



ORIGINAL ARTICLE

WILEY

Predictive factors of allergy to pistachio in children allergic to cashew nut

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Editor: Hugh Sampson

Abstract

Background: Cashew nut (CN) allergy prevalence has increased over the last few years. In children allergic to CN, complete avoidance of pistachio is usually recommended, but recent study showed that only one third of children allergic to CN were also allergic to pistachio. The aim of our study was to identify predictive factors of allergy to pistachio in children allergic to CN.

Methods: All children who had a positive oral food challenge (OFC) to CN between November 2013 and October 2017 in the Paediatric Allergy Department of the University Hospital of Nancy were included. Logistic regression models were used to predict the probability of allergy to pistachio.

Results: Among the 147 children included, tolerance or allergy to pistachio was known for 51. Out of these, 40 were allergic to pistachio (78.4%). Children allergic to pistachio had a larger weal size of skin prick test to CN ($P = .01$) and pistachio ($P = .0007$) and a lower reaction dose to CN ($P < .0001$). In multivariate analysis, only the reaction dose to CN was significantly associated with allergy to pistachio. Children with a low reaction dose to CN were significantly more at risk to have an allergy to pistachio ($P = .01$).

Conclusion: A low reaction dose to CN seems to be a predictive factor of allergy to pistachio in children allergic to CN. In order to limit unnecessary food eviction, a pistachio OFC should be performed in children having high reaction dose whatever the importance of the skin or the specific IgE sensitization to pistachio.

KEYWORDS

allergy, cashew nut, children, pistachio, threshold dose, tree nut

1 | INTRODUCTION

Cashew nut (CN) allergy prevalence has increased in the last few years. In a recent study on 1045 positive oral food challenges (OFCs), CN was the second most common allergen, after peanut.¹ In the

SchoolNuts study, CN allergy was the most frequent tree nut (TN) allergy.² CN can cause immediate anaphylactic reaction even more severe than peanut.^{3,4} CN allergy, along with other TN allergies, appears around the age of two, when CN and pistachio are introduced into the child's diet.⁵

The peer review history for this article is available at <https://publons.com/publon/10.1111/pai.13238>

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CN and pistachio belong to the same botanical family called the anacardiaceae⁶; therefore, the avoidance of pistachio is also currently recommended in case of allergy to CN.

Avoidance of TN is becoming more and more difficult to realize. The presence of CN and pistachio in very low doses is difficult to eliminate, due to cross-contamination in food lines.⁷ Moreover, the consumption of CN and pistachio has increased in the past few years due to the changes in food habits, and they are now used in products such as snacks, butters, pesto, bakery, and confectionary items.⁸

In vitro reactivity between CN and pistachio has been established by specific IgE (sIgE) inhibition tests.⁹ Willison et al¹⁰ demonstrated that Ana o 1 (specific CN protein) and Pis v 3 (specific pistachio protein) had large structural homologies. Moreover, Uotila et al¹¹ reported that pistachio and CN had one of the strongest co-sensitization linkages among edible nuts.

Regarding potential clinical cross-reactivity, the recently published PRONUT study found that CN and pistachio were the most highly correlated nut allergies.¹² However, so far, the only way to confirm or invalidate an allergy to pistachio in children allergic to CN is to undergo an OFC. It is also known that an unnecessary allergen avoidance for a child sensitized to this allergen could lead to the emergence of a clinically relevant allergy to this food.¹³

The aim of this study was therefore to identify predictive factors of clinical allergy to pistachio in children with CN allergy.

2 | METHODS

2.1 | Study population

All children, with a positive OFC to CN performed in the Paediatric Allergy Department of the University Hospital of Nancy between November 1, 2013, and October 31, 2017, were included. The non-inclusion criteria were as follows: children with negative OFC up to 2700 mg of CN protein and incomplete evaluation of CN allergy, that is, who did not have OFCs to CN up to 2700 mg. Children with unknown status for allergy to pistachio (never eaten and/or incomplete evaluation of pistachio allergy by OFC) were excluded.

2.2 | Oral food challenge

OFCs to CN and pistachio were performed as described by the consensus report of Niggeman et al.¹⁴ Raw CN and pistachio were given in a neutral vector such as applesauce or plain white yogurt. The starting dose and the progression schedule used for cashew and pistachio OFC are described in Table 1. The protein content of CN (18.0%) and pistachio (21.7%) was taken from the US Department of Agriculture's data and the Ciquel table.¹⁵ Antihistaminic treatment had to be discontinued during the previous 7 days, and any

Key Message

Almost 80% of children allergic to cashew nut are also allergic to pistachio. There is a moderate correlation between skin prick test (SPT) to cashew nut and SPT to pistachio and a strong correlation among IgE to cashew nut, IgE to rAna o 3, and IgE to pistachio. Sensitization to cashew nut and pistachio does not differentiate children allergic to cashew nut only from children allergic to both anacardiaceae. In multivariate analysis, low threshold dose to cashew nut is the only significant factor associated with allergy to pistachio in children allergic to cashew nut. In order to limit unnecessary food eviction, a pistachio oral food challenge should be performed in children having high threshold dose for cashew nut.

uncontrolled atopic features would contraindicate the challenge. The majority of the OFCs were open OFC because of time limitations. As recommended by the PRACTALL consensus, OFC was considered as positive if objective allergic symptoms appeared or if intense abdominal pain persisted for more than 40 minutes.¹⁶ In case of subjective symptoms, the OFC was considered uncertain and the patient was invited to come back another day for a double-blinded placebo-controlled OFC (DBPCFC).

2.3 | Collected variables

Data were retrospectively collected from patients' medical record. Social and demographic characteristics, history of CN or pistachio allergy, atopic comorbidities (asthma, atopic dermatitis, allergic rhinitis), co-allergy or co-sensitization to peanut, and other TN were collected. Skin prick test (SPT) and sIgE to CN and pistachio were all performed during the previous 6 months.

The SPT was performed with fresh food extract conditioned by the hospital food laboratory. We used two positive controls, the first one was histamine chlorhydrate (10 mg/mL), and the second one was codeine phosphate (9%). The weal size was measured 15 minutes after the prick-to-prick tests. sIgE was performed by ImmunoCAP fluorescence enzyme immunoassay (Thermo Fisher Scientific®) for CN, pistachio, and rAna o 3.

Regarding OFC, cumulative reaction dose (CD), eliciting dose (ED), symptoms, and severity of the allergic reaction according to Astier's classification were collected.¹⁷

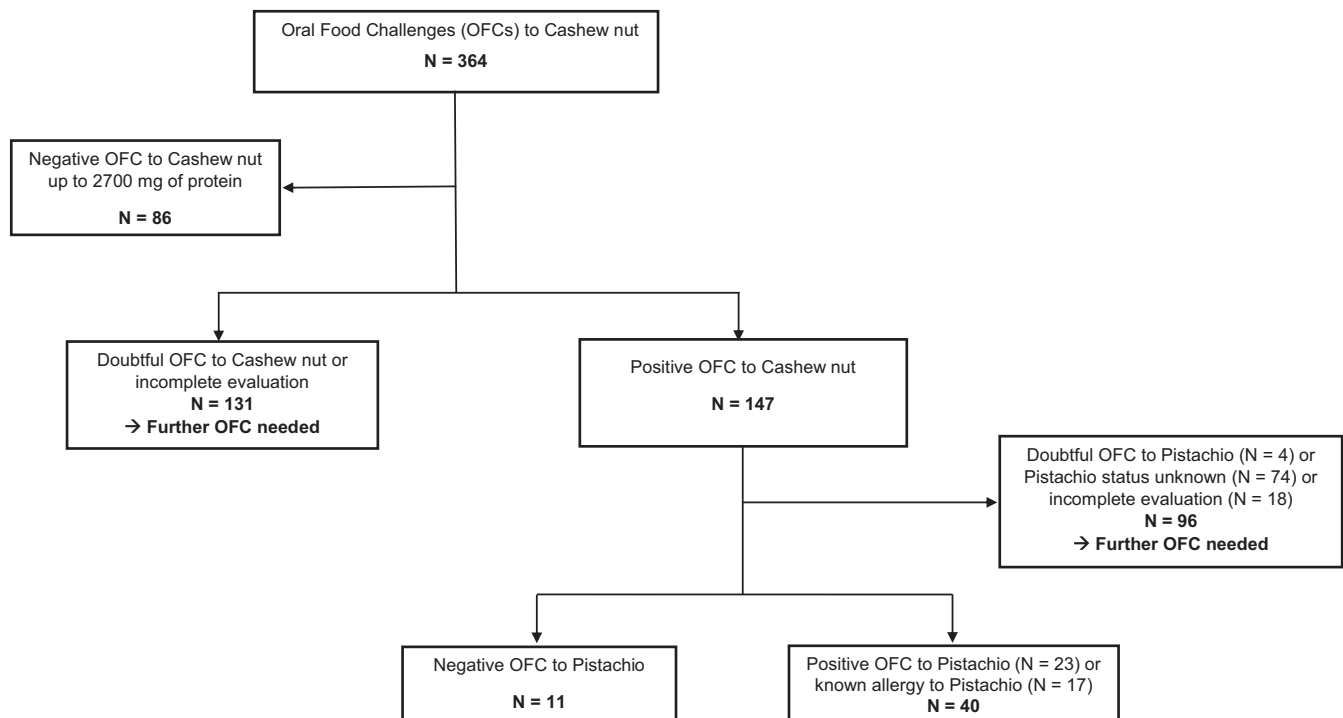
Children and their parents were informed by the physician and gave their written consent regarding the OFC course and the use of clinical data. The study was approved by the ethical committee of the University Hospital of Nancy. The clinical database was declared to the French Data Protection Authority under number R2018-01.

TABLE 1 Challenge doses (in mg of protein) used in oral food challenge A for cashew nut and B for pistachio*

A	Progression 1		Progression 2		Progression 3		Progression 4	
	Dose	Cumulative dose	Dose	Cumulative dose	Dose	Cumulative dose	Dose	Cumulative dose
Dose 1	0.18	0.18	2.7	2.7	90	90	180	180
Dose 2	0.54	0.72	9	11.7	180	270	360	540
Dose 3	1.8	2.52	27	38.7	360	630	540	1080
Dose 4	5.4	7.92	51.3	90	630	1260	720	1800
Dose 5			90	180			900	2700

B	Progression 1		Progression 2		Progression 3		Progression 4	
	Dose	Cumulative dose	Dose	Cumulative dose	Dose	Cumulative dose	Dose	Cumulative dose
Dose 1	0.22	0.22	3.25	3.25	108.5	108.5	217	217
Dose 2	0.65	0.87	10.85	14.1	217	325.5	434	651
Dose 3	2.17	3.04	32.55	46.65	434	759.5	651	1302
Dose 4	6.51	9.55	61.85	108.5	759.5	1519	868	2170
Dose 5			108.5	217			1085	3255

*The interval between doses is 20 min, and each progression takes place on separate days.

**FIGURE 1** Flowchart

2.4 | Statistical analysis

Categorical data are presented as numbers (%); continuous data are presented as median with first and third quartiles [Q1; Q3]. In order to compare the characteristics of our population, Pearson's chi-square test or Fisher's exact test, as appropriate, for the qualitative variable and Wilcoxon test for the quantitative variable were used.

Logistic regression models were used to predict the probability of pistachio allergy. Factors with a significant association

at a threshold of 0.2 in the univariate model were included in the multivariate model with stepwise method (SLE = 0.2, SLS = 0.05). Spearman's rank correlation coefficient was used to test correlation between input variables. Age, gender, prior history of allergic reaction to CN, atopic comorbidities, and severity of the reaction to CN OFC and sIgE to rAna o 3 were forced into the model as variables of importance.

Statistical analyses were performed using SAS 9.4 (SAS Institute).

TABLE 2 Characteristics of the children with a positive oral food challenge for cashew nut

	Total N = 147			Unknown pistachio status N = 96 (65.3%)			Pistachio status known N = 51 (34.7%)			P**
	N	%/med*	IQR*	N	%/med*	IQR*	N	%/med*	IQR*	
Gender										
Boys	85	57.8		54	56.3		31	60.8		.5962
Girls	62	42.2		42	43.8		20	39.2		
Age	146	8.4	5.6-11.7	95	7.4	5.2-11.6	51	9.3	6.1-12.4	.0362
Prior allergic reaction to cashew nut										
No	95	64.6		63	65.6		32	62.7		.7281
Yes	52	35.4		33	34.4		19	37.3		
Atopic dermatitis										
No	55	37.4		35	36.5		20	39.2		.7423
Yes	92	62.6		61	63.5		31	60.8		
Asthma										
No	85	57.8		55	57.3		30	58.8		.8579
Yes	62	42.2		41	42.7		21	41.2		
Rhinoconjunctivitis										
No	103	70.1		69	71.9		34	66.7		.5116
Yes	44	29.9		27	28.1		17	33.3		
Another food allergy										
No	42	28.6		33	34.4		9	17.6		.0326
Yes	105	71.4		63	65.6		42	82.4		
Another tree nut allergy										
No	97	66		66	68.8		31	60.8		.3319
Yes	50	34		30	31.2		20	39.2		
Skin prick test to cashew nut (mm)	146	9.0	5.5-12.0	96	9.3	6.0-12.0	50	9.0	5.5-12.5	.7542
Skin prick test to pistachio (mm)	145	9.0	6.0-12.5	96	8.7	6.0-12.0	49	9.5	5.0-12.5	.9900
Specific IgE to cashew nut (kU/L)	128	3.4	1.1-9.8	81	3.7	1.2-10.5	47	3.2	1.1-8.5	.4873
Specific IgE to pistachio (kU/L)	124	4.4	1.7-10.3	77	4.8	1.9-9.9	47	3.5	1.5-10.5	.5775
Specific IgE to r Ana o 3 (kU/L)	113	3.7	1.7-10.3	69	3.8	1.0-10.1	44	3.7	1.7-9.4	.4315
Cumulative reaction dose of cashew nut (mg of protein)	147	38.7	11.7-180.0	96	38.7	14.4-180.0	51	38.7	9.9-270.0	.5596
Eliciting dose of cashew nut (mg of protein)	147	27	9-90	96	27.0	9.0-90	51	27.0	5.4-180	.5389

Note: Boldface value: $P < .05$.

*Med: median; IQR: interquartile (Q1-Q3).

**Chi-square test or fisher's exact test for qualitative variables, and Wilcoxon signed rank test for quantitative variables.

3 | RESULTS

3.1 | Patient characteristics

We included 147 children with a positive OFC to CN. Among them, tolerance or allergy to pistachio was known for 51 children. The remaining 96 children were excluded because they had never eaten pistachio and because the evaluation of their oral tolerance to pistachio by OFC was incomplete at the time of the analysis. The flow-chart is detailed in Figure 1.

To ensure no selection bias, the characteristics of the 51 children with a known pistachio status were compared with the 96 remaining children allergic to CN with unknown status for pistachio. There was no significant difference except for age and for the presence of another food allergy ($P = .03$; Table 2).

Regarding the study population of 51 children, the median age was 9.3 [6.0; 12.4] years with a majority of boys (60.8%). Regarding atopic comorbidities, 60.8% (31) had atopic dermatitis, 41.2% (21) had asthma, and 33.3% (17) had rhinoconjunctivitis. Concerning other food allergies, 82.4% (42) of them had at least one another

TABLE 3 Characteristics of the children allergic to cashew nut with a known pistachio status

	N = 51			Cashew N = 11 (21.6%)			Cashew and pistachio N = 40 (78.4%)			P**
	N	%/med*	IQR*	N	%/med*	IQR*	N	%/med*	IQR*	
Gender										
Boys	31	60.8		7	63.6		24	60.0		.8268
Girls	20	39.2		4	36.4		16	40.0		
Age	51	9.3	6.0-12.4	11	10.6	5.5-13.2	40	9.0	6.9-12.1	.6903
Prior allergic reaction to cashew nut										
No	32	62.7		8	72.7		24	60.0		.4394
Yes	19	37.3		3	27.3		16	40.0		
Atopic dermatitis										
No	20	39.2		5	45.5		15	37.5		.6323
Yes	31	60.8		6	54.5		25	62.5		
Asthma										
No	30	58.8		9	81.8		21	52.5		.802
Yes	21	41.2		2	18.2		19	47.5		
Rhinoconjunctivitis										
No	34	66.7		9	81.8		25	62.5		.2287
Yes	17	33.3		2	18.2		15	37.5		
Another food allergy										
No	9	17.6		2	18.2		7	17.5		.9581
Yes	42	82.4		9	81.8		33	82.5		
Another tree nut allergy										
No	31	60.8		7	63.6		24	60		.8268
Yes	20	39.2		4	36.4		16	40		
Skin prick test to cashew nut										
<8 mm	24	48		9	90		15	37.5		.0030
≥8 mm	26	52		1	10		25	62.5		
Skin prick test to pistachio										
<8 mm	18	36.7		9	90		9	23.1		<.0001
≥8 mm	31	63.3		1	10		30	76.9		
Specific IgE to cashew nut										
<15 kU/L	43	91.5		9	81.8		34	94.4		.2093
≥15 kU/L	4	8.5		2	18.2		2	5.6		
Specific IgE to pistachio										
<15 kU/L	41	87.2		8	72.7		33	91.7		.1147
≥15 kU/L	6	12.8		3	27.3		3	8.3		
Specific IgE to r Ana o 3										
<15 kU/L	40	90.9		10	90.1		30	90.9		1
≥15 kU/L	4	9.1		1	9.1		3	9.1		
Cumulative reaction dose to cashew nut (mg of protein)										
<11.7	13	25.5		0	0		13	32.5		<.0001
11.7-38.7	14	27.5		1	9.1		13	32.5		
38.7-180	10	19.6		0	0		10	25.0		
≥180	14	27.5		10	90.9		4	10.0		

(Continues)

TABLE 3 (Continued)

	N = 51			Cashew N = 11 (21.6%)			Cashew and pistachio N = 40 (78.4%)			
	N	%/med*	IQR*	N	%/med*	IQR*	N	%/med*	IQR*	P**
Eliciting dose to cashew nut (mg of protein)										
<9	13	25.5		0	0		13	32.5		<.0001
9-27	8	15.7		0	0		8	20.0		
27-90	14	27.5		1	9.1		13	32.5		
≥90	16	31.4		10	90.9		6	15.0		
Allergic reaction according to Astier's classification										
1	6	11.8		1	9.1		5	12.5		.5576
2	21	41.2		6	54.5		15	37.5		
3	19	37.3		4	36.4		15	37.5		
4	5	9.8		0	0		5	12.5		
5	0	0		0	0		0	0		

Note: Boldface value: $P < .05$.

*Med: median; IQR: interquartile (Q1-Q3).

**Chi-square test or Fisher's exact test for qualitative variables, and Wilcoxon signed rank test for quantitative variables.

food allergy, and 39.2% (20) had another TN allergy. All the 51 children were sensitized to both anacardiaceae (SPT ≥ 3 mm and sIgE ≥ 0.35 kU/L).

The median CN SPT weal size was 9 mm [5.5; 12.5], and 52% had a SPT superior or equal to 8 mm, the cut-off value suggested by Ho et al.¹⁸ The median pistachio SPT weal size was 9.5 mm [5.0; 12.5] with 63.3% having a SPT superior or equal to 8 mm. Regarding the OFC to CN, the median CD was 38.7 mg of protein [9.9; 270], the median ED was 27 mg [5.4; 180], and 50% of the children had a severe reaction with at least two organs involved (Astier's score superior or equal to 3). There was no grade 5. Among the 51 children, 5 had a DBPCFC because of abdominal pain to the first open OFC.

3.2 | Allergy to pistachio

Among the 51 children allergic to CN and whose oral tolerance of pistachio was known, 40 (78.4%) were allergic to pistachio, and 11 (21.6%) had a negative OFC to pistachio to more than 3000 mg of protein. Among the 40 children allergic to pistachio, 23 had an open positive OFC to pistachio and 17 had a prior history of allergic reaction to pistachio (Tables S1 and S2).

There was no significant difference regarding demographic and atopic characteristics (Table 3).

Children allergic to pistachio had a larger weal size of SPT to CN ($P = .01$) and to pistachio ($P = .0007$) (Figure 2). There was no difference for the ratio between SPT to CN and SPT to pistachio. There was a moderate correlation between SPT to CN and SPT to pistachio ($r = .73$, $P < .001$). In children allergic to pistachio, weal size of SPT to CN and SPT to pistachio was respectively superior or equal to 8 mm in 62.5% and 76.9% of the children. Whereas in children without allergy to pistachio, weal size of SPT to CN and SPT to pistachio

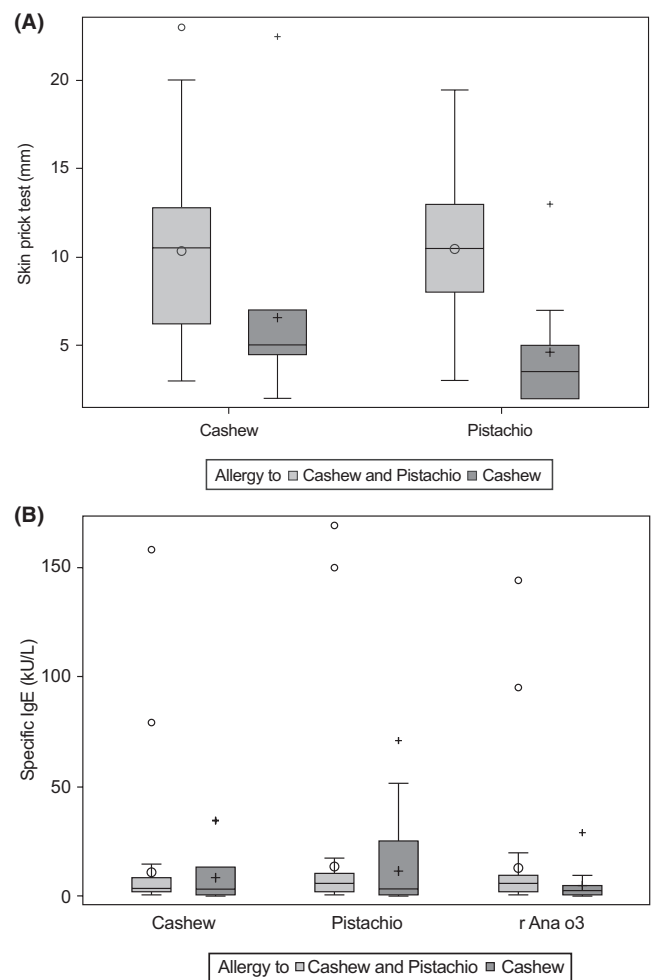


FIGURE 2 Sensitization to cashew nut and pistachio according to allergy to cashew nut alone or to cashew nut and pistachio (2A: skin prick test; 2B: specific IgE)

TABLE 4 Predictive factor of being allergic to pistachio

	N	Pistachio Allergy		Univariate regression			Multivariate regression		
		n	%	Odds ratio	CI 95%	P	Odds ratio	CI 95%	P
Age	51	40	78.4	0.966	0.810-1.152	.7018	0.855	0.584-1.253	.4221
Prior allergic reaction to cashew nut									
No	32	24	75.0	1		.4430	1		.8230
Yes	19	16	84.2	1.778	0.409-7.732		1.416	0.067-29.89	
Skin prick test to pistachio									
<8 mm	18	9	50.0	1		.0024	1		.0650
≥8 mm	31	30	96.8	30.00	3.337-269.7		50.88	0.784-3303	
Reaction dose to cashew nut (mg of protein)	51	40	78.4	0.994	0.990-0.997	.0005	0.993	0.988-0.999	.0161
Gender									
Boys	31	24	77.4	1		.8269			
Girls	20	16	80.0	1.167	0.293-4.646				
Atopic dermatitis									
No	20	15	75.0	1		.6330			
Yes	31	25	80.6	1.389	0.361-5.349				
Asthma									
No	30	21	70.0	1		.0960			
Yes	21	19	90.5	4.071	0.779-21.26				
Rhinoconjunctivitis									
No	34	25	73.5	1		.2411			
Yes	17	15	88.2	2.700	0.513-14.21				
Another food allergy									
No	9	7	77.8	1		.9581			
Yes	42	33	78.6	1.048	0.185-5.943				
Skin prick test to cashew nut									
<8 mm	24	15	62.5	1		.0141			
≥8 mm	26	25	96.2	15.00	1.725-130.4				
IgE rAna o 3									
<5 kU/L	26	17	65.4	1		.3900			
5-15	14	13	92.9	6.882	0.771-61.41				
15-50	3	2	66.7	1.059	0.084-13.33				
≥50 kU/L	1	1	100	NA					
Allergic reaction according to Astier's classification									
1	6	5	83.3	1		.9179			
2	21	15	71.4	0.500	0.048-5.225				
3	19	15	78.9	0.750	0.067-8.382				
4	5	5	100	NA					
5	0	0	0	NA					

Note: Boldface value: $P < .05$. The Hosmer and Lemeshow goodness-of-fit test underlines the good quality of the model ($P = .9423$).

Abbreviations: CI, confidence interval; NA, non-applicable.

was superior or equal to 8 mm in 10% of the children. Regarding sIgE, there was no significant difference between the two groups for CN ($P = .50$), rAna o 3 ($P = .35$), and pistachio ($P = .39$). There was no difference either for the ratio between sIgE CN and sIgE pistachio. There was a strong correlation between sIgE to CN and sIgE to

pistachio ($r = .99$, $P < .0001$), and between sIgE to pistachio and sIgE to rAna o 3 ($r = .96$, $P < .0001$) in both groups.

Children allergic to pistachio had a significantly lower CD for CN ($P < .0001$) with a median of 22.5 mg CN protein [7.9; 90.0]. Only one child (9.1%) non-allergic to pistachio had a CD under

38.7 mg of protein, vs 65.0% in children allergic to pistachio ($P = .002$). Moreover, 90.9% of children non-allergic to pistachio had a CD to CN over 189 mg of protein vs only 10.0% in the group allergic to pistachio.

3.3 | Predictive factors for pistachio allergy

In multivariate analysis, only the CD to CN was significantly associated with allergy to pistachio in children allergic to CN. A CD of 10 mg more of CN proteins was associated with a 10-fold decreased risk of allergy to pistachio ($P = .01$) (Table 4). Considering ED to CN in the multivariate analysis instead of CD did not change these results ($P = .01$) (Table S3).

3.4 | Children with positive OFC to pistachio

Among the 23 children with a positive OFC, digestive symptoms were more frequent (77.8%), followed by skin reaction (25.9%). The median CD was 108.5 mg pistachio protein [46.6; 759.5], and the median ED was 108.5 mg [32.5; 434.0].

The comparison between CD for CN and CD for pistachio in each child showed a CD for pistachio always superior or equal to CN CD ($P = .0026$). Considering ED to CN instead of CD did not change these results ($P = .0018$).

4 | DISCUSSION

Among the 51 children allergic to CN with a known status for pistachio, 78.4% were allergic to pistachio. We found significant differences between the two groups concerning SPT to CN and pistachio with a larger weal size in children allergic to both anacardiaceae, whereas there was no significant difference regarding sIgE sensitization. Reactive dose for CN was lower in children allergic to pistachio, and in multivariate analysis, it was the only predictive factor for pistachio allergy.

Our work showed that a low reactive dose to CN is associated with a higher risk of allergy to pistachio. One limit of these results is the non-reproducibility of the reactive dose during OFC as suggested by Glaumann et al¹⁹ for peanut. However, in this study, there was a high variation for individual reactive dose, especially when subjective allergic symptoms such as mouth itch were considered. In our study, we only considered objective symptoms or abdominal pain that persisted more than 40 minutes.

In all children with allergy to both anacardiaceae, pistachio CD appeared to be higher or equal to CN CD. This result is not concordant with the study of Purington et al,¹ in which the lowest ED was found for pistachio. However, in this study, pistachio OFC was started at a lower dose (1 mg instead of 2 mg) due to safety concern in children known to be allergic to CN, which could have an impact on the comparison of ED.

According to Soller et al,²⁰ OFC has a positive outcome on quality of life of the children and their family. Knowing precisely which foods to avoid is essential for allergic children and reduces anxiety. The possibility of eating pistachio is considered to be a benefit especially not only because the consumption of pistachio is increased in our society but also because in case of sensitization to a food allergen, continued avoidance might induce an allergy to this food allergen.²¹

Whereas sIgE rAna o 3 seems to be associated with the severity of CN allergy,²² we found a strong correlation among sIgE to CN, sIgE to rAna o 3, and sIgE to pistachio with no statistical difference between children allergic to both nuts and children allergic only to CN. The cross-reactivity between sIgE to CN and sIgE to pistachio is well established in vitro and could explain this results.²³ In the IDEAL study, skin sensitization and sIgE sensitization to pistachio were found in all the children allergic to CN, but with the dot-plot technique, 34% were mono-sensitized to CN, suggesting that other proteins could differentiate children only allergic to CN.²⁴

Regarding skin sensitization, a positive SPT to pistachio is not relevant to distinguish children allergic to pistachio from children non-allergic to pistachio. However, children allergic to pistachio had a larger weal size of SPT to CN and SPT to pistachio. Associations between skin sensitization to both nuts and allergy to pistachio disappeared in multivariate analysis, probably due to the strong effect of CD to CN. The NUT CRACKER study also found that children allergic to CN only had lower SPT weal size to CN compared to those allergic to CN and pistachio.²⁵ Van der Valk et al²⁶ also demonstrated that SPT was stronger predictor of a positive outcome for CN OFC than sIgE to Ana o 1, 2, and 3. In our study, we used prick-to-prick technique because SPT with fresh food is known to be more sensitive and representative of the protein complexity of each food compared with SPT with commercial food extracts. Nevertheless, these prick-to-prick tests are not standardized. The use of fresh CN and pistachio for SPT might be considered to reduce the generalization of these findings.

We found a high prevalence of allergy to pistachio in children allergic to CN (78.4%). This prevalence is similar to that reported by the IDEAL study and the NUT CRACKER study but higher than the prevalence described by Van der Valk et al (31%).^{24,25,27} In our study, the 96 children allergic to CN with an unknown status to pistachio were significantly younger and had less additional food allergies than the studied population. It might have an impact on the estimation of the prevalence of allergy to pistachio. Another limitation of our study is the OFC maximal dose of 1 g of proteins. Our OFC cumulative doses are based on the daily consumption of a child (15 g of food), but this is lower than the 2 g recommended by PRACTALL and the NUT CRACKER study that showed a risk of false-negative OFC up to 14.3% for pistachio and 8.3% for CN if the last dose is fewer than 2 g of proteins.^{16,25}

In conclusion, our study showed that a low reactive dose to CN is a predictive factor for allergy to pistachio in children. Therefore, in order to limit unnecessary food eviction, a pistachio OFC should be

proposed to children with a high reactive dose to CN whatever the importance of skin or sIgE sensitization.

AUTHORS' CONTRIBUTIONS

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Dr Saba conceptualized and designed the study, contributed to data collection, interpreted the results, and drafted the initial manuscript. Dr Clerc-Urmès conducted the statistical analyses and contributed to the interpretation of the results. Dr Delahaye contributed to data collection and contributed to the interpretation of the results. Drs Chevillot, Jarlot-Chevaux, Dumond, and Pr Schweitzer contributed to the interpretation of the results and critically reviewed the manuscript. Dr Divaret-Chauveau conceptualized and designed the study, contributed to the interpretation of the results, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Saba L, Clerc-Urmès I, Delahaye C, et al. Predictive factors of allergy to pistachio in children allergic to cashew nut. *Pediatr Allergy Immunol*. 2020;00:1-9. <https://doi.org/10.1111/pai.13238>

Table E1: Clinical characteristics, age, gender and pistachio sensitization for children with prior allergic reaction to pistachio

Patient number	Age*(years)	Gender**	Clinical characteristics***	Pistachio sensitization*	
				Specific IgE (kU/L)	Skin Prick test (mm)
9	10	F	OAS,D	1.16	12.5
19	10	M	U,V,D	16.2	8
39	8	M	A	MV	14.5
62	5	M	AO,V	12.5	18.5
95	8	F	V	3.7	10.5
102	15	M	U	1.18	13
158	12	F	AO,V	6.71	7.5
173	9	M	AO	2.77	5
174	5	M	AO	MV	4.5
192	14	F	AO	1.22	9
253	9	M	AO	MV	16
272	5	M	AO	4.73	9
275	11	M	AO,U	1.77	14
307	15	F	V,AP	13.1	15.5
311	10	F	AO	6.5	3
328	12	M	AP	0.97	4
332	8	F	V,AP	1.79	10

* Age and pistachio sensitization were collected during the cashew nut OFC - MV: Missing Value

**F: Female; M: Male

***OAS: Oral Allergy Syndrome (defined as the onset of immediate oral itching with or without angioedema of the lips and oral mucosa); D: Dyspnea; U: Urticaria; V: Vomiting; A: Asthma; AO: Angio-oedema; AP: Abdominal Pain.

Table E2: Clinical characteristics, age, gender and pistachio sensitization for children with a positive pistachio Oral Food Challenge (OFC)

Patient number	Age*(years)	Gender**	Clinical Characteristics***	Pistachio sensitization*	
				Specific IgE (kU/L)	Skin Prick test (mm)
22	10	M	AP,V	1.08	13.5
66	6	M	AP,D	3	13,5
84	15	M	AP	11.7	15
98	10	M	V,U,D	MV	MV
104	15	M	U	0.97	10
108	15	F	OAS,AP,C	6.67	15
121	5	F	V	13.2	10.5
125	11	M	V,C	13.1	14
130	9	M	AP,V,OAS	1.43	9.5
141	15	M	U	1.05	9
165	5	F	AP,V	150	15.5
170	10	F	AP,V,OAS	2.43	12
182	8	M	OAS,U	0.5	12.5
206	10	M	AP	9.72	6
220	7	F	AP	4.99	7
228	5	M	AP,V,OAS,C	7.12	6.5
266	7	M	OAS,AP	1.34	9
275	11	M	U,V	MV	9
283	10	M	OAS,V	3.8	5
292	2	F	AP,V	8.47	6.5
300	3	F	U	0.27	6
309	8	F	V,AP	169	10
325	6	M	AP	1.61	11.5

* Age and pistachio sensitization at the time of the pistachio OFC- MV: Missing Value

**F: Female; M: Male

***OAS: Oral Allergy Syndrome (defined as the onset of immediate oral itching with or without angioedema of the lips and oral mucosa); D: Dyspnea; U: Urticaria; V: Vomiting; A: Asthma; AO: Angio-oedema; AP: Abdominal Pain C: Conjunctivitis

Table E3: Predictive factor of being allergic to pistachio considering eliciting dose to cashew nut

	N	Pistachio Allergy		Univariate regression			Multivariate regression		
		n	%	Odds ratio	CI* 95%	p	Odds ratio	CI* 95%	p
Age	51	40	78.4	0.966	0.810 - 1.152	0.7018	0.807	0.549 - 1.186	0.2743
Prior allergic reaction to cashew nut						0.4430			0.6795
No	32	24	75.0	1			1		
Yes	19	16	84.2	1.778	0.409 - 7.732		1.889	0.0092 - 38.62	
Skin prick test to pistachio						0.0024			0.0566
< 8 mm	18	9	50.0	1			1		
≥ 8 mm	31	30	96.8	30.00	3.337 - 269.7		59.25	0.892 - 3935	
Eliciting dose to CN (mg of protein)	51	40	78.4	0.989	0.983 - 0.995	0.0003	0.989	0.980 - 0.997	0.0115
Gender						0.8269			
Boys	31	24	77.4	1					
Girls	20	16	80.0	1.167	0.293 - 4.646				
Atopic Dermatitis						0.6330			
No	20	15	75.0	1					
Yes	31	25	80.6	1.389	0.361 - 5.349				
Asthma						0.0960			
No	30	21	70.0	1					
Yes	21	19	90.5	4.071	0.779 - 21.26				
Rhino conjunctivitis						0.2411			
No	34	25	73.5	1					
Yes	17	15	88.2	2.700	0.513 - 14.21				
Another food allergy						0.9581			
No	9	7	77.8	1					
Yes	42	33	78.6	1.048	0.185 - 5.943				
Skin prick test to cashew nut						0.0141			
< 8 mm	24	15	62.5	1					
≥ 8 mm	26	25	96.2	15.00	1.725 - 130.4				
IgE rAna o 3						0.3900			
<5 kU/L	26	17	65.4	1					
[5-15[	14	13	92.9	6.882	0.771 - 61.41				
[15-50[	3	2	66.7	1.059	0.084 - 13.33				
≥ 50 kU/L	1	1	100	NA**					
Allergic reaction according to Astier's classification						0.9179			
1	6	5	83.3	1					
2	21	15	71.4	0.500	0.048 - 5.225				
3	19	15	78.9	0.750	0.067 - 8.382				
4	5	5	100	NA**					
5	0	0	0	NA**					

* CI: Confidence Interval - ** NA: Non Applicable

Bold face value: p < 0.05

The Hosmer and Lemeshow Goodness-of-Fit test underlines the good quality of the model (p=0.2262)