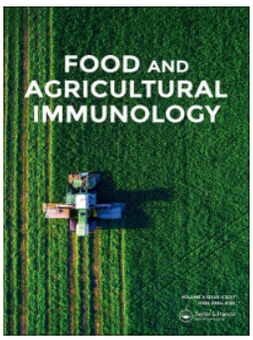

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Demographic, clinical and diagnostic correlation of almond allergy in a cohort of nut allergy patients

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ABSTRACT

Tree nut anaphylaxis commonly categorizes almond as a potential allergen. However, large studies on allergic cohorts focused on almond allergy are rare. Food allergy is increasing globally. In parallel, almond consumption is increasing in developed nations. This study presents serological data in a large paediatric cohort of food anaphylaxis patients specifically assessing almond allergy risk. The purpose of this study is to describe the correlation of almond allergy specific to demographic, clinical and diagnostic markers in a cohort of 411 nut-allergic children. In this cohort with a history of food allergy, the prevalence of almond allergy was 67.6%. Approximately 25% of patients demonstrated both almond sensitivity (sIgE > 0.35 kU/L) and clinical reactivity (wheal size > 3 mm). Interestingly, peanut allergy was listed in the top 3 allergens of 71.8% of patients with almond sensitivity and reactivity. A better understanding of these relationships is essential as more patients are receiving personalized care.

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KEYWORDS
Allergy; Anaphylaxis; Immunotherapy; Almond; IgE; Peanut

Abbreviations

LTP Lipid Transfer Protein
OASOral Allergy Syndrome
sIgE Specific Immunoglobulin E

Introduction

Food allergy is a major public health condition impacting approximately 8% of children in the United States (Gupta et al., 2011). The most common food allergens which elicit IgE-mediated reactions include milk, egg, peanut, tree nuts, wheat, soy, fish, and shellfish (The Big Eight) (Boyce et al., 2010). Of these, peanut allergy is the most common cause of anaphylaxis in children presenting to the emergency department, as well as the most common cause of fatal food anaphylaxis (Bock et al., 2001; Bock et al., 2007). Tree nut anaphylaxis is less studied. Tree nut allergy accounts for 18–40% of fatalities from

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food-induced anaphylaxis and, in some cases, allergic reactions have been reported to be more severe to tree nuts than to peanut (Clark et al., 2007; McWilliam et al., 2015). Due to the anxieties associated with the potentially fatal consequences of inadvertently consuming allergens, peanut and tree nut allergic individuals are often recommended, for safety, to avoid all nuts including almonds (Avery et al., 2003).

Limited data are reported on the prevalence of almond allergy. Instead, due to the high cross-reactivity between almonds and other tree nuts, reports focus on cross-sensitivity of antibodies and cross-reactivity of species proteins. Cross-reactivity occurs when a patient has clinical reactivity (i.e. allergic symptoms) to a closely related food. By contrast, cross-sensitization occurs when a patient has a positive IgE or skin test to a closely related food, but does not necessarily exhibit allergic symptoms upon ingestion of the food (Kazatsky & Wood, 2016). Therefore, it is important to distinguish if a patient is cross-reactive or cross-sensitized to minimize unnecessary food avoidance. For example, a recent study found that 49 of 83 individuals (59%) with suspected tree nut allergy were sensitized to almond (reactive via skin prick test), but only one individual was allergic to almond (Elizur et al., 2018). Additionally, another study had a large cohort, but again, the cohort was not selected as an almond allergic cohort rather an almond food challenge was administered to a large randomized cohort (Virkud et al., 2019). It is interesting to note that these similar small studies reflect on other sensitizing measures which predispose the development of almond sensitization. The peach lipid transfer protein, Pru p 3, is allergenic and has been shown to be the primary sensitizing allergen for cross-reactivity with other lipid transfer proteins, including Ara h 9 (peanut), Cor a 8 (hazelnut), Jug r 3 (walnut), and Pru du 3 (almond) (Mothes-Luksch et al., 2017).

Sensitization is a reflection of IgE production and binding properties. Acceptance of the comorbidity of tree nut and peanut allergy has led to studies focused on correlation of allergic markers among this population. A previous study measured the correlation between peanut-, tree nut- and seed-specific IgE (sIgE) in patients with Spearman's rank-order correlation coefficients. The highest correlations were between walnut and pecan (0.96), cashew and pistachio (0.95), and almond and hazelnut (0.84). Interestingly, peanut was not highly correlated with any tree nut or seed; the highest correlation was with almond (0.53) (Maloney et al., 2008).

Given the limited number of tree nut anaphylaxis clinical studies to date, clear limitations exist in the interpretation of almonds regarding allergy. Further confounding almond allergy is the simultaneous presence of other tree nut and peanut allergy. The Southern California Food Allergy Institute (SCFAI) under the Translational Pulmonary and Immunology Research Center has conducted data-driven analytics-based food immunotherapy for tree nut and peanut allergies since 2007. SCFAI and its affiliation at Miller Children's Hospital conduct food immunotherapy in a controlled, monitored, and outpatient setting. The centre has treated over 6000 children aged 2–21 years. The centre's protocol has led to the successful desensitization and tolerance induction in patients to milk, eggs, wheat, soy, peanuts, tree nuts, seeds, fish, and some shellfish. The patient intake process requires a comprehensive assessment of food allergy history and diagnostics. All patients undergo a complete food allergy history including classification of food allergy reactions based on the WAO Anaphylaxis Grading Score (Simons et al., 2011). All patients undergo comprehensive diagnostic blood testing including skin testing, associated component resolved diagnostics and ImmunoCAP for several

allergens including tree nuts and peanuts. All patients undergo food desensitization therapy utilizing tolerance induction data analytics as a patient-specific protocol. However, all patients reach the same dietary maintenance food doses upon completion of treatment. Isolated reports of almond anaphylaxis are rare but reported (Senders et al., 2018). The purpose of this study is to describe and evaluate the correlation of almond allergy specific to demographic, clinical, and diagnostic markers prior to initiating OIT in a cohort of 411 nut-allergic children.

Methods

In preparation for this correlation study, patient charts were obtained via electronic medical record from June 2015 to 2019. Demographic, clinical, and diagnostic marker data were pulled and analysed. The project underwent Institutional Review Board evaluation and approval from the Memorial Health Research Administration and the Western Institutional Review Board. Informed consent was obtained once patients met inclusion criteria.

Inclusion criteria:

- Age between 2 and 21 years
- History of food allergy anaphylaxis
- Treatment at the Southern California Food Allergy Institute any time between June 2015 to October 2019
- Complete electronic medical record
- Complete blood results for: Complete blood count for peripheral eosinophilia, total IgE, Immunocap to airborne allergens, IgG4 food allergen specific testing, urticarial induced basophil activation, interleukin testing (IL-4, IL-5, IL-10, IL-13) and component resolved diagnostic testing (Pirl laboratories)
- Completed comprehensive skin prick testing and patch testing for food specific allergens
- Completed food allergy treatment (desensitization) to at least one known clinical anaphylactic food; knowledge of anaphylaxis is based on either history, or during clinical reaction while undergoing desensitization treatment

Exclusion criteria:

- History of known immunodeficiency, coeliac disease, or eosinophilic enteritis
- Oral steroid dependence (daily use)
- Prior omalizumab therapy

Statistical analyses

Prevalence of almond allergy was characterized into diagnostic marker groups defined by sensitivity (+ if sIgE $\geq$0.35 kU/L) and clinical reactivity (+ if wheal size $\geq$ 3 mm): (1) non-allergic to almonds, (2) + sensitivity/− clinical reactivity, (3) − sensitivity/+ clinical reactivity, and (4) + sensitivity/+ clinical reactivity. Potential contributing factors to diagnostic marker group were evaluated using ANOVA (normally distributed continuous

factors), Kruskal–Wallis test (non-normally distributed continuous factors), and Chi-square test for categorical variables. The prevalence of almond allergy (diagnostic marker groups 2–4 combined) was then described overall and across potential contributing factors. Generalized linear models (GLM) analyses with binomial logistic regression specified assessed the unadjusted odds of almond positive status for each respective factor level compared to the reference category. A multivariate analysis determined the combination of factors that impact the prevalence of almond allergen with selection based on forward entry procedure and variables retained at the 0.05 level of significance. Analyses were conducted using SPSS V18.0 (Chicago, IL).

Results

Prevalence and diagnostic marker of almond allergy in the study population

Of the patients screened, 411 met all criteria. In our population of paediatric patients with a history of food allergy, the prevalence of almond allergy was 67.6%, Table 1. Approximately 1 in 4 patients (25.0%) demonstrated both almond sensitivity (sIgE ≥ 0.35 kU/L) and clinical reactivity (wheal size ≥3 mm). Nearly 1 in 3 patients (32.1%) were sensitive, but not clinically reactive to almonds. Less common was lack of almond sensitivity when patient showed clinical reactivity (10.5%). Those patients resembled the non-allergic group in terms of percentage positive to outdoor allergens, which trended much lower than observed for patients who were sensitive to almonds ($p < .01$). Majority of patients sensitive and clinically reactive to almonds were positive to dander (57.8%), mold/mite (53.9%), tree (52.9%), and grass (51.0%) allergens. The most common outdoor allergens in almond-sensitive patients who were not clinically reactive followed a similar trend with 58.9% allergic to dander and slightly less than half were positive to mold/mite, tree, and grass allergens. As expected, almond sIgE was significantly higher in almond-sensitive patients who had a positive compared to negative almond skin test result [median = 3.89 kU/L vs. 1.39 kU/L, $p < .01$). Diagnostic markers of almond allergy described by the four categories did not show differentiation in terms of percentage whose IL-4 or IL-13 value ≥5 ($p > .05$). IgG4 values trended higher in patients with almond sensitivity than without in the overall cohort ($p = .016$), although differences across all four groups were not significant at the $p = 0.05$ level.

Top 3 + allergens described by almond sensitivity and clinical reactivity

Of 41 food allergies investigated, the most common included in patient's top 3 according to sIgE value were peanut (62.0%), sesame (39.2%), cashew (36.3%), hazelnut (31.4%), pecan (15.6%), and almond (11.7%), Table 2. Interestingly, peanut allergy was listed in the top 3 of 71.8% of patients with almond sensitivity and reactivity, compared to 64.4% of those sensitive but not reactive, and 51.2–55.6% of non-sensitive patients ($p = .029$). Sensitivity to almonds rather than clinical reactivity showed stronger correspondence to multiple food allergens; whereby nearly all patients with almond sIgE ≥0.35 kU/L had ≥3 positive food allergens compared to 48.1% of those not allergic to almonds and 62.8% of those clinically reactive, but not sensitive ($p < .001$). Overall, the highest median sIgE level across food allergens was 27.90 kU/L [IQR 6.00, >100]. This did not vary by

Table 1. Description of study population by almond sensitivity and clinical reactivity status. Inclusion criteria: (1) ≤22 years of age, (2) history of food allergy, (3) treated at TPIRC from 2013 to 18, (4) Almond sensitivity and clinical reactivity known.

		Almond sensitivity (sIgE) and clinical reactivity (SPT) status[a]				
	Overall	−sIgE −SPT	+sIgE −SPT	−sIgE + SPT	+sIgE +SPT	*p*-value[b]
	N = 411	*N* = 133	*N* = 132	*N* = 43	*N* = 103	
Age, mean (SD)	8.4 (4.3)	8.6 (4.4)	8.7 (3.8)	7.1 (4.4)	8.3 (4.4)	*p* = .187
<5 years	23.6%	22.3%	17.4%	35.7%	28.2%	
5–11 years	56.5%	56.9%	61.4%	50.0%	52.4%	
12–17 years	17.9%	16.9%	21.2%	11.9%	17.5%	
18–22 years	2.0%	3.8%	0.0%	2.4%	1.9%	
Male, %	60.6%	53.4%	65.2%	58.1%	65.0%	*p* = .171
Tree +, %	35.7%	19.5%	40.3%	24.2%	52.9%	*p* < .001*
Dander +, %	47.8%	32.5%	58.9%	30.3%	57.8%	*p* < .001*
Weed +, %	22.7%	6.5%	29.5%	9.1%	38.2%	*p* < .001*
Mold/Mite +, %	44.7%	33.3%	49.6%	39.4%	53.9%	*p* = .009*
Grass +, %	33.3%	15.4%	41.1%	15.2%	51.0%	*p* < .001*
Almond sIgE (kU/L) in Pts.: w/+sIgE, median [IQR]	1.78 [0.73, 6.24]		1.39 [0.63, 4.06]		3.89 [0.98, 8.77]	*p* = .001*
Almond IgG4 (mcg/ml) in Pts.: Overall, median [IQR]	0.41 [0.10, 1.30]	0.34 [0.10, 0.87]	0.49 [0.10, 2.43]	0.24 [0.10, 1.79]	0.41 [0.10, 1.45]	*p* = .070
w/+sIgE, median [IQR]	*0.47* [0.10, 2.02]					
w/-sIgE, median [IQR]	*0.30* [0.10, 0.89]					
	p = .016*					
IL 4 ≥ 5, %	9.6%	7.3%	10.0%	10.0%	11.8%	*p* = .713
IL 13 ≥ 5, %	6.8%	9.7%	3.8%	7.5%	6.9%	*p* = .330

[a]Sensitivity defined by sIgE results: negative (<.35 kU/L) and positive (≥0.35 kU/L);
Clinical reactivity defined by skin test results: negative (<3 mm) and positive (≥3 mm).
[b]*p*-value based on ANOVA for comparison of average age across four almond status groups; Kruskal–Wallis test for comparison of non-normally distributed variables across groups where median [IQR] reported (Mann–Whitney U test for comparison of almond sIgE distribution between those with − and + almond SPT and comparison of IgG4 distribution between + vs − almond sIgE groups); Chi-square test was used for distributional comparison of categorical factors across four almond status groups;
Valid % presented in table (*N* = 24 missing outdoor allergen test results).

exclusion of almond allergen, indicating that the highest sIgE within patient tended to be for other food allergies. Interestingly, median sIgE value observed across food allergens was highest in patients with almond sensitivity who were not reactive (64.85 kU/L), followed by those with both almond sensitivity and reactivity (53.20 kU/L), non-sensitive but reactive patients (31.20), and lowest in those negative to almond (5.89) ($p < .001$).

Potential factors influencing the prevalence of almond allergy

Almond allergy was significantly more prevalent in patients who were male, were positive to outdoor allergens, had an almond sIgG4 value in the highest quartile, had an sIgE level other than almond that exceeded 100 kU/L, and those who had sesame, cashew, and/or hazelnut among their top 3 allergies unadjusted for other factors, ($p < .05$), Table 3. Figure 1 shows influence on prevalence of almond allergen of factors significant in the

Table 2. Description of patient's Top 3 + allergens by almond sensitivity and clinical reactivity status.

		Almond sensitivity (sIgE) and clinical reactivity (SPT) status[a]				
	Overall $N = 411$	−sIgE −SPT $N = 133$	+sIgE −SPT $N = 132$	−sIgE + SPT $N = 43$	+sIgE +SPT $N = 103$	p-value[b]
Allergen listed in + "Top 3" by rank order of sIgE result:						
Peanut	62.0%	55.6%	64.4%	51.2%	71.8%	$p = .029$*
Sesame	39.2%	27.8%	47.7%	27.9%	47.6%	$p = .001$*
Cashew	36.3%	24.1%	40.2%	32.6%	48.5%	$p = .001$*
Hazelnut	31.4%	17.3%	43.9%	25.6%	35.9%	$p < .001$*
Pecan	15.6%	11.3%	16.7%	18.6%	18.4%	$p = .402$
Almond	11.7%	–	18.2%	–	23.3%	$p < .001$*
sIgE level for + "Top 3" allergens median [IQR]:						
Peanut	37.05 [3.99, >101]	3.66 [0.75, 40.45]	87.70 [18.20, >101]	35.60 [2.71, 98.40]	42.00 [8.73, >101]	$p < .001$*
Sesame	3.96 [0.78, 11.90]	0.66 [0.24, 1.44]	6.57 [1.87, 16.45]	3.08 [0.32, 8.37]	9.22 [3.97, 22.00]	$p < .001$*
Cashew	10.30 [3.21, 49.40]	1.85 [0.75, 7.54]	10.20 [4.93, 34.60]	2.49 [0.79, 6.95]	52.20 [15.10, 82.80]	$p < .001$*
Hazelnut	5.87 [1.22, 16.30]	1.03 [0.46, 1.84]	10.70 [2.45, 24.85]	0.80 [0.44, 4.90]	13.10 [6.62, 24.70]	$p < .001$*
Pecan	5.01 [1.57, 20.00]	1.38 [0.35, 3.48]	14.05 [4.95, 26.70]	1.26 [0.80, 3.09]	15.45 [5.84, 29.00]	$p < .001$*
Almond	3.10 [0.44, 14.40]	0.17 [0.12, 0.21]	2.28 [0.50, 5.84]	0.13 [0.12, 0.21]	12.90 [2.57, 38.00]	$p < .001$*
# + sIgE allergens:						
None	2.5%	7.0%	0.0%	2.3%	0.0%	$p < .001$ ≥3 vs <3
One	11.8%	27.1%	0.0%	27.9%	1.0%	
Two	7.4%	17.8%	2.3%	7.0%	1.0%	
Three or more	78.4%	48.1%	97.7%	62.8%	98.7%	
Highest sIgE level[c], median [IQR]	27.90 [6.00, >100]	5.89 [1.60, 23.40]	64.85 [16.50, >100]	31.20 [2.78, 69.90]	53.20 [18.40, >100]	$p < .001$
Highest sIgE level excluding almond[c], median [IQR]	27.90 [5.86, >100]	5.89 [1.60, 23.40]	64.85 [16.50, >100]	31.20 [2.78, 69.90]	53.20 [18.40, >100]	$p < .001$

[a]Sensitivity defined by sIgE results: positive (≥0.35 kU/L); Clinical reactivity defined by skin test results: positive (≥3 mm).
[b]*P*-value based on Kruskal–Wallis test for comparison of non-normally distributed variables across groups where median [IQR] reported; Chi-square test was used for distributional comparison of categorical factors across four almond status group.
[c]Allergen could be different than six highest ranking sIgE levels.

final adjusted analyses. In the multivariate model, sIgE for food allergen other than almond that exceeded 100 kU/L versus <100 kU/L corresponded to 7 times higher odds of patient testing positive for sIgE to almond allergen (OR = 7.77, 95% CI 3.33, 18.09, $p < .01$). The estimated prevalence of almond allergy in those with sIgE to other food allergy > vs. ≤ 100 kU/L was 93.9% vs. 66.0%, respectively. Although weed allergen was not as prevalent as other outdoor allergens, positivity translated to 4.6 increased odds of having almond sensitivity and/or clinical reactivity ($p < .05$). Top 3 food allergens that included sesame, cashew, and/or hazelnut continued to correspond to higher odds of almond allergen positivity ($p < .05$). Almond sIgG4 in the highest quartile, not surprisingly, translated to higher odds of testing positive to almonds. Interestingly, in this model, peanut was not contributory likely because all almond allergic patients were allergic to peanuts as well.

Discussion

The field of almond allergy research is very limited. With this study, we set out to characterize the largest almond allergic cohort to date. Due to the beneficial effects of almonds, their consumption has increased in developed countries. Almonds are rich in monounsaturated fats, magnesium, copper, and fibre. The fat and fibre contribute to their beneficial hypercholesteremic effect and may also lead to other benefits such as better cardiovascular health and reduced diabetes risk (Kamil & Chen, 2012). Of the eight allergens that have been isolated from almonds, only six are currently tested via ImmunoCap and only four are currently recognized as allergens by WHO-IUIS list of allergens (Pomes et al., 2018). The primary storage protein in almonds, almond major protein (AMP or amandin), is an 11S albumin, which has been identified as a heat stable allergen. The AMP likely will result in cross-reactions with other foods that contain 2S and/or 11S albumins such as peanut, walnut, and sunflower seeds. Of note, Ara h 2, likely the most potent allergen in peanuts, is a 2S albumin that shares IgE binding epitopes with almond and Brazil nut allergens (Glaspole et al. 2007). Lipid transfer proteins (LTP) are major allergens in Rosaceae fruits and can result in varying degrees of cross-reactivity with other foods as well. For instance, almond LTP has 94% amino acid sequence homology with that of apricot LTP.

Oral allergy syndrome, or OAS, is a type of food allergy characterized by allergic reactions in the mouth and throat in response to eating certain nuts, fruits, and vegetables (often raw) as a result of primary sensitization to a different allergen. In almonds, this is often a result of a patient being allergic to birch, a common cause of spring hay fever. It is important to note that OAS can be experienced upon first exposure to a food. Almonds can frequently sensitize individuals and may commonly lead to symptoms of food allergy. In general, nut allergies are potentially life threatening and it is uncommon for children to outgrow almond allergy. This allergy has the potential to cause a severe life-threatening allergic reaction known as anaphylaxis.

Almond allergy is prevalent in a significant portion of patients that have other forms of food anaphylaxis. In our cohort of paediatric patients, this portion was 67.6%, Table 1. These almond allergic patients have atopy to pollen and dander and they also have a wide range of sIgE levels. In the end, the patients at the highest risk category are patients with positive SPT (wheal size ≥3 mm) and high sIgE results (≥0.35 kU/L); this was 1 in 4 of

Table 3. Prevalence of almond allergy (sIgE ≥ 0.35 kU/L or SPT ≥3 mm) examined by potential confounding factors in 411 patients with history of food allergy.

	% w/Almond allergy	Unadjusted OR (95% CI)	*p*-value[a]
Overall	67.6%		
Age			$p = .990$
<5 years	69.8%	1.16 (0.61, 2.18)	$p = .656$
5–11 years	67.8%	1.05 (0.62, 1.81)	$p = .848$
≥12 years	66.7%	Reference	
Gender:			$p = .039$*
Male	71.5%	1.55 (1.02, 2.37)	
Female	61.7%	Reference	
Tree Allergen			$p < .001$*
Positive	82.6%	3.14 (1.89, 5.21)	
Negative	60.2%	Reference	
Dander Allergen			$p < .001$*
Positive	78.4%	2.53 (1.62, 3.96)	
Negative	58.9%	Reference	
Weed			$p < .001$*
Positive	90.9%	6.25 (2.91, 13.41)	
Negative	61.5%	Reference	
Mold/Mite			$p = .002$*
Positive	76.3%	2.00 (1.28, 3.12)	
Negative	61.7%	Reference	
Grass			$p < .001$*
Positive	85.3%	3.91 (2.26, 6.76)	
Negative	59.7%	Reference	
Almond IgG4 (mcg/ml):			
≤0.10 (≤25th percentile)	65.4%	Reference	
0.11–1.30 (26–75th %)	60.9%	0.83 (0.51, 1.33)	$p = .427$
>1.30 (>75th %)	82.2%	2.44 (1.31, 4.58)	$p = .005$*
IL 4			$p = .289$
<5	67.9%	Reference	
≥5	76.3%	1.53 (0.70, 3.33)	
IL 13			$p = .135$
<5	69.6%	Reference	
≥5	55.6%	0.55 (0.25, 1.21)	
Allergen in Top 3			
Peanut			$p = .065$
Positive	71.0%	1.49 (0.98, 2.27)	
Negative	62.2%	Reference	
Sesame			$p = .001$*
Positive	77.0%	2.09 (1.34, 3.27)	
Negative	61.6%	Reference	
Cashew			$p < .001$*
Positive	78.5%	2.29 (1.44, 3.65)	
Negative	61.5%	Reference	
Hazelnut			$p < .001$*
Positive	82.2%	2.95 (1.77, 4.91)	
Negative	61.0%	Reference	
Pecan			$p = .099$
Positive	76.6%	1.68 (0.91, 3.13)	
Negative	66.0%	Reference	
Highest sIgE level excluding almond [c]			$p < .001$*
≤100 kU/L		Reference	
>100		9.05 (4.06, 20.16)	

[a]GLM analyses with binomial logistic regression specified.

the patients in this cohort. It would be interesting to explore the first time a reaction was developed in these patients and define the grade of anaphylaxis experienced (1–4). There is undoubtedly a relationship between the biosimilar species-based proteins that we would expect to influence this group of sensitized and reactive patients. We would

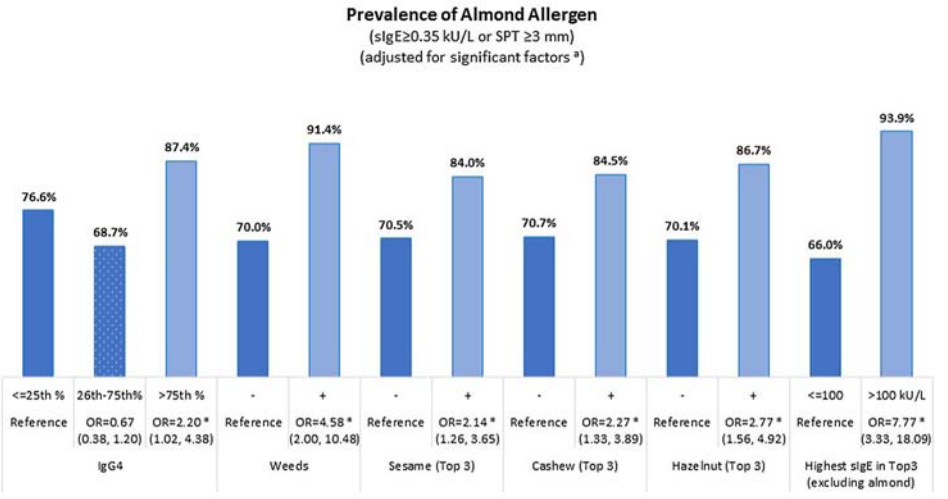

Figure 1. Prevalence of almond positivity (sIgE > 0.35 kU/L or SPT ≥3 mm) adjusted for factors listed in figure. [a]GLM poison regression analyses estimated prevalence at distribution of remaining factors in study population for each factor level.

anticipate that hazelnut, peanut, sesame, and their related proteins to all interact during the sensitization process when the patient is first exposed either sequentially or concurrently. Therefore, future studies that analyse when first exposure to these foods took place would be of great importance to the field.

Biosimilar protein sensitization has great potential for predicting risk to other food groups. Clearly, peanut allergic patients are at a high risk for almond allergy. Although, in this multivariate model we did not see peanut as contributory because all of the patients who were almond allergic were also allergic to peanuts. To put it another way, 71% percent of peanut-allergic patients have almond allergies while all of the patients with almond allergy had peanut allergy in this cohort (Table 2). These findings may have implications for oral immunotherapy (OIT) practices. Prior to OIT for peanut, it is important to investigate if the patient also has almond allergy as these particular patients may require a different dosing strategy as we learn more about the complex immunological responses taking place to a variety of food antigens concurrently or over time. A better understanding of these relationships is essential as more patients are receiving personalized care.

Acknowledgement

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Disclosure statement

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References

Avery, N. J., King, R. M., Knight, S., & Hourihane, J. O. (2003). Assessment of quality of life in children with peanut allergy. *Pediatric Allergy and Immunology*, *14*(5), 378–382. https://doi.org/10.1034/j.1399-3038.2003.00072.x

Bock, S. A., Munoz-Furlong, A., & Sampson, H. A. (2001). Fatalities due to anaphylactic reactions to foods. *Journal of Allergy and Clinical Immunology*, *107*(1), 191–193. https://doi.org/10.1067/mai.2001.112031

Bock, S. A., Munoz-Furlong, A., & Sampson, H. A. (2007). Further fatalities caused by anaphylactic reactions to food, 2001-2006. *Journal of Allergy and Clinical Immunology*, *119*(4), 1016–1018. https://doi.org/10.1016/j.jaci.2006.12.622

Boyce, J. A., Assa'ad, A., Burks, A. W., Jones, S. M., Sampson, H. A., Wood, R. A., Plaut, M., Cooper, S. F., Fenton, M. J., Arshad, S. H., & Bahna, S. L. (2010). Guidelines for the diagnosis and management of food allergy in the United States: Summary of the NIAID-sponsored Expert Panel Report. *Journal of Allergy and Clinical Immunology*.

Clark, A. T., Anagnostou, K., & Ewan, P. W. (2007). Cashew nut causes more severe reactions than peanut: Case-matched comparison in 141 children. *Allergy*, *62*(8), 913–916. https://doi.org/10.1111/j.1398-9995.2007.01447.x

Elizur, A., Appel, M. Y., Nachshon, L., Levy, M. B., Epstein-Rigbi, N., Golobov, K., & Goldberg, M. R. (2018). NUT co reactivity – acquiring knowledge for elimination recommendations (NUT CRACKER) study. *Allergy*, *73*(3), 593–601. https://doi.org/10.1111/all.13353

Glaspole, I. N., de Leon, M. P., Rolland, J. M., & O'Hehir, R. E. (2007). Anaphylaxis to lemon soap: Citrus seed and peanut allergen cross-reactivity. *Annals of Allergy, Asthma & Immunology*, *98*(3), 286–289. https://doi.org/10.1016/S1081-1206(10)60720-X

Gupta, R. S., Springston, E. E., Warrier, M. R., Smith, B., Kumar, R., Pongracic, J., & Holl, J. L. (2011). The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*, *128*(1), e9–17. https://doi.org/10.1542/peds.2011-0204

Kamil, A., & Chen, C. Y. (2012). Health benefits of almonds beyond cholesterol reduction. *Journal of Agricultural and Food Chemistry*, *60*(27), 6694–6702. https://doi.org/10.1021/jf2044795

Kazatsky, A. M., & Wood, R. A. (2016). Classification of food allergens and cross-reactivity. *Current Allergy and Asthma Reports*, *16*(3), 22. https://doi.org/10.1007/s11882-016-0601-1

Maloney, J. M., Rudengren, M., Ahlstedt, S., Bock, S. A., & Sampson, H. A. (2008). The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. *Journal of Allergy and Clinical Immunology*, *122*(1), 145–151. https://doi.org/10.1016/j.jaci.2008.04.014

McWilliam, V., Koplin, J., Lodge, C., Tang, M., Dharmage, S., & Allen, K. (2015). The prevalence of Tree Nut Allergy: A systematic review. *Current Allergy and Asthma Reports*, *15*(9), 54. https://doi.org/10.1007/s11882-015-0555-8

Mothes-Luksch, N., Raith, M., Stingl, G., Focke-Tejkl, M., Razzazi-Fazeli, E., Zieglmayer, R., Wohrl, S., & Swoboda, I. (2017). Pru p 3, a marker allergen for lipid transfer protein sensitization also in central Europe. *Allergy*, *72*(9), 1415–1418. https://doi.org/10.1111/all.13151

Pomes, A., Davies, J. M., Gadermaier, G., Hilger, C., Holzhauser, T., Lidholm, J., Lopata, A. L., Mueller, G. A., Nandy, A., Radauer, C., Chan, S. K., Jappe, U., Kleine-Tebbe, J., Thomas, W. R., Chapman, M. D., van Hage, M., van Ree, R., Vieths, S., Raulf, M., Goodman, R. E. & Who Iuis Allergen Nomenclature Sub-Committee (2018). WHO/IUIS allergen nomenclature:

Providing a common languagem. *Molecular Immunology*, *100*, 3–13. https://doi.org/10.1016/j.molimm.2018.03.003

Senders, A. S., Oropeza, A. R., Kristensen, B., Eller, E., Kjaer, H. F., Bindslev-Jensen, C., & Mortz, C. G. (2018). Food-dependent exercise-induced anaphylaxis due to almond in a PR-10-sensitized patient. *The Journal of Allergy and Clinical Immunology: In Practice*, *6*(2), 683–684. https://doi.org/10.1016/j.jaip.2017.12.018

Simons, F. E., Ardusso, L. R., Bilo, M. B., El-Gamal, Y. M., Ledford, D. K., Ring, J., Sanchez-Borges, M., Senna, G. E., Sheikh, A.Thong, B. Y., & Organization World Allergy. (2011). World Allergy Organization anaphylaxis guidelines: Summary. *Journal of Allergy and Clinical Immunology*, *127*(3), 587–593. e1-22 https://doi.org/10.1016/j.jaci.2011.01.038

Virkud, Y. V., Chen, Y. C., Stieb, E. S., Alejos, A. R., Renton, N., Shreffler, W. G., & Hesterberg, P. E. (2019). Analysis of oral food challenge outcomes in IgE-mediated food allergies to almond in a large cohort. *The Journal of Allergy and Clinical Immunology: In Practice*, *7*(7), 2359–232368. e3. https://doi.org/10.1016/j.jaip.2019.03.049