39.5)	104 (21.4)	205 (69.3)
Wheat	86 (11.0)	20 (4.1)	66 (22.3)
Sesame	182 (23.3)	77 (15.8)	105 (35.5)
Other legume	32 (4.1)	16 (3.3)	16 (5.4)
Other	319 (40.8)	147 (30.2)	172 (58.1)
Other atopic diseases (%)			
Atopic dermatitis	554 (70.8)	298 (61.3)	256 (86.5)
Allergic rhinitis	448 (57.3)	300 (61.7)	148 (50.0)
Asthma	436 (55.8)	266 (54.7)	170 (57.4)
Eosinophilic esophagitis	24 (3.1)	9 (1.9)	15 (5.1)
Family history (%)			
Sibling with food allergy	119 (15.2)	66 (13.6)	53 (17.9)
Sibling with peanut allergy	54 (6.9)	24 (4.9)	30 (10.1)

Abbreviations: IQR, interquartile range; P-IgE, peanut-specific IgE; P-SPT, peanut-specific skin prick test; yrs, years.

^aFor 31 of the 76 patients, their only peanut reaction occurred during the peanut challenge.

kU/L, based on studies documenting that these patients are more than 95% likely to have true peanut allergy.²⁶ To account for the potential for underestimating the reaction rate by including patients with no clinical reactivity, analyses were also performed including only patients with documented reactions.

All analyses were performed using StataSE 11. Multivariate logistic regression was done to model relationships between potential predictors and reaction severity. Generalized estimating equations were used to account for repeated observations within patients. Potential predictors included in the model were age, sex, asthma, reaction number, and initial or peak P-IgE. When evaluating predictors for treatment in the emergency department (ED) and with epinephrine, only postdiagnosis exposures were included in the analyses. For models that evaluated whether reaction severity increased with repeated exposure, only patients with 2 or more exposures were included.

Results

Patient demographics

Seven hundred eighty-two patients were included (Table 1). Four hundred eighty-six (62.1%) had a clear history of reaction, either in the community or during an oral food challenge, and 296 (37.9%) did not have a history of reaction but had a P-IgE greater than 14 kU/L. Five hundred twenty-four (67.0%) were male. The median age at first observation was 1.4 years (range, 0–16.0 years),

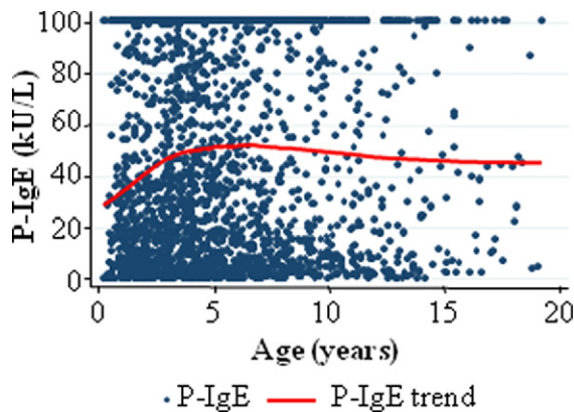


Figure 1. Scatter plot of all peanut-specific IgE (P-IgE) levels recorded ($n = 2,441$). Nonparametric smoothed curve shows the trend in P-IgE levels over time.

and the median duration of follow-up was 5.3 years (range, 0–19.6) with a total of 4,526 patient-years observed. Two hundred five (26.2%) patients were lost to follow-up. Seventy-six (9.7%) patients underwent an oral peanut challenge. At some point during the observation period, 554 (70.8%) were diagnosed with atopic dermatitis, 448 (57.3%) with allergic rhinitis, and 436 (55.8%) with asthma. At the time of the last visit, 728 (93.1%) were avoiding other foods because of a history of a reaction to the food, evidence of sensitization with a result highly suggestive of true food allergy, or concern for cross-reactivity or contamination. In all, 685 (87.6%) were avoiding tree nuts, 309 (39.5%) egg, 279 (35.7%) milk, 182 (23.3%) sesame, 103 (13.2%) soy, 86 (11.0%) wheat, and 319 (40.8%) one or more other non-legume foods. Thirty-two (4.1%) patients had a clear history of reaction to other legumes, including 6 with reactions to lentil, 5 chickpea, 13 pea, 6 green bean, and 4 other beans. Fifty-four (6.9%) patients had a sibling with peanut allergy.

Trends in P-IgE

Patients had a median of 3 P-IgE values (range, 0–12) and a total of 2,441 P-IgE levels were recorded. Values for P-IgE were not available for 9 patients. The median initial P-IgE was 28.0 kU/L (inter quartile ratio [IQR], 6.0–99.0 kU/L) and the median peak P-IgE was 68.1 kU/L (IQR 18.3–>100 kU/L). In general, P-IgE levels tended to increase until age 6 and then, overall, remained steady (Fig 1, Table 2).

Route and source of peanut exposures

A total of 685 peanut exposures, including 355 prediagnosis and 330 postdiagnosis, were experienced in the community by 455 patients (eTable 1). The median number of peanut exposures was 1 (range, 0–6). Three hundred fifty-five patients had a prediagnosis reaction. Postdiagnosis, 30.9% of patients had exposures (median 0, range 0–6). One hundred seventy-seven patients had 1 postdiagnosis exposure, 52 had 2, 7 had 3, 3 had 4, 2 had 5, and 1 had 6.

Two hundred twelve (64.2%) postdiagnosis exposures were attributable to ingestion, 64 (19.4%) to contact, and 30 (9.1%) airborne (Fig 2A, B). The most common source of postdiagnosis ingestion was peanut butter (24.1%, others were peanuts [17.0%], candy [17.0%], cookies [11.3%], peanut oil [5.7%], ice cream [3.3%], ethnic food [1.4%], and other baked goods [0.5%]) (eFig 1).

Symptoms and treatment received with peanut exposures

Symptoms resulting from all peanut exposures, including both prediagnosis and postdiagnosis, are characterized in eTable 1 and Figure 2C. Of prediagnosis exposures, 82.3% resulted in urticaria/angioedema, 24.2% lower respiratory symptoms, 20.6% gastrointestinal symptoms, 5.1% oral erythema/pruritus, 6.5% upper respiratory symptoms, 1.4% cardiovascular symptoms, 1.7% atopic

dermatitis, and in 12 (3.4%), symptoms were not recorded. Ninety-three (26.2%) resulted in a severe reaction. For postdiagnosis exposures, 64.5% resulted in urticaria/angioedema, 20.0% lower respiratory symptoms, 21.8% gastrointestinal symptoms, 10.6% oral erythema/pruritus, 4.8% upper respiratory symptoms, 1.5% cardiovascular symptoms, 0.6% atopic dermatitis, and in 37 (11.2%), symptoms were not recorded. Seventy-one (21.5%) resulted in a severe reaction.

Treatment of reactions after diagnosis is characterized in eTable 1 and Figure 2D. Treatment included antihistamines (31.5%), epinephrine (14.5%), systemic corticosteroids (6.4%), albuterol (3.9%), intravenous fluids (0.3%), and no treatment (27.9%). Patients were treated in the ED for 13.0% of exposures, and for 29.7%, treatment was not documented. Of the 66 postdiagnosis exposures with lower respiratory symptoms, 34.8% were treated in the ED, and 31.8% received epinephrine. Of the 5 exposures with cardiovascular symptoms, 80.0% were treated in the ED, and 60.0% received epinephrine. Of the 71 postdiagnosis exposures resulting in severe reactions, 36.6% were treated in the ED, and 33.8% received epinephrine.

Frequency of postdiagnosis exposures

The rate of any symptomatic postdiagnosis peanut exposure was 7.3% per year, and the rate of symptomatic ingestion was 4.7% per year (Table 3). The rates of postdiagnosis exposures with lower respiratory symptoms, resulting in a severe reaction, receiving treatment in the ED, or receiving treatment with epinephrine were 1.5%, 1.6%, 1.0%, and 1.1% per year, respectively. The rates of symptomatic postdiagnosis exposures tended to decrease with age and then appeared to increase after age 12 (Fig 2E). Sensitivity analyses, including only those with documented clinical reactivity, revealed a rate of any postdiagnosis reaction of 10.8% per year, with 49.8% of patients experiencing a symptomatic postdiagnosis peanut exposure over a median of 5.6 years (eTable 2).

Predictors of reaction severity

In a multivariate model, higher initial P-IgE significantly increased the odds of a more severe reaction, whereas age, sex, and a history of asthma did not (Table 4). Compared with the lowest initial P-IgE group (P-IgE < 4.8 kU/L), the odds ratio for lower respiratory symptoms was 1.77 ($P = .10$) for P-IgE between 4.8 and 24.7 kU/L, 2.02 ($P = 0.04$) for P-IgE between 24.8 and 99.9, and 3.29 ($P < .001$) for P-IgE of at least 100 ($P < .001$ for trend). Using a similar multivariate model, similar trends were seen for peak P-IgE as a predictor of reaction severity (Table 4). A similar multivariate model found that patients 12 years of age or older did not have more severe reactions by any definition.

A multivariate model that included age, sex, asthma, reaction number, and initial P-IgE was used to determine whether reaction severity increased with repeated exposure. Among 159 patients with at least 2 reactions, reaction severity did not change with

Table 2
Median peanut-specific IgE levels by age

Age (years)	P-IgE (kU/L) Median (IQR)	Number of P-IgE levels	Number of patients
<2	19.0 (5.0–71.4)	379	287
2 to <4	34.4 (10.9–100)	655	458
4 to <6	47.6 (12.5–>100)	585	434
6 to <8	42.9 (7.9–>100)	353	275
8 to <10	48.1 (10.3–>100)	206	167
10 to <12	29.4 (7.3–>100)	122	101
12 to <14	24.0 (4.0–95.0)	73	60
14 to <16	49.7 (10.4–>100)	38	30
≥16	41.9 (11.2–>100)	30	21

Abbreviations: IQR, interquartile range; P-IgE, peanut-specific IgE.

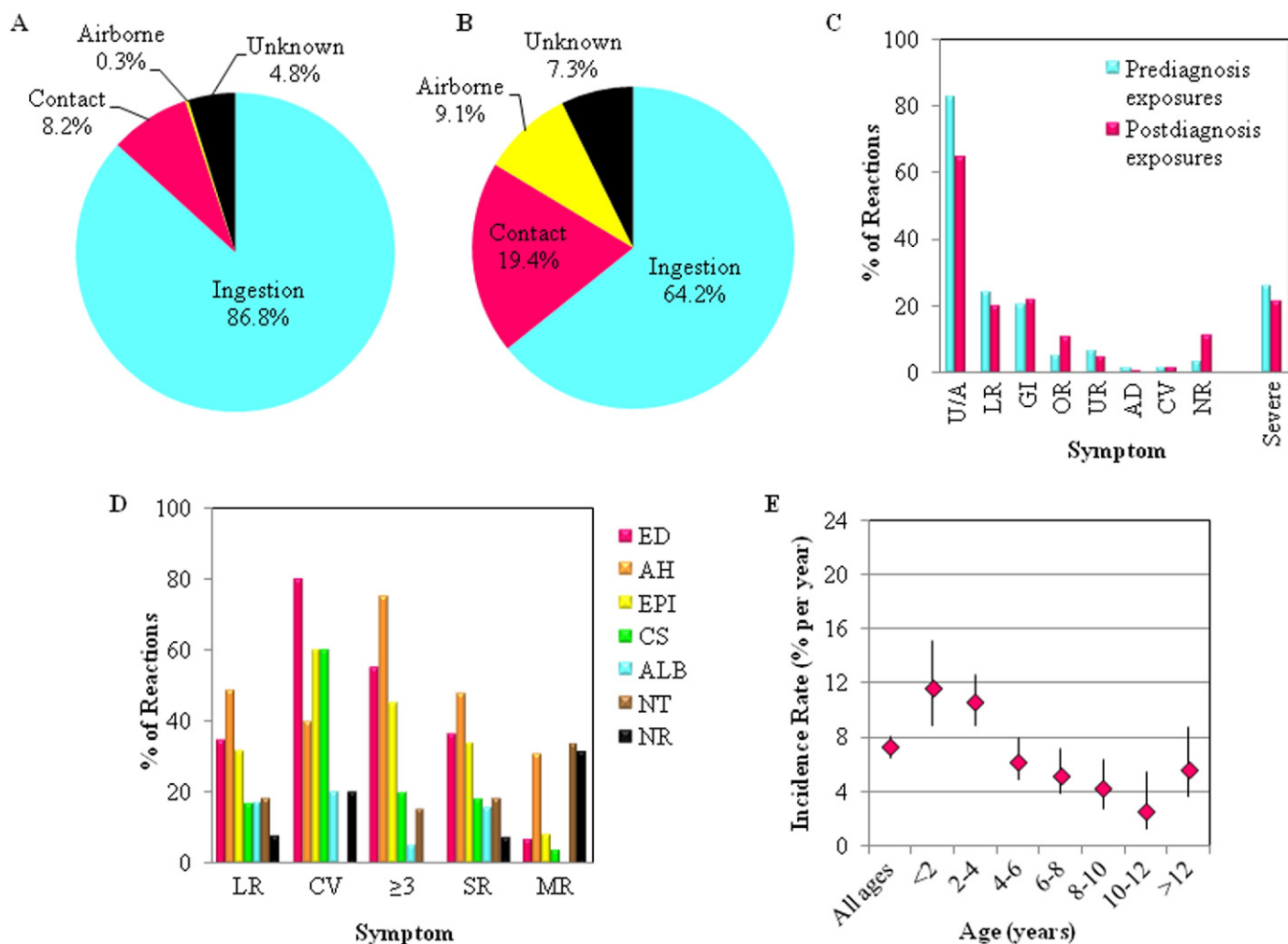


Figure 2. A, Routes of prediagnosis peanut exposure; $n = 355$. B, Routes of postdiagnosis peanut exposure; $n = 330$. C, Symptoms resulting from prediagnosis ($n = 355$) and postdiagnosis peanut exposures ($n = 330$). D, Treatment received segregated by symptoms for postdiagnosis peanut exposures. Lower respiratory symptoms; $n = 66$. Cardiovascular symptoms, $n = 5$. Three or more systems, $n = 20$. Severe reaction; $n = 71$. Mild reaction; $n = 222$. E, Rate (percent/year) of symptomatic postdiagnosis peanut exposures by age. U/A indicates urticaria/angioedema; LR, lower respiratory symptoms; GI, gastrointestinal symptoms; OR, oral erythema/pruritus; UR, upper respiratory symptoms; AD, atopic dermatitis; CV, cardiovascular symptoms; NR, not recorded; SR, severe reaction; ≥ 3 , ≥ 3 systems; MR, mild reaction; ED, treatment in the emergency department; AH, antihistamine; EPI, epinephrine; CS, corticosteroids; ALB, albuterol; NT, no treatment.

repeated exposure by any definition: lower respiratory symptoms (OR = 1.16, 95% CI = 0.88–1.53, $P = .28$), severe reactions (OR = 1.11, 95% CI = 0.85–1.45, $P = 0.45$), receiving treatment in the ED (OR = 1.06, 95% CI = 0.73–1.53, $P = .77$), or treatment with epinephrine (OR = 1.10, 95% CI = 0.71–1.70, $P = 0.68$).

Discussion

In this study of 782 patients with persistent peanut allergy, we found a low rate of postdiagnosis reaction at 7.3% per year, with 30.9% of patients experiencing a postdiagnosis reaction over a median of 5.3 years. Prior studies describing accidental exposures have reported 3.1% to 33.0% nut or peanut reactions per year.^{15,17–20,27}

For example, 1 early study of 32 children reported that 50% and 75% had an accidental exposure over 1 and 5 years, respectively, whereas another study of 83 children found that 60% had a reaction over a median of 5.9 years.^{15,17} In 1998, among a cohort of 102 children, 55% experienced a reaction over a median of 5.4 years.²⁷ Although our lower reaction rates may reflect different study methods, likely there has been some true decrease in accidental peanut reactions over the past 10 to 15 years secondary to greater public awareness, greater implementation of personal and public avoidance strategies, and stricter laws regarding food labeling.

Prior studies have provided conflicting information regarding trends in reaction severity with repeated exposure. Sicherer et al

Table 3
Incidence rates of postdiagnosis peanut exposures

Postdiagnosis exposure	Incidence rate (%/year) (95% CI)	Number of exposures	Number of subjects with an exposure
Any exposure route + any symptom	7.3 (6.5–8.1)	330	242
Ingestion + any symptom	4.7 (4.1–5.4)	212	170
Any exposure route + lower respiratory symptoms	1.5 (1.1–1.9)	66	54
Any exposure route + severe reaction	1.6 (1.2–2.0)	71	59
Any exposure route + treatment in the emergency department	1.0 (0.7–1.3)	43	38
Any exposure route + treatment with epinephrine	1.1 (0.8–1.4)	48	40

Table 4
Potential predictors of reaction severity

Potential predictor of severe reactions	Odds ratio for specified outcome (95% Confidence Interval), <i>P</i> -Value			
	Lower respiratory symptoms (<i>n</i> = 443 patients, 663 reactions)	Severe reaction (<i>n</i> = 443 patients, 663 reactions)	Treatment in the ED (<i>n</i> = 235 patients, 317 reactions)	Treatment with Epinephrine (<i>n</i> = 235 patients, 317 reactions)
Initial P-IgE <4.8 kU/L	1.00 by definition		1.00 by definition	
Initial P-IgE 4.8–24.7 kU/L	1.77 (0.90–3.48), .10	1.80 (0.93–3.48), .08	2.08 (0.63–6.82), .23	1.32 (0.40–4.33), .64
Initial P-IgE 24.8–99.9 kU/L	2.02 (1.04–3.90), .04	2.30 (1.22–4.33), .01	3.37 (1.10–10.37), .03	2.84 (0.99–8.18), .05
Initial P-IgE ≥100 kU/L	3.29 (1.71–6.32), <.001	3.44 (1.82–6.51), <.001	3.57 (1.20–10.58), .02	3.23 (1.17–8.95), .02
Age (1-year increase)	0.94 (0.86–1.03), .19	0.95 (0.88–1.03), .24	0.98 (0.90–1.07), .71	0.98 (0.87–1.11), .77
Female sex	0.93 (0.60–1.45), .75	0.90 (0.59–1.39), .65	0.78 (0.36–1.70), .54	0.84 (0.39–1.80), .65
History of asthma	1.29 (0.83–2.01), .26	1.22 (0.80–1.88), .35	1.08 (0.50–2.33), .85	1.75 (0.80–3.82), .16
Peak P-IgE <7.7 kU/L	1.00 by definition		1.00 by definition	
Peak P-IgE 7.7–34.5 kU/L	0.94 (0.44–2.02), .88	1.00 (0.48–2.08), .99	1.70 (0.44–6.56), .44	0.90 (0.23–3.53), .88
Peak P-IgE 34.6–99.9 kU/L	1.47 (0.74–2.90), .27	1.71 (0.89–3.29), .11	2.89 (0.85–9.81), .09	2.58 (0.82–8.19), .11
Peak P-IgE ≥100 kU/L	2.20 (1.17–4.14), .02	2.27 (1.23–4.22), .01	2.07 (0.64–6.67), .22	1.73 (0.57–5.25), .33
Age (1-year increase)	0.95 (0.87–1.03), .22	0.96 (0.88–1.04), .28	1.00 (0.92–1.09), .95	1.00 (0.88–1.11), .86
Female sex	0.90 (0.58–1.40), .65	0.88 (0.57–1.34), .54	0.76 (0.35–1.67), .50	0.80 (0.37–1.70), .56
History of asthma	1.30 (0.83–2.03), .25	1.24 (0.81–1.90), .33	1.09 (0.51–2.36), .80	1.89 (0.85–4.22), .12

Odds ratios calculated in two multivariate models that included the above variables and reaction number, and accounted for repeated measurements over time. Bolded values are statistically significant.

Initial IgE was divided into approximate quartiles. For analyses of lower respiratory symptoms and severe reactions, there were 110, 111, 117, and 105 patients in the <4.8 kU/L, 4.8–24.7 kU/L, 24.8–99.9 kU/L and ≥100 kU/L groups, respectively. For analyses of treatment in the emergency department and with epinephrine, there were 63, 58, 59 and 55 patients, respectively.

Peak IgE was divided into approximate quartiles. For analyses of lower respiratory symptoms and severe reactions, there were 90, 88, 93, and 172 patients in the <7.7 kU/L, 7.7–34.5 kU/L, 34.6–99.9 kU/L and ≥100 kU/L groups, respectively. For analyses of treatment in the emergency department and with epinephrine, there were 48, 43, 55, and 89 patients respectively.

Abbreviations: ED, emergency department; P-IgE, peanut-specific IgE.

found that among 4685 patients with a self-reported allergy to peanut, reactions became more severe with subsequent exposure and were more likely to be treated with epinephrine.²⁸ Similar results with increasing reaction severity were reported by Hourihane et al²² and by Vander Leek et al.¹⁷ However, 3 more recent studies found that reaction severity tended to decrease or remain the same with repeated exposure.^{18–20} In the current study, reaction severity did not change with repeated exposure by any definition.

In our study population, 71 (21.5%) postdiagnosis exposures were characterized as severe, and of these only 33.8% were treated with epinephrine, including only 45.0% involving 3 or more systems. These rates are slightly higher than that seen by Yu et al, who reported a 20% treatment rate of severe reactions with epinephrine.²⁰ These data are especially striking because every patient received education about the management of allergic reactions at each visit, pointing to the need for improved educational approaches for all patients with potentially severe food allergy and ED personnel.

We examined several potential predictors of reaction severity, including age, sex, asthma, and P-IgE levels, and found higher initial and peak P-IgE to be associated with reaction severity. Although P-IgE was associated with reaction severity, age, sex, and a history of asthma did not predict severity. These findings differ from those of prior studies showing that patients with asthma were more likely to have severe reactions, and with the clinical impression that more severe reactions occur in adolescents.^{28,29} One possible explanation for this difference is that we analyzed asthma diagnosed at any time during the observation period as a predictor of reaction severity rather than active asthma at the time of reaction.

With 2,441 P-IgE levels over 4,526 patient-years, we have compiled the largest data set of P-IgE levels yet reported. Although the relationship between P-IgE levels and reaction severity as defined by treatment in the ED or with epinephrine may simply be a reflection of heightened levels of concern secondary to the higher P-IgE levels, the higher prevalence of lower respiratory symptoms and severe reactions is less likely to be confounded by patient or parental concern. These data are similar to the findings by van Odijk et

al.²⁵ Hourihane et al did not find an association between P-IgE and reaction severity in the community, but they did find an association in food challenge, as did Wainstein et al.^{22–24} Although this association is an important novel finding, it does not suggest a change in patient management, as many patients with high P-IgE levels did not have severe reactions, and some with low levels did.

In addition to the relationship to reaction severity, overall, very little information has been published regarding trends in P-IgE over time. We found that P-IgE tended to increase until age 6 and then remain steady until age 10, after which levels decreased slightly. However, because P-IgE levels are not routinely monitored once a patient's long-term prognosis is established, our P-IgE data set becomes increasingly smaller as patients grow older.

Finally, we were able to use this study to assess cross-reactivity of peanut with other legumes. In our population, 32 (4.1%) patients had a clear reaction to another legume. However, we recognize that many patients may have never introduced all legumes into their diet, so the true rate of cross-reactivity might be somewhat higher. Although 103 (13.2%) patients were avoiding soy, we did not include this in our estimate of legume cross-reactivity because we had less clear data about clinical reactions to soy. Our results are similar to those seen in prior studies, showing a low rate of cross-reactivity between peanuts and other legumes ranging from 0 to 6.5%.^{15,30,31}

Although strengthened by the large sample size and duration of follow-up, our study has several limitations. It was done retrospectively, and not all patients had a documented clinical allergy to peanut, with 296 patients included based solely on a P-IgE greater than 14 kU/L. These patients were included because they are more than 95% likely to have a true allergy, and they were not offered oral challenges because of their high likelihood of reaction. Although including patients with a likely peanut allergy but without documented clinical reactivity may have biased our estimated reaction rates, only a small number of patients (approximately 15) without true peanut allergy would be included, so that any underestimate of the rate of postdiagnosis peanut reaction was trivial. In fact, excluding these patients would have resulted in an overestimation of the postdiagnosis reaction rate. However, to account for the potential

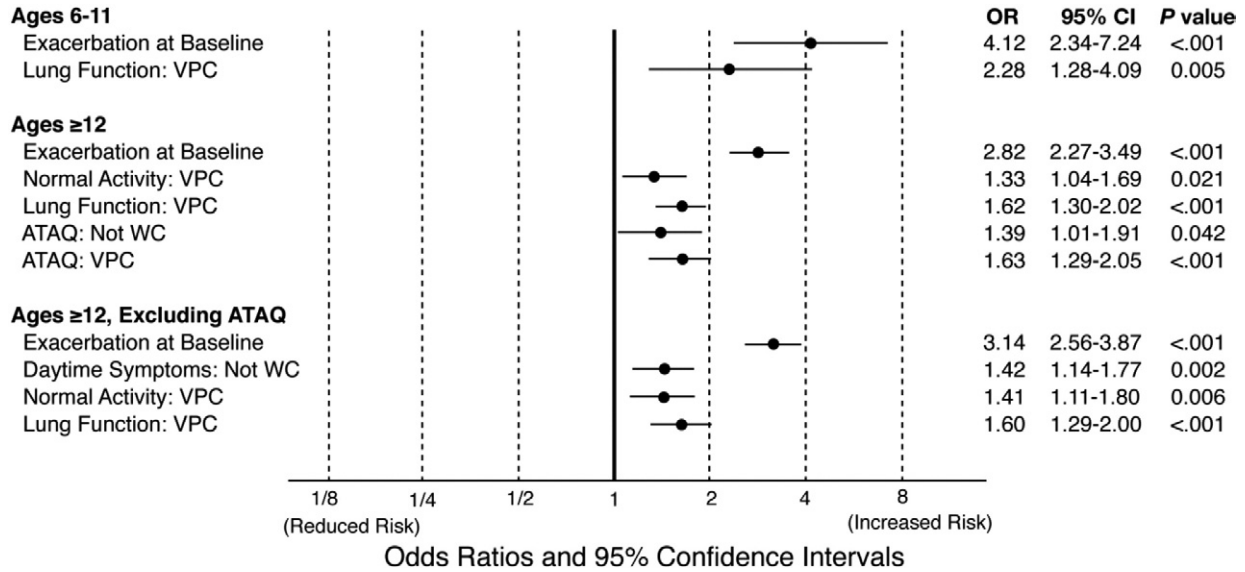
for underestimating the reaction rate by including these patients, analyses were also performed that only included patients with a documented clinical allergy, revealing a postdiagnosis reaction rate of 10.8% per year, with 49.8% experiencing a reaction over a median of 5.6 years. Therefore, the true rate of postdiagnosis peanut reaction is likely somewhere between 7.3 and 10.8% per year.

Another limitation of our study was the determination of “persistent” peanut allergy. As a retrospective chart review, 26.2% of patients were lost to follow-up and, therefore, we cannot be certain that these patients continue to be peanut allergic. Similarly, patients who continue to be labeled as peanut allergic were done so based on diagnostic testing and postdiagnosis reactions, and food challenges to assess the development of peanut tolerance are not routinely offered unless P-IgE has become sufficiently low (<5 kU/L), and some patients may have developed peanut tolerance despite an elevated P-IgE. Finally, we are limited by the fact that this study was conducted in tertiary pediatric allergy clinics, so our data may not be generalizable.

In conclusion, we have shown that in a large referral population of children with persistent peanut allergy, rates of postdiagnosis peanut exposure and severe reaction were low and, in comparison with earlier studies, may have decreased over the past 10 to 15 years. Unfortunately, however, epinephrine was not administered as often as clinically indicated. We have also demonstrated a strong association between higher P-IgE levels and reaction severity, as well as the clear trends in P-IgE levels over time. Each of these results will help to inform clinicians and patients alike regarding the optimal management of patients with persistent peanut allergy.

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eFigure 1. Sources of peanut exposure for prediagnosis (n = 308) and postdiagnosis (n = 212) ingestion. Abbreviations: PNB, peanut butter; PN, peanut; CA, candy; CO, cookies; OBG, other baked goods; IC, ice cream; EF, ethnic food; PNO, peanut oil; OTH, other; UNK, unknown.

eTable 1
Peanut exposure characteristics

	All peanut exposures number (%)					Prediagnosis peanut exposures number (%)					Postdiagnosis peanut exposures number (%)				
	Ingestion 520 (75.9)	Contact 93 (13.6)	Airborne 31 (4.5)	Unknown 41 (6.0)	All routes 685 (100)	Ingestion 308 (86.8)	Contact 29 (8.2)	Airborne 1 (0.3)	Unknown 17 (4.8)	All routes 355 (100)	Ingestion 212 (64.2)	Contact 64 (19.4)	Airborne 30 (9.1)	Unknown 24 (7.3)	All routes 330 (100)
Food source															
Peanut butter	208 (40.0)	57 (61.3)	9 (29.0)	2 (4.9)	276 (40.3)	157 (51.0)	16 (55.2)	0	1 (5.9)	174 (49.0)	51 (24.1)	41 (64.1)	9 (30.0)	1 (4.2)	102 (30.9)
Peanut	106 (20.4)	20 (21.5)	18 (58.1)	10 (24.4)	154 (22.5)	70 (22.7)	11 (37.9)	1 (100)	6 (35.3)	88 (24.8)	36 (17.0)	9 (14.1)	17 (56.7)	4 (16.7)	66 (20.0)
Candy	62 (11.9)	1 (1.1)	0	2 (4.9)	65 (9.5)	26 (8.4)	0	0	0	26 (7.3)	36 (17.0)	1 (1.6)	0	2 (8.3)	39 (11.8)
Cookies	49 (9.4)	0	0	0	49 (7.2)	25 (8.1)	0	0	0	25 (7.0)	24 (11.3)	0	0	0	24 (7.3)
Other baked goods	5 (1.0)	0	0	1 (2.4)	6 (0.9)	5 (1.6)	0	0	0	4 (1.1)	1 (0.5)	0	0	1 (4.2)	2 (0.6)
Ice cream	10 (1.9)	0	0	0	10 (1.5)	3 (1.0)	0	0	0	3 (0.8)	7 (3.3)	0	0	0	7 (2.1)
Ethnic food	6 (1.2)	0	0	0	6 (0.9)	3 (1.0)	0	0	0	3 (0.8)	3 (1.4)	0	0	0	3 (0.9)
Peanut oil	16 (3.1)	1 (1.1)	0	0	17 (2.5)	4 (1.3)	0	0	0	4 (1.1)	12 (5.7)	1 (1.6)	0	0	13 (3.9)
Other	13 (2.5)	5 (5.4)	1 (3.2)	3 (7.3)	22 (3.2)	0	0	0	0	0	13 (6.1)	5 (7.8)	1 (3.3)	3 (12.5)	22 (6.7)
Unknown	45 (8.7)	9 (9.7)	3 (9.7)	23 (56.1)	80 (11.7)	16 (5.2)	2 (6.9)	0	10 (58.8)	28 (7.9)	29 (13.7)	7 (10.9)	3 (10.0)	13 (54.2)	52 (15.8)
Symptom															
Lower respiratory	129 (24.8)	6 (6.5)	10 (32.3)	7 (17.1)	152 (22.2)	82 (26.6)	0	0	4 (23.5)	86 (24.2)	47 (22.2)	6 (9.4)	10 (33.3)	3 (12.5)	66 (20.0)
Upper respiratory	31 (6.0)	0	8 (25.8)	0	39 (5.7)	23 (7.5)	0	0	0	23 (6.5)	8 (3.8)	0	8 (26.7)	0	16 (4.8)
Urticaria, angioedema	387 (74.4)	83 (89.2)	18 (58.1)	17 (41.5)	505 (73.7)	253 (82.1)	27 (93.1)	1 (100)	11 (64.7)	292 (82.3)	134 (63.2)	56 (87.5)	17 (56.7)	6 (25.0)	213 (64.5)
Atopic dermatitis	4 (0.8)	1 (1.1)	0	3 (7.3)	8 (1.2)	3 (1.0)	0	0	3 (17.6)	6 (1.7)	1 (0.5)	1 (1.6)	0	0	2 (0.6)
Gastrointestinal	135 (26.0)	0	2 (6.5)	8 (19.5)	145 (21.2)	69 (22.4)	0	0	4 (23.5)	73 (20.6)	66 (31.1)	0	2 (6.7)	4 (16.7)	72 (21.8)
Oral erythema/pruritus	46 (8.8)	4 (4.3)	0	3 (7.3)	53 (7.7)	15 (4.9)	2 (6.9)	0	1 (5.9)	18 (5.1)	31 (14.6)	2 (3.1)	0	2 (8.3)	35 (10.6)
Cardiovascular	8 (1.5)	1 (1.1)	0	1 (2.4)	10 (1.5)	4 (1.3)	1 (3.4)	0	0	5 (1.4)	4 (1.9)	0	0	1 (4.2)	5 (1.5)
Not recorded	25 (4.8)	9 (9.7)	1 (3.2)	14 (34.1)	49 (7.2)	9 (2.9)	1 (3.4)	0	2 (11.8)	12 (3.4)	16 (7.5)	8 (12.5)	1 (3.3)	12 (50.0)	37 (11.2)
Treatment															
Diphenhydramine	190 (36.5)	26 (28.0)	9 (29.0)	4 (9.8)	229 (33.4)	114 (37.0)	10 (34.5)	0	1 (5.9)	125 (35.2)	76 (35.8)	16 (25.0)	9 (30.0)	3 (12.5)	104 (31.5)
Emergency department	102 (19.6)	5 (5.4)	2 (6.5)	4 (9.8)	113 (16.5)	67 (21.8)	1 (3.4)	0	2 (11.8)	70 (19.7)	35 (16.5)	4 (6.3)	2 (6.7)	2 (8.3)	43 (13.0)
Epinephrine	78 (15.0)	4 (4.3)	3 (9.7)	5 (12.2)	90 (13.1)	40 (13.0)	0	0	2 (11.8)	42 (11.8)	38 (17.9)	4 (6.3)	3 (10.0)	3 (12.5)	48 (14.5)
Systemic corticosteroids	47 (9.0)	2 (2.2)	3 (9.7)	1 (2.4)	53 (7.7)	31 (10.1)	0	0	1 (5.9)	32 (9.0)	16 (7.5)	2 (3.1)	3 (10.0)	0	21 (6.4)
Albuterol	17 (3.3)	3 (3.2)	2 (6.5)	0	22 (3.2)	9 (2.9)	0	0	0	9 (2.5)	8 (3.8)	3 (4.7)	2 (6.7)	0	13 (3.9)
Intravenous fluids	1 (0.2)	1 (1.1)	0	0	2 (0.3)	1 (0.3)	0	0	0	1 (0.3)	0	1 (1.6)	0	0	1 (0.3)
No treatment	129 (24.8)	26 (28.0)	11 (35.5)	14 (34.1)	180 (26.3)	73 (23.7)	5 (17.2)	1 (100)	9 (52.9)	88 (24.8)	56 (26.4)	21 (32.8)	10 (33.3)	5 (20.8)	92 (27.9)
Not recorded	143 (27.5)	38 (40.9)	8 (25.8)	14 (34.1)	203 (29.6)	91 (29.5)	12 (41.4)	0	2 (11.8)	105 (29.6)	52 (24.5)	26 (40.6)	8 (26.7)	12 (50.0)	98 (29.7)

eTable 2

Incidence rates of postdiagnosis peanut exposures including only those patients with a documented clinical history of peanut allergy

Postdiagnosis exposure	Incidence rate (%/year) (95% CI)	Number of exposures	Number of subjects with an exposure
Any exposure route + any symptom	10.8 (9.7–12.0)	330	242
Ingestion + any symptom	6.9 (6.0–7.9)	212	170
Any exposure route + lower respiratory symptoms	2.2 (1.7–2.7)	66	54
Any exposure route + severe reaction	2.3 (1.8–2.9)	71	59
Any exposure route + treatment in the emergency department	1.4 (1.0–1.9)	43	38
Any exposure route + treatment with epinephrine	1.6 (1.2–2.1)	48	40