

Sensitization profiles to hazelnut allergens across the United States



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ABSTRACT

Background: Measurement of IgE antibody to hazelnut components can aid in the prediction of allergic responses to the food.

Objective: To investigate the association between patient demographics (age, location) and patterns of allergic sensitization to hazelnut components across the United States and to investigate the degree of correlation between hazelnut sensitization with sensitization to other tree nuts, peanuts, and their components.

Methods: Serum samples from 10,503 individuals with hazelnut extract specific IgE (sIgE) levels of 0.35 kU_A/L or higher were analyzed for IgE antibodies to Cor a 1, 8, 9, and 14 by ImmunoCAP. A subset of these patients were analyzed for IgE antibodies to peanut, walnut, and cashew nut IgE along with associated components.

Results: Among hazelnut sensitized individuals, children (< 3 years old) were predominantly sensitized to Cor a 9 and Cor a 14. Conversely, Cor a 1 sIgE sensitization was much higher in adults than children, especially in the Northeastern United States. Cor a 8 sensitization was relatively constant (near 10%) across all ages. Cosensitization of hazelnut with other tree nuts and peanuts was related to correlation of IgE concentrations of individual component families.

Conclusion: We conclude that sensitization to individual hazelnut components is highly dependent on age and/or geographic location. Component correlations suggest that cosensitization to hazelnut and walnut may be caused by their pathogenesis-related protein 10 allergens, nonspecific lipid transfer proteins, or seed storage proteins, whereas hazelnut and peanut cosensitization is more often caused by cross-reactivity of pathogenesis-related protein 10 (Cor a 1 and Ara h 8) and nonspecific lipid transfer proteins (Cor a 8 and Ara h 9).

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Introduction

Hazelnut is a widely consumed tree nut and among the top 5 most serious instigators of food allergic reactions.^{1–4} Hazelnut allergy can manifest symptoms that range from mild oral itching to fatal anaphylaxis.^{4–7} Population-based surveys have found that the incidence of hazelnut allergy varies greatly from location to location, depending on exposure to cross-reacting pollen allergens.^{8–10} The prevalence of hazelnut allergy is estimated to be 0.2% in children and up to 4.5% in adults in regions with heavy exposure to pollen of birch or related tree species.⁵ Primary sensitization to hazelnut is more common in children than in adults, and children more often develop severe systemic reactions.^{1,11–14}

Accurate diagnosis is vital to ensure that patients at risk for a severe reaction avoid hazelnut exposure. However, overdiagnosis can result in unnecessary anxiety and the elimination of this

high-protein food from the diet.^{8,14,15} The diagnosis of hazelnut allergy begins with a thorough clinical history and evaluation of a patient's reaction after hazelnut exposure.^{4–8,16–19} Sensitization can be assessed by skin prick testing or specific IgE (sIgE) measurements to hazelnut extract.¹⁷ A definitive diagnosis of hazelnut allergy can be based on a food challenge, which is often performed at referral centers because it is a time- and labor-intensive process, requiring specialist competence and emergency facilities.^{8,17–19} In clinical practice, an oral food challenge in a patient with a confirmed allergen sensitization is often deferred unless there is uncertainty in the history. Although the sensitivity of both extract-based in vivo and in vitro tests is generally high, their clinical specificity is less than optimal in the presence of concomitant pollen sensitization.^{4,14,20,21} As a result, the positive predictive value of the test may be low when testing is performed in a population with a low pretest probability of allergy (ie, in the absence of a suggestive case history or a specific clinical suspicion). In addition, patients' self-reported reactions to food items do not always represent true food allergy.

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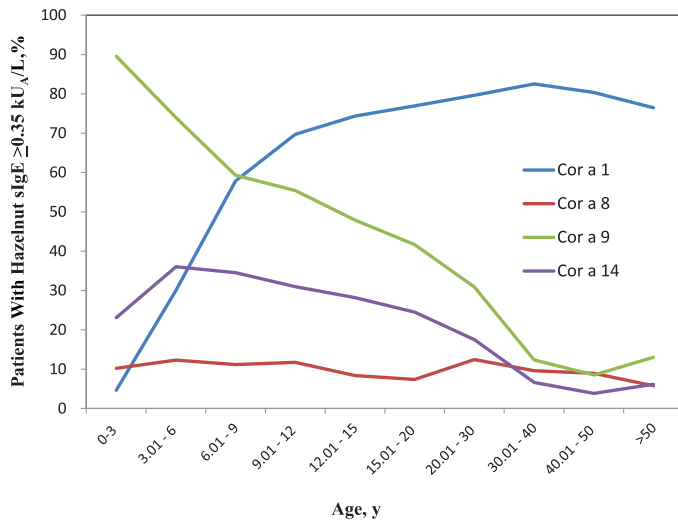


Figure 1. Age dependency of component sensitization (≥ 0.35 kU_A/L) for all reflexed serum samples that were tested for specific IgE (sIgE) to Cor a 1, 8, 9, and 14.

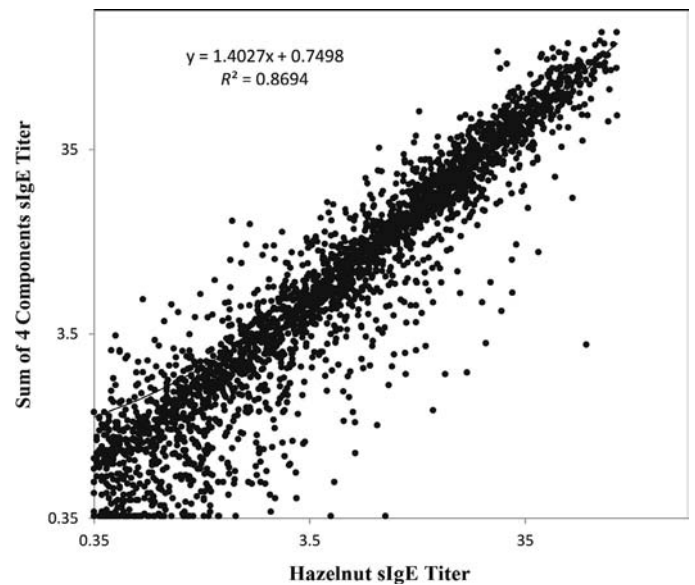


Figure 2. Graph of the hazelnut specific IgE (sIgE) titer vs the sum of IgE to the 4 hazelnut components tested.

Patients who test IgE antibody positive for hazelnut extract can often test positive to extracts of botanically related nuts.²²⁻²⁵ For reasons that are not well understood, patients who test positive for hazelnut often test positive for peanut, a legume that is not closely related to hazelnut or other tree nuts.^{23,26} A positive IgE antibody test result should be regarded as a potential risk factor, but it is often difficult to discern to what extent it represents a substantial risk of a serious allergic reaction or a less consequential, weakly cross-reactive binding of IgE antibodies formed against proteins of a different allergen source, acting as primary sensitizer.^{14,26} Pollen sensitization can add to diagnostic uncertainty because of the existence of cross-reactive determinants shared with foods such as nuts and legumes.^{27,28} Some pollen sensitized individuals will react to ingestion of nuts or peanuts with localized oropharyngeal symptoms (oral allergy syndrome), but they usually do not manifest systemic allergic reactions. An ability to distinguish patients who are at risk for systemic, potentially life-threatening, reactions from those who are more likely to experience no more than symptoms of oral allergy syndrome would markedly improve patients' quality of life. Laboratory diagnostics that have the potential to obviate the need to avoid an entire class of

foods and reduce the anxiety associated with a diagnosis of food allergy could be of tremendous value.

An important recent development in the investigation of suspected hazelnut allergy has been the introduction of IgE antibody measurements to 4 important hazelnut allergen components (Cor a 1, 8, 9, and 14).^{29,30} Cor a 1 is a hazelnut protein that belongs to the pathogenesis-related protein 10 (PR-10) family and is susceptible to digestion and the extreme pH conditions in the stomach.³¹ An isolated IgE response to Cor a 1 is most often associated with no or mild oropharyngeal symptoms on intake of hazelnut and rarely to systemic reactions. The clinical significance of sensitization to Cor a 8, a nonspecific lipid transfer protein (nsLTP), appears to vary geographically, with more severe symptoms reported from the Mediterranean region than in central and northern Europe.²⁰ The seed storage proteins Cor a 9 (11S globulin) and Cor a 14 (2S albumin) are highly abundant in hazelnut and IgE antibody sensitization to these structurally stable molecules has been associated with severe systemic symptoms.^{10,12,22,25,32-36} Several studies have found that most

Table 1
Regional Rates of IgE Test Result Positivity for Hazelnut Components by Age

Component	Positivity rate by age range in years, %										
	Combined	0-2	3-5	6-8	9-11	12-14	15-19	20-29	30-39	40-49	> 49
West											
Cor a 1	36.4	1.1	15.6	41.9	43.3	43.0	54.8	57.6	63.0	61.1	50.0
Cor a 8	16.4	14.0	17.2	17.6	19.4	14.0	12.3	21.2	18.5	16.7	12.5
Cor a 9	58.7	83.9	75.4	58.1	62.7	57.0	34.2	48.5	14.8	27.8	25.0
Cor a 14	30.7	26.9	39.3	31.6	35.1	36.0	26.0	30.3	0.0	11.1	12.5
Midwest											
Cor a 1	55.6	13.6	33.7	58.0	64.4	73.9	70.3	80.0	87.5	100.0	71.4
Cor a 8	12.7	12.3	13.9	14.8	11.9	11.8	12.1	20.0	0.0	0.0	0.0
Cor a 9	58.8	90.1	69.3	71.0	58.1	42.0	44.0	20.0	12.5	0.0	7.1
Cor a 14	31.7	30.9	34.3	36.9	36.9	31.1	23.1	10.0	25.0	16.7	0.0
South											
Cor a 1	54.9	7.8	38.1	55.0	62.3	70.0	75.4	76.6	75.5	67.1	62.0
Cor a 8	11.2	10.6	13.6	12.0	11.7	8.8	8.9	14.3	7.1	8.2	9.0
Cor a 9	53.7	86.3	68.8	56.7	55.9	44.0	46.0	26.0	11.2	5.5	17.0
Cor a 14	27.6	24.3	36.1	33.8	31.0	27.5	23.6	13.6	5.1	4.1	5.0
Northeast											
Cor a 1 ^a	72.3	15.9	51.5	72.0	80.1	81.4	80.8	84.8	87.9	91.0	92.6
Cor a 8	8.5	11.0	10.7	8.9	9.0	6.2	6.6	10.3	8.4	8.2	2.5
Cor a 9	48.7	85.6	65.7	55.2	49.5	46.1	39.6	28.3	10.5	9.8	6.6
Cor a 14	26.8	32.9	34.7	32.8	28.3	27.5	22.3	16.4	4.7	4.1	5.8

^aCor a 1 in Northeast was significantly higher than in other regions.

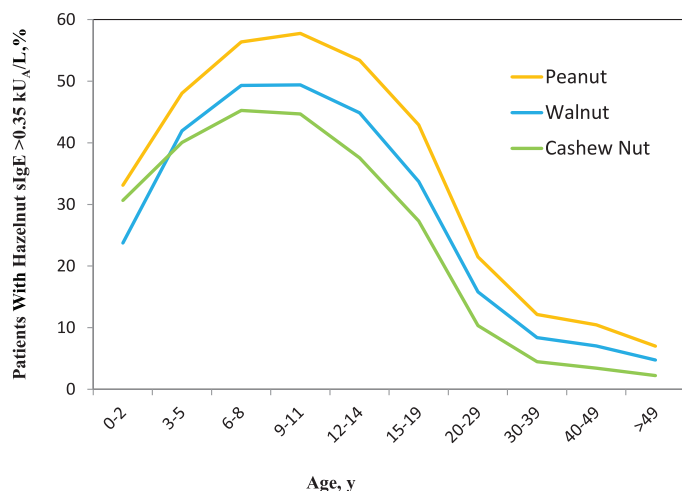


Figure 3. Age dependency of cosensitization (>0.35 kUA/L) to hazelnut and other allergens. f17 indicates the hazelnut allergen extract; sIgE, specific IgE.

children with generalized reactions to hazelnut tested positive for sIgE to Cor a 9 and/or Cor a 14.^{1,25,32-35}

The aim of this study was to investigate the rates and patterns of sensitization to hazelnut extract and components in a large North American population tested for suspected hazelnut allergy. The degree of cosensitization to other tree nuts and peanut and their components to assess possible cross-reactivity between these allergens was also evaluated.

Methods

Study Population

Consecutively received, deidentified patient samples were analyzed between April 1, 2016, and December 31, 2017, by LabCorp, after clinicians' referrals for a hazelnut allergen extract (f17) sIgE antibody measurement with automatic reflex of positive results to testing for sIgE to Cor a 1, 8, 9, and 14. A total of 10,503 of 24,368 samples submitted for hazelnut sIgE testing produced values of 0.35 kUA/L or higher, triggering the reflex to components. A subset of the 10,503 hazelnut-positive samples were tested for 1 or more other allergens: peanut (f13, n=2,408), walnut (f256, n=2,343), and/or cashew (f202, n=2,355) and produced positive results that triggered reflex testing for sensitization to their components (Ara h 1, 2, 3, 8, and 9 for peanut, Jug r 1 and 3 for walnut, and Ana o 3 for cashew nut). Allergen extract cosensitization was analyzed in a larger group of 66,527 samples tested for hazelnut, peanut, walnut, and cashew nut sIgE, which in most instances were not in panels with reflex to components.

The analytical IgE antibody data and demographic variables were retrieved from the core laboratory computerized database at LabCorp. Other than the reason that their physician would have had to request the tests, no information on the patients' clinical reactivity to the tested allergens was available. All analyses of

Table 3
Correlation Coefficient (r) Values Comparing Hazelnut Components to Hazelnut, Other Nut Components, and Peanut Components

Hazelnut component	Hazelnut components			Other nut components			Peanut components				
	Cor a 8	Cor a 9	Cor a 14	Jug r 1	Jug r 3	Ano o 3	Ara h 1	Ara h 2	Ara h 3	Ara h 8	Ara h 9
Cor a 1	0.0173	0.0346	0.0283	0.0200	0.1039	0.0173	0.0458	0.0490	0.0714	0.8197	0.1196
Cor a 8		0.0424	0.0922	0.0412	0.7432	0.0583	0.0387	0.0640	0.0387	0.0825	0.6707
Cor a 9			0.3010	0.4913	0.1658	0.5070	0.2581	0.2486	0.3030	0.0469	0.1345
Cor a 14				0.6725	0.1520	0.4343	0.1241	0.1616	0.1371	0.0100	0.1539

Table 2

Correlation Coefficient (r) Values Comparing Hazelnut Extract Specific IgE to Other Allergen Extracts for Various Tested Age Groups

Age, y	Peanut	Walnut	Cashew
< 3	0.499	0.457	0.622
3-12	0.242	0.455	0.446
> 12	0.211	0.432	0.282

deidentified serum specimens were performed under protocols approved by the Western Institutional Review Board.

Allergen sIgE Measurements

Sensitization to whole allergen extracts and to components was measured by ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden). Analyses were performed in accordance with the manufacturer's instructions. Concentrations of IgE antibody of 0.35 kUA/L or higher were defined as positive for the purposes of this study.

Statistical Analysis

Microsoft Excel was used to analyze data and produce the figures in this report.

Results

Patient Hazelnut sIgE Antibody Serologic Testing

Figure 1 depicts the frequency of sensitization to Cor a 1, 8, 9, and 14 in different patient age intervals. The frequencies of positive test results for Cor a 9 and 14 were maximal in the group of 0- to 3-year-old children (89.6% and 23.1%, respectively), and both decreased with increasing age. In contrast, the presence of Cor a 1 sIgE increased from 4.7% at 0 to 3 years of age to 82.5% at 30 to 40 years of age. The pattern of component sensitization for different age intervals and the entire population are tabulated in eTable 1. Of the 10,503 individuals with positive IgE results to hazelnut (≥ 0.35 kUA/L), only 6.7% had sIgE levels less than 0.35 kUA/L for all 4 available hazelnut components, and only 2.1% had measured component levels all less than 0.1 kUA/L, the limit of detection of the test. This fact, along with the finding that the sum of IgE values to components correlated well with the level of hazelnut sIgE (Fig 2), suggest that the IgE-binding epitopes in hazelnut extract are well represented by the 4 hazelnut components that are commercially available for testing.

Regional Variation of Sensitization to Peanut in the United States

Table 1 lists regional rates of positivity (≥ 0.35 kUA/L) across the age groups for IgE antibodies specific for the various hazelnut components. The data are tabulated by regions of the United States (Northeast [n=5,633], South [n=3,251], Midwest [n=859], and West [n=760]) as defined by the US Census Bureau.³⁷ A 2-way analysis of variance revealed that the rate of sensitization to Cor a 1 was significantly higher in the Northeast relative to other regions of the United

States ($P < .001$). This presumably reflects a more intense exposure to pollen of tree species, such as birch, which contain major allergens belonging to the PR-10 protein family.

Cosensitization of Hazelnut to Other Tree Nuts and Peanut

Figure 3 depicts the percentage of hazelnut-positive ($f17 \geq 0.35$ kU_A/L) patients who also tested positive (≥ 0.35 kU_A/L) for peanut (f13), walnut (f256), and cashew nut (f202). Table 2 lists the correlation coefficient values obtained from a linear regression analysis comparing the hazelnut extract sIgE values with the sIgE values for peanut, walnut, and cashew nut. The strongest correlation was observed for children younger than 3 years. Table 3 lists the correlation coefficient values obtained from a linear regression analysis comparing each of the 4 hazelnut components to (1) the other hazelnut components, (2) other tree nut components, and (3) peanut components. There was a strong correlation between the Bet v 1 homologs Cor a 1 and Ara h 8 and between the nsLTPs Cor a 8, Jug r 3, and Ara h 9. There was also a strong correlation between Cor a 14 and Jug r 1 and, to a lesser extent, Ana o 3. Weak correlations were also observed between Cor a 9 and Jug r 1 and Ana o 3. All other component pairs exhibited low correlation.

Discussion

Component-resolved diagnostics have proven to be an important tool in the investigation of patients with suspected hazelnut allergy, in particular for the purpose of distinguishing between primary and cross-reactive (pollen) sensitization. This report provides unique demographic and geographic information about sensitization profiles of Americans evaluated for suspected hazelnut allergy.

Hazelnut allergy has demonstrated age-related sensitization profiles with distinct clinical outcomes.^{11,12,21,24,29,30,34,35} A number of clinical studies have found that young children with clinical hazelnut reactivity are most often sensitized to Cor a 9 and/or Cor a 14.^{11,12,21,25,30,34,35} Sensitization to one or both of these storage proteins has been associated with immediate-type systemic reactions in hazelnut allergic patients.^{1,5,12,22,25,30–36} Several European studies have reported that measurement of sIgE to Cor a 14 provided a higher positive predictive value for clinical hazelnut allergy in children than skin prick testing or measurement of sIgE to hazelnut extract or to other hazelnut components, including Cor a 9.^{22,25,32,36} These findings are contrasted by a small US study³⁴ that found Cor a 9 to be comparable to Cor a 14 and a larger Dutch study³⁵ that found Cor a 9 to be superior to Cor a 14 for discriminating between children with severe or mild to no hazelnut allergy. Of studies that found Cor a 14 superior to Cor a 9, 2 noted that a small subset of patients with hazelnut allergy were Cor a 14 negative and Cor a 9 positive, pointing to the unique clinical importance of each of these components in hazelnut allergy.^{25,32} The seemingly disparate conclusions of these studies with regard to the efficacy of Cor a 14 relative to Cor a 9 in identifying hazelnut reactive individuals may reflect differences in study design, patient demographics (age, geography), concomitant occurrence of other nut sensitizations, inclusion criteria (suspicion of peanut allergy vs elevated s-IgE to hazelnut), challenge protocol, and classification of symptoms.

This study reveals hazelnut component sensitization patterns in the United States that are consistent with some of the previous clinical studies in Europe. A total of 89.6% of hazelnut-positive children up to 3 years of age were sensitized to Cor a 9, and 23.1% were sensitized to Cor a 14. Sixty-two percent of this subpopulation were sensitized to Cor a 9 but not to any of the other hazelnut components tested, whereas only 1.6% of these children were Cor a 14 monosensitized. In older children and adults, a higher proportion of patients were monosensitized to Cor a 14. Because of the mutually

nonoverlapping sensitization to Cor a 9 and Cor a 14 found here and in the other cited reports, both components need to be considered to ensure detection of hazelnut storage protein sensitization. The percentage of patients sensitized to hazelnut storage proteins decreased with age as Cor a 1 sensitization increased.

Among hazelnut allergic adults, pollen-related oral allergy syndrome that was associated with Cor a 1 sensitization tends to predominate.^{6,7,38,39} In the population reported here, we observed a markedly higher prevalence of Cor a 1 sensitization in adults than in children, with sensitization rates plateauing near 80% in adulthood. Hazelnut allergen Cor a 1 has a high degree of structural homology to PR-10 proteins from the pollen of the Fagales order (eg, birch, hazel, oak, alder, beech, hornbeam).⁴⁰ In most cases, sensitization to such a pollen PR-10 allergen results in the development of IgE antibodies that cross-react with related allergens in many fruits, vegetables, legumes (including peanut), and tree nuts.^{11,12,34,35} Ingestion of such foods typically manifests in no more than mild, oropharyngeal symptoms (the pollen-food syndrome) unless the patient additionally has a primary food sensitization.^{1–3,6,9–13,25,27,30,34,41,42} Patients who are monosensitized to PR-10 allergens and have a clinical history of oral allergy symptoms rarely progress to severe systemic reactions,⁸ even if systemic reactions to raw hazelnuts in highly Cor a 1 mono sensitized adults have been reported to occur.^{12,35}

The relatively high rate of Cor a 1 sensitization in hazelnut extract –positive adults that was observed in our study can be explained, in part, by the fact that the commercially available ImmunoCAP for whole hazelnut is supplemented with recombinant Cor a 1,^{43,44} leading to inclusion of patients who might otherwise have tested negative to hazelnut extract, despite their Cor a 1 sensitization. In our study, 23% of individuals older than 20 years were sensitized to Cor a 9 and/or Cor a 14, whereas 79.8% were Cor a 1 sensitized (eTable 1). Sensitization to PR-10 allergens can confound the interpretation of hazelnut IgE test results in birch endemic regions unless hazelnut component testing is included in the patient evaluation.^{23,25,32} A recent study suggested that patients sensitized to birch pollen-related allergens (such as Cor a 1) as well as hazelnut storage proteins may be less likely to develop severe symptoms than those without cosensitization to pollen proteins.³⁰ A similar protective effect of PR-10 sensitization has also been described for LTP-sensitized patients in regard to their risk of severe food allergy.²⁸

These data show that in the United States, approximately 10% of hazelnut-positive individuals were sensitized to the Cor a 8, regardless of age. The nsLTP from peach (Pru p 3) has been implicated as a main primary inducer of nsLTP sensitization, although other food nsLTPs may play a role as sensitizers in some cases.^{45,46} Although studies of Mediterranean populations have found Cor a 8 to be linked to severe symptoms,^{3,10,12,42,47} sensitization to this component has not been shown to be predictive of severe clinical reactivity to hazelnut in other geographic regions.^{3,13,20,25,32,35,42,48,49}

Geographic variation in hazelnut component sensitization patterns have been documented across Europe. The predominance of specific allergens appears to be strictly related to the geographical origin of the allergic subjects and likely reflects exposure to different pollen and variance in local dietary traditions.²⁹ A high prevalence of sensitization to the cross-reactive allergen Cor a 1 is mainly observed in birch endemic regions.^{10,27} Hazelnut allergic patients from Mediterranean countries are mainly sensitized to the nsLTP Cor a 8 (ostensibly because of exposure to peach).^{1,3,9,10,42,47,48} Our ability to make inferences regarding the geographic distribution of component sensitization was somewhat limited by the lower number of samples from individuals living in the Western and Midwestern United States. Nonetheless, comparison of hazelnut component sensitization patterns in our data set revealed a regional difference for Cor a 1 sensitization, which was significantly higher in the Northeast than in other regions of the

United States, similar to the geographic distribution of Ara h 8 sensitization previously described.⁵⁰ The European regional variation in sensitization to Cor a 8 was not replicated in the United States. In a previous study, a similar lack of regional variation was observed for sensitization to Ara h 9, the nsLTP from peanut.⁵¹

Clinical observations frequently report an association of hazelnut allergy with allergies to other nuts.^{8,13,14,23,52} The differentiation between clinical cross-reactivity (co-allergy) and serologic cross-reactivity in the absence of clinically manifest co-allergy is a well-known diagnostic challenge in food allergy to peanut, tree nuts, and other seeds.^{14,23,52} Molecular cross-reactivity relies on the presence of conserved epitope structures of proteins and is hence observed in general among closely related members of the same protein family.^{29,53} We observed a moderate correlation⁵⁴ between the 2S albumins Cor a 14 and Jug r 1 from walnut (Table 3). A low correlation was seen between Cor a 14 and the 2S albumin from cashew (Ano o 3). Interestingly, a low to moderate correlation was observed between the 11S globulin from hazelnut (Cor a 9) and the 2S albumins from walnut (Jug r 1) and cashew nut (Ano o 3). We also found a relatively strong correlation between nsLTPs from hazelnut (Cor a 8) and walnut (Jug r 3). These findings suggest that the observed extent of cosensitization among hazelnut, walnut, and cashew nut may be attributed, at least in part, to IgE recognition of epitopes shared by homologous allergens present in these nuts, rather than immunologically unrelated concomitant sensitization, even though their degree of molecular similarity and cross-reactivity is limited.

Despite a distant botanical association, a number of reports have found that as many as half of all children with hazelnut allergy have concomitant peanut allergy.^{22–24,53} In addition, more than 50% of the hazelnut sensitized adolescents in this US population were also sensitized to peanut. The sequence homology among the 2S globulins, the major components associated with clinical allergy, in peanut and hazelnut is very low.^{22–25} Consistent with this, Masthoff and coworkers²³ reported that no cross-reactivity could be detected between Ara h 2 and Cor a 14, and we found little correlation⁵³ between Cor a 14 and any of the peanut components tested (Table 3). In regard to 11S globulins, Masthoff and coworkers²³ reported that Ara h 3 almost completely inhibited IgE binding to Cor a 9 in some of their patient samples tested. However, our component correlation data showed a poor correlation between Cor a 9 and Ara h 3, suggesting that such extensive cross-reactivity between Cor a 9 and Ara h 3 may not apply to most individuals in this population. Previous studies have found that concomitant peanut allergy affects neither decision points nor the diagnostic value of Cor a 14 for the prediction of hazelnut allergy.^{23,25} These findings are consistent with the contention that sensitization to hazelnut and peanut storage proteins is largely independent. Instead, the component correlation data point to cross-reactivity of PR-10 proteins (Cor a 1 and Ara h 8) and LTPs (Cor a 8 and Ara h 9) as major causes of hazelnut/peanut cosensitization.

We conclude that sensitization to hazelnut storage proteins (Cor a 9 and 14) is more common in children than adults who are evaluated for suspected hazelnut allergy. In contrast, the opposite is true for the Bet v 1–related PR-10 family of proteins, which includes Cor a 1. Sensitization to the nsLTP Cor a 8 occurs at a modest prevalence and appears not to be related to the subject's age or geographic region. Component correlations suggest that cross-reactivity may exist between PR-10 and nsLTP allergens hazelnut and walnut and, to a lesser extent, between their homologous seed storage proteins. This finding is divergent from the pattern observed for the less closely related hazelnut and peanut allergens where cross-reactivity of seed storage proteins may play a lesser role than cross-reactivity of PR-10 and nsLTPs proteins. Additional studies incorporating information on allergen exposure–related patient symptoms are needed to more precisely define the clinical utility of hazelnut component testing. To our knowledge, this study provides the first widespread detailed

assessment of sensitization pattern heterogeneity to hazelnut allergens across the United States, which we believe provides useful information on the occurrence of distinct subtypes of hazelnut sensitization and their cross-reactive associations with other nut allergens.

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Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.anaai.2018.09.466>.

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eTable 1
Sensitization to Combinations of Components by Patient Age

	No. (%) of patients by age, y										Combined
	0.00-3.00	3.01-6.00	6.01-9.00	9.01-12.00	12.01-15.00	15.01-20.00	20.01-30.00	30.01-40.00	40.01-50.00	> 50.00	
Total patients (f17 > 0.35 kU _A /L)	450	1,334	1,878	2,148	1,755	1,469	634	332	234	276	10,510
Cor a 1 > 0.35 kU _A /L ^a	21 (4.7)	40 (30.1)	1,086 (57.8)	1,497 (69.7)	1,305 (74.4)	1,130 (76.9)	505 (79.7)	274 (82.5)	188 (80.3)	211 (76.4)	6,618 (63.0)
Cor a 8 > 0.35 kU _A /L ^a	46 (10.2)	164 (12.3)	210 (11.2)	252 (11.7)	147 (8.4)	109 (7.4)	79 (12.5)	32 (9.6)	21 (9.0)	16 (5.8)	1,076 (10.2)
Cor a 9 > 0.35 kU _A /L ^a	403 (89.6)	987 (74.0)	1,114 (59.3)	1,191 (55.4)	841 (47.9)	612 (41.7)	196 (30.9)	41 (12.3)	20 (8.5)	36 (13.0)	5,441 (51.8)
Cor a 14 > 0.35 kU _A /L ^a	104 (23.1)	481 (36.1)	649 (34.6)	666 (31.0)	495 (28.2)	360 (24.5)	111 (17.5)	22 (6.6)	9 (3.8)	17 (6.2)	2,914 (27.7)
Only Cor a 1 > 0.35 kU _A /L	6 (1.3)	143 (10.7)	467 (24.9)	664 (30.9)	678 (38.6)	655 (44.6)	336 (53.0)	232 (69.9)	172 (73.5)	186 (67.4)	3,539 (33.7)
Only Cor a 8 > 0.35 kU _A /L ^a	7 (1.6)	18 (1.3)	21 (1.1)	21 (1.0)	8 (0.5)	12 (0.8)	12 (1.9)	7 (2.1)	8 (3.4)	7 (2.5)	121 (1.2)
Only Cor a 9 > 0.35 kU _A /L	279 (62.0)	413 (31.0)	282 (15.0)	233 (10.8)	165 (9.4)	115 (7.8)	42 (6.6)	12 (3.6)	9 (3.8)	13(4.7)	1,563 (14.9)
Only Cor a 14 > 0.35 kU _A /L ^a	7 (1.6)	48 (3.6)	49 (2.6)	43 (2.0)	34 (1.9)	22 (1.5)	9 (1.4)	4 (1.2)	4 (1.7)	1 (0.4)	221 (2.1)
Any of Cor a 9 and/or 14 > 0.35 kU _A /L ^a	410 (91.1)	1,054 (79.0)	1,226 (65.3)	1,312 (61.1)	943 (53.7)	707 (48.1)	2 (335.2)	51 (15.4)	25 (10.7)	40 (14.5)	5,991 (57.0)
Cor a 9 > 0.35 with Cor a 14 < 0.35 kU _A /L ^a	306 (68.0)	573 (43.0)	577 (30.7)	646 (30.1)	448 (25.5)	347 (23.6)	12 (17.7)	29 (8.7)	16 (6.8)	23 (8.3)	3,077 (29.3)
Cor a 14 > 0.35 kU _A /L with Cor a 9 < 0.35 kU _A /L	7 (1.6)	67 (5.0)	112 (6.0)	121 (5.6)	102 (5.8)	95 (6.5)	27 (4.3)	10 (3.0)	5 (2.1)	4 (1.4)	550 (5.2)
Both Cor a 9 and Cor a 14 > 0.35 kU _A /L ^a	97 (21.6)	414 (31.0)	537 (28.6)	545 (25.4)	393 (22.4)	265 (18.0)	84 (13.2)	12 (3.6)	4 (1.7)	13 (4.7)	2,364 (28.6)
Both Cor a 9 and Cor a 14 < 0.35 kU _A /L ^a	40 (8.9)	280 (21.0)	652 (34.7)	836 (38.9)	812 (46.3)	762 (51.9)	411 (64.8)	281 (84.6)	209 (89.3)	236 (85.5)	4,519 (43.0)
All components < 0.35 kU _A /L ^a	27 (6.0)	116 (8.7)	148 (7.9)	119 (5.5)	97 (5.5)	72 (4.9)	32 (5.0)	29 (8.7)	21 (9.0)	39 (14.1)	700 (6.7)
All components < 0.10 kU _A /L ^a	5 (1.1)	22 (1.6)	49 (2.6)	45 (2.1)	27 (1.5)	23 (1.6)	14 (2.2)	13 (3.9)	8 (3.4)	18 (6.5)	224 (2.1)

^aCutoff level of specific IgE applied.