



Association of tree nut and coconut sensitization

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ABSTRACT

Background: Coconut (*Cocos nucifera*), despite being a drupe, was added to the US Food and Drug Administration list of tree nuts in 2006, causing potential confusion regarding the prevalence of coconut allergy among tree nut allergic patients.

Objective: To determine whether sensitization to tree nuts is associated with increased odds of coconut sensitization.

Methods: A single-center retrospective analysis of serum specific IgE levels to coconut, tree nuts (almond, Brazil nut, cashew, chestnut, hazelnut, macadamia, pecan, pistachio, and walnut), and controls (milk and peanut) was performed using deidentified data from January 2000 to August 2012. Spearman correlation (ρ) between coconut and each tree nut was determined, followed by hierarchical clustering. Sensitization was defined as a nut specific IgE level of 0.35 kU/L or higher. Unadjusted and adjusted associations between coconut and tree nut sensitization were tested by logistic regression.

Results: Of 298 coconut IgE values, 90 (30%) were considered positive results, with a mean (SD) of 1.70 (8.28) kU/L. Macadamia had the strongest correlation ($\rho = 0.77$), whereas most other tree nuts had significant ($P < .05$) but low correlation ($\rho < 0.5$) with coconut. The adjusted odds ratio between coconut and macadamia was 7.39 (95% confidence interval, 2.60–21.02; $P < .001$) and 5.32 (95% confidence interval, 2.18–12.95; $P < .001$) between coconut and almond, with other nuts not being statistically significant.

Conclusion: Our findings suggest that although sensitization to most tree nuts appears to correlate with coconut, this is largely explained by sensitization to almond and macadamia. This finding has not previously been reported in the literature. Further study correlating these results with clinical symptoms is planned.

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Introduction

Coconut (*Cocos nucifera*) is a single-seeded drupe belonging to the Arecaceae family. A staple food of many countries, coconut provides a valuable source of protein, medium chain triglycerides, and other potential health benefits, including antioxidant and antimicrobial compounds.^{1,2} Despite classification as a fruit, coconut was designated as a tree nut in a 2006 addition to the Food Allergy Labeling and Consumer Protection Act³ for food labeling purposes. Unfortunately, this label has the potential to cause confusion for the ever-increasing population of tree nut allergic patients,^{4,5} who are often instructed to avoid all tree nuts and peanut because of concerns about cross-contamination.

Few studies exist to evaluate the incidence of coconut sensitization in tree nut allergic patients; hence, there is limited evidence to advise nut allergic patients about coconut consumption. Of 5,149 patients evaluated by the Food Allergy and Anaphylaxis Network Peanut and Tree Nut Allergy Registry in the United States, only 4 individuals self-reported allergy to coconut.⁶ Other large-scale, survey-based studies did not further subcategorize tree nut allergy into individual nuts.^{4,5} Another group of researchers did not find an association between tree nut or peanut sensitization or clinical allergy and coconut sensitization via skin prick testing in 40 patients.⁷

Although the prevalence of food allergy in children is increasing,^{4,5} clinical allergy to coconut appears to be relatively rare. Since the first description in 1999 by Teuber and Peterson,⁸ there have been only 10 published cases of coconut allergy.^{8–15} Although findings from case reports have revealed potentially cross-reactive proteins between coconut and hazelnut, walnut, and lentils,^{8,9,11,14} the significance of these findings remains unclear.

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Because of the lack of published data, the true prevalence of coconut sensitization is poorly defined, and the association between sensitization to tree nuts and coconut is largely unknown. We sought to examine serum specific IgE (sIgE) cosensitization patterns between tree nuts and coconut and to determine whether sIgE sensitization to tree nut(s) is associated with increased odds of coconut sensitization.

Methods

Data Set

A data set that contained all food sIgE data (ImmunoCAP; Thermo Fisher Scientific, Uppsala, Sweden) obtained at a single tertiary care pediatric center between January 2000 and August 2012 ($N = 5,843$) was queried for coconut IgE. In the data set, 298 patients were tested for coconut. In these patients, 274 of the coconut sIgE values had been obtained as part of a standard tree nut panel order set that assessed for sIgE to almond, Brazil nut, cashew, chestnut, coconut, hazelnut, macadamia, pecan, pistachio, and walnut. Milk ($n = 128$) and peanut ($n = 285$) sIgE samples obtained from the same 298 patients were used as controls, as available.

Statistical Analyses

Descriptive statistics and sensitization incidence were calculated for coconut, tree nut, and control sIgE values. Spearman rank correlation coefficients (Spearman ρ) between coconut sIgE and sIgE to each tree nut or control were determined, excluding double-zero pairings to avoid spurious correlation. Sensitization was defined as a positive food sIgE level of 0.35 kU/L or higher. Cosensitization rates between coconut and each tree nut or control were calculated.

The association between individual tree nut sensitization and coconut sensitization was examined by univariate and multiple logistic regression analysis on the entire cohort and randomly generated subsets. Corresponding unadjusted and adjusted odds ratios (ORs) were calculated with 95% confidence intervals (CIs) and the P value for differing from 1. Hierarchical clustering of anti-food allergen sIgE levels was performed using Spearman correlation as the measure of distance between foods, including peanut and milk sIgE values as negative controls. Average linkage was used to determine the distance between clusters. This procedure was repeated multiple times on random subsets of the data and the consensus clustering reported.

Decision tree analysis to predict coconut positivity was performed after dichotomizing the sIgE measurements as negative or positive based on a threshold of 0.35 kU/L. Gini impurity was used as the criterion for splitting. Cross-validation with pruning was performed to determine the optimal tree. Analyses were performed using R statistical software, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria), and SAS statistical software, version 9.4 (SAS Institute Inc, Cary, North Carolina). Exempt status was obtained from our institutional review board.

Results

The demographic profile of children attending our institution during the 12-year study period was 1 in 2 white, 1 in 4 African American, and 1 in 10 Hispanic. During the study period, 298 patients underwent testing for coconut sIgE, with a median age of 5.7 years (range, 2.1–30.7 years; interquartile range, 4.7 years). There were slightly more males than females (57.6% vs 42.4%). Coconut sIgE values ranged from 0 to greater than 100 kU/L (interquartile range, 0.46 kU/L), and 90 patients (30.2%) had a positive coconut sIgE test result (Table 1). Sensitization rates varied for each food, with peanut having the highest sensitization incidence, followed by pistachio and hazelnut. In general, the

Table 1

Descriptive Statistics for Coconut, Tree Nut, and Control Specific IgE Values

Nut or control	No. of patients	No. (%) with positive test results	Mean	Median	IQR
Coconut	298	90 (30.2)	1.70	0	0.46
Almond	281	91 (30.5)	1.29	0	0.65
Brazil nut	272	82 (27.5)	1.59	0	0.52
Cashew	277	135 (45.3)	5.11	0.28	2.75
Chestnut	221	96 (32.2)	1.83	0.14	1.28
Hazelnut	270	146 (49.0)	6.96	0.47	3.33
Macadamia	270	103 (34.6)	1.71	0	0.86
Pecan	279	109 (36.6)	4.12	0	23.2
Pistachio	275	151 (50.7)	6.30	0.47	1.31
Walnut	278	117 (39.3)	4.03	0	4.04
Peanut	285	182 (61.1)	18.88	1.93	1.42
Milk	128	56 (18.8)	3.57	0.12	1.42

Abbreviation: IQR, interquartile range.

highest rates of sensitization were observed in the 5- to 10-year age range (Fig 1).

Coconut cosensitization rates (Table 2) were highest for macadamia (71%) and almond (69%). Spearman correlation analysis was performed in lieu of Pearson correlation to identify monotonic associations that were not necessarily linear and to minimize the effect of outliers. The Spearman correlation coefficient with coconut was highest for macadamia ($\rho = 0.77$, $P < .001$) followed by hazelnut ($\rho = 0.56$, $P < .001$) and almond ($\rho = 0.52$, $P < .001$) (Table 3). Correlation between coconut and peanut was quite weak ($\rho = 0.26$, $P < .001$), and no significant correlation was found between coconut and milk ($\rho = -0.0025$, $P = .98$).

Unadjusted ORs had a significant association between sensitization to each tree nut and coconut. Adjusted multiple logistic regression analysis, however, yielded a significant association only between almond and coconut sensitization (adjusted OR, 5.31; 95% CI, 2.18–12.95; $P < .001$) and between macadamia and coconut sensitization (adjusted OR, 7.39; 95% CI, 2.60–21.02; $P < .001$) (Table 4).

Hierarchical clustering revealed that coconut is the closest to macadamia in terms of sIgE levels (Fig 2). Additional evidence of the robustness of the clustering results is based on the fact that pistachio and cashew also tended to cluster together, as did pecan and walnut. Multiple trials of clustering were performed on random subsets of the data to minimize the chance of coincidental findings. The clustering association among the nuts was largely preserved, with milk and peanut being isolated from the nuts.

Decision tree analysis on the dichotomized data for prediction of coconut sensitization based on the results of testing for tree nut sensitization resulted in a very simple rule: "If macadamia tests positive, then coconut tests positive." The corresponding positive predictive value and negative predictive value for sensitization were 0.75 and 0.96, respectively. The sensitivity and specificity of predicting a coconut sensitization based on the presence of sensitization to macadamia were 0.93 and 0.86, respectively.

Given the significant association between macadamia and coconut sensitization from the adjusted OR, clustering, and decision tree analysis, we performed linear regression between the corresponding levels of macadamia and coconut sIgE. Although the fit was statistically significant for the entire data set, Figure 3 highlights the fit to the 95% of data that have values less than 10 kU/L for both coconut and macadamia sIgE.

Discussion

Contrary to its name, the coconut fruit is not a nut. In botanical terms, a nut is a hard-shelled fruit that contains a single seed. Chestnut and hazelnut are nuts, although coconut is considered a drupe. Also known as a stone fruit, a drupe is an indehiscent fruit in

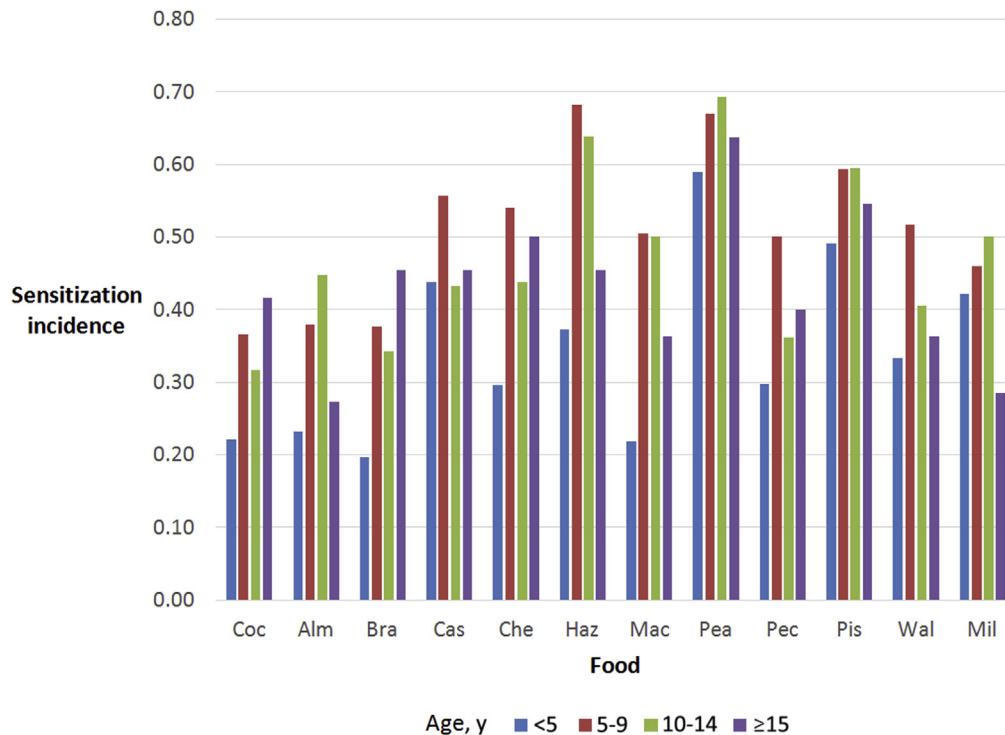


Figure 1. Incidence of sensitization in different age groups. Alm indicates almond; Bra, Brazil nut; Cas, cashew; Coc, coconut; Haz, hazelnut; Mac, macadamia; Mil, milk; Pea, peanut; Pec, pecan; Pis, pistachio; and Wal, walnut.

which an outer fleshy layer (exocarp) covers a dense, fibrous mesocarp, surrounding a stone or pit that contains a hardened endocarp with a single seed derived from the flower's ovary.¹⁶ Other examples of drupes include walnut, almond, pistachio, cherry, and peach. Macadamia is a seed, an, to complicate matters even more, the cashew nut is actually a seed surrounded by a toxic shell that grows outside its fruit. The term *tree nut* is used quite broadly for culinary purposes and is not necessarily indicative of botanical similarities or cross-reactive proteins.

Coconut is taxonomically classified as a monocot in the palm family (order Arecales, family Arecaceae). From the perspective of evolutionary history, it is estimated that monocots diverged from dicots, which include all other nuts, seeds, legumes, and drupes in this study, approximately 140 million to 150 million years ago.¹⁷ Core eudicots (including almond, Brazil nut, cashew, chestnut, hazelnut, peanut, pecan, pistachio, and walnut) subsequently diverged from the basal eudicots (including macadamia) an estimated 100 million to 115 million years ago.¹⁷ Our findings may be explained by a phylogenetic association because the results of hierarchical clustering (Fig 2) are consistent with taxonomic classification (Table 5). The clustering result and adjusted OR on the full data set suggest that almond sensitization may be associated with a positive coconut sIgE test result; other findings, however, indicate that this association is less compelling. Multiple trials of logistic regression on random subsets of the data revealed only macadamia to be consistently associated with higher odds of coconut sensitization, and the decision tree after cross-validation retained only macadamia as a significant predictor. The *P* value for association with macadamia sensitivity remains significant even after applying the Bonferroni correction for multiple testing. This study suggests, based on a relatively small sample, that there is a less than 5% chance that someone who tests negative for macadamia will test positive for coconut. Conversely, if someone tests positive for macadamia, there is a 75% chance that the test result for coconut IgE will also be positive.

Although a botanical association between coconut and macadamia may play a part in the high rate of cosensitization to both foods, determining whether this cosensitization is a result of independent sensitization to both foods vs true cross-reactive proteins has not yet been evaluated. Currently recognized tree nut allergens are primarily seed storage proteins, such as legumins, vicilins, and albumins; defense-related proteins, including lipid transfer proteins; and pan allergens, such as profilins and hevein-related proteins. To date, coconut has 2 identified food allergens: an 11S globulin similar to soy glycinin (Coc n 4)⁸ and a 7S vicilin-like protein (Coc n 2),⁹ neither of which are completely sequenced. Coconut also possesses a newly sequenced additional 7S vicilin (Coc n 1), which appears to be significant in Indian patients with environmental allergy to coconut palm pollen,¹⁸ and a profilin (Coc n 5), which has been isolated and sequenced from *Cocos nucifera* pollen, although it has not been implicated in food allergy.¹⁹

Coc n 4 or cocosin, a 35-kDa 11S globulin similar to soy glycinin, was first described by Teuber and Peterson in 1999 in a case report

Table 2
Cosensitization Rates Between Coconut and Tree Nut Pairings

Tree nut or control (No. of pairs)	No. of patients				Cosensitization, %
	Both negative	Coconut positive	Tree nut positive	Both positive	
Almond (281)	176	14	19	72	69
Brazil nut (272)	167	23	21	61	58
Cashew (277)	131	11	59	76	52
Chestnut (221)	114	11	35	61	57
Hazelnut (270)	122	2	65	81	55
Macadamia (270)	161	6	26	77	71
Pecan (276)	147	20	43	66	51
Pistachio (275)	120	4	70	81	52
Walnut (278)	144	17	47	70	52
Peanut (285)	99	4	97	85	46
Milk (128)	62	10	26	30	45

Table 3
Spearman Correlation Coefficients Between Coconut and Tree Nut Pairings

Nut or control	ρ	P value	No. of pairs
Almond	0.52	<.001	129
Brazil nut	0.38	<.001	135
Cashew	0.18	.02	168
Chestnut	0.42	<.001	128
Hazelnut	0.56	<.001	163
Macadamia	0.77	<.001	131
Pecan	0.36	<.001	135
Pistachio	0.30	<.001	173
Walnut	0.42	<.001	144
Peanut	0.26	<.001	193
Milk	−0.0025	.98	74

analysis of 2 individuals with a history of walnut anaphylaxis who subsequently reported anaphylaxis to coconut. Both patients had sIgE sensitization to both walnut and coconut.⁸ The allergenicity of this protein was substantiated in further studies.^{10,14} One patient who experienced anaphylaxis to coconut after severe oral allergy symptoms to tree nuts, IgE binding occurred to a 35-kDa protein found in both coconut and hazelnut extracts.¹¹ Coc n 2, a 7S coconut globulin (vicilin-like protein) similar to that of oil palm, was first described by Benito et al⁹ in 2006 on analysis of serum from 2 patients: an adult with severe oral allergy syndrome mono-sensitized to coconut and a child with anaphylaxis to coconut and previous anaphylaxis to walnut. The 7S globulin was also demonstrated in subsequent studies.^{14,15}

These isolated case reports illustrate potential cross-reactive proteins between coconut and both walnut and hazelnut that our findings reaffirm (moderate correlations between coconut and hazelnut [$\rho = 0.56$] and between coconut and walnut [$\rho = 0.42$]). Novel findings in our study are the high rate of cosensitization between coconut and macadamia ($\rho = 0.71$, co-sensitization rate of 77%) and between coconut and almond ($\rho = 0.52$, cosensitization rate of 68%). To our knowledge, no prior studies have reported coconut protein cross-reactivity with macadamia or almond. Regression analysis of our data reveals that sensitization to macadamia or almond increases the odds of being sensitized to coconut, an observation that has not been previously described in the literature.

It is possible that the previously described proteins, or perhaps other proteins, may have cross-reactivity with almond or macadamia as well. To date, no allergenic proteins have been described for macadamia (*Macadamia integrifolia*), so the question of independent cosensitization vs cross-reactivity with a potential clinical effect cannot readily be answered. As a relatively more frequent allergenic tree nut, almond (*Prunus dulcis*) has multiple recognized (and sequenced) allergenic proteins, 2 of which may correspond to coconut allergens. Almond's major allergen is Amandin (Pru du 6), an 11S globulin that has been fully sequenced.²⁰ Although cocosin, coconut's 11S globulin, has not been sequenced, it is possible that

Table 4
ORs Between Each Tree Nut and Coconut

Nut or control	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P value
Almond	23.81 (11.79–48.11)	5.31 (2.18–12.95)	<.001
Brazil nut	11.30 (5.96–21.40)	1.61 (0.57–4.52)	.36
Cashew	6.96 (3.61–13.44)	1.98 (0.58–6.70)	.26
Chestnut	6.02 (3.36–10.80)	1.38 (0.56–3.43)	.48
Hazelnut	9.50 (4.47–20.20)	0.76 (0.24–2.45)	.64
Macadamia	24.16 (11.76–49.61)	7.39 (2.60–21.02)	<.001
Pecan	5.90 (3.27–10.62)	0.69 (0.18–2.74)	.59
Pistachio	8.21 (3.86–17.47)	1.12 (0.33–3.86)	.85
Walnut	6.55 (3.57–12.02)	1.31 (0.35–4.97)	.68

Abbreviations: CI, confidence interval; OR, odds ratio.

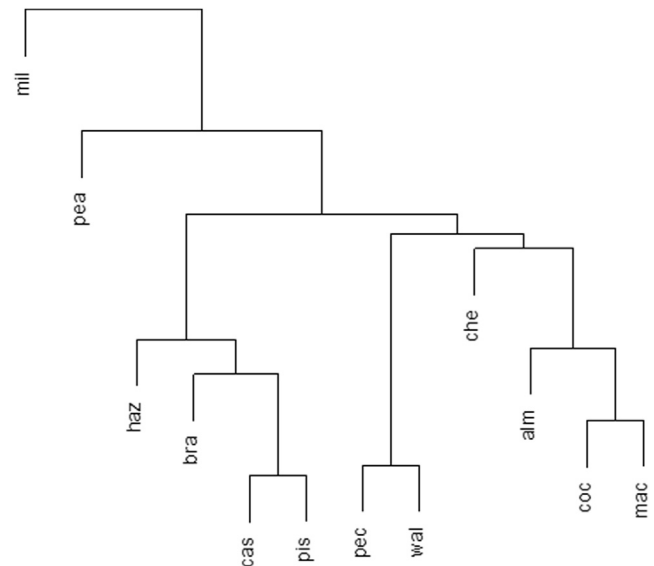


Figure 2. Hierarchical clustering of IgE levels. Bra indicates Brazil nut; Cas, cashew; Che, chestnut; Coc, coconut; Haz, hazelnut; Mac, macadamia; Mil, milk; Pea, peanut; Pec, pecan; Pls, pistachio; and Wal, walnut.

these proteins may share structural homologous features. Almond and coconut also each possess a fully sequenced profilin protein (Pru du 4 and Coc n 5, respectively). Profilins are ubiquitous eukaryotic proteins, commonly referred to as pan allergens, that share significant sequence homology.²¹ Because of this well-conserved structure, profilin sensitization is a risk factor for allergy to multiple foods and for food-pollen syndrome.²² Pru du 4 is potentially clinically relevant to food allergy; in a small analysis by Tawde et al,²³ nearly half (8 of 18) of almond allergic patients in a small analysis reacted to Pru du 4 on dot blot analysis and enzyme-linked immunosorbent assay. Notably, most of these patients were self-reported to be pollen allergic as well. The clinical relevance of Coc n 5 has yet to be established.

In summary, our results suggest that sensitization to most tree nuts is not correlated with coconut sensitization, with the exception

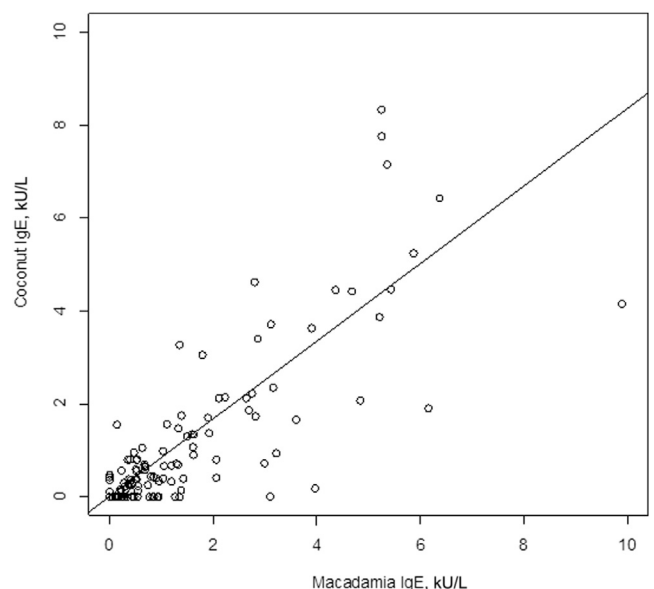


Figure 3. Plot of macadamia vs coconut IgE levels overlaid with linear regression fit ($P < .001$; adjusted $R^2 = 0.52$).

Table 5
Phylogenetic Orders of Tree Nuts, Coconut, and Peanut

Monocots				
Arecales	Coconut			
Eudicots				
Proteales	Macadamia			
Core eudicots				
Rosales	Almond			
Fagales	Walnut	Pecan	Hazelnut	Chestnut
Sapindales	Cashew	Pistachio		
Ericales	Brazil nut			
Fabales	Peanut			

of macadamia and almond, and that only macadamia is consistently associated with increased odds of coconut sensitization. The apparent correlation between coconut and tree nuts is primarily explained by being sensitized to macadamia. This observation has not previously been reported in the literature. A speculative clinical application may be that if a patient has been sensitized to a tree nut and is wondering whether it is safe to ingest coconut, testing for sensitization to macadamia can provide guidance.

Strengths of our study include a relatively long study period with more than 12 years of data and the use of adjusted ORs based on multiple logistic regression. Because of the rarity of reported clinical coconut allergy, there is no standard of comparison of coconut sIgE values to provide positive or negative predictive values diagnostic of clinical allergy. We therefore used 0.35 kU/L or higher as a standard cutoff for positivity in our determinations. Notably, of the 90 positive values to coconut, 82 fell below the generally accepted 95% positive predictive cutoff value for tree nut allergens of 15 kU/L.²⁴ In addition, we believe that our study population is generally representative of the Midwestern United States; however this may not be reflective of sensitization patterns within other populations. As with any study based solely on sIgE results, we acknowledge limitations in that cosensitization does not necessarily imply cross-reactivity and that sensitization must correlate with symptoms to determine clinical allergy. Because ours was a retrospective analysis of laboratory data without accompanying history, further prospective studies to determine clinical relevance are planned.

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