Prediction of cashew nut allergy in sensitized children

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combined profile of these six eicosanoids (0.913) was significantly larger than bronchial hyper-responsiveness (BHR, estimated by Δ% FEV1) and FeNO (0.765 and 0.826). The analysis of the ROC curve with Youden Index for pattern eicosanoid profiles indicated the value of 0.514 as having the strong discriminatory ability. At this cutoff value, 35 of 39 asthmatic children were correctly classified, as well as 21 of 27 healthy subjects, giving a sensitivity of 89.7% and specificity of 90.2%.

In summary, this study demonstrated excessive concentration of eicosanoids in asthmatic children, making them useful and valuable biomarkers for pediatric asthma. The pattern eicosanoids profiles, which take into account levels of PGD2, 6keto-PGF1α, TXB2 LTE4, 5-HETE, and 15-HETE, allowed highly accurate discrimination of asthmatic and control children. In fact, there is still a lack of appropriate diagnostic and monitoring tool for pediatric asthma. It seems that the measurement of serum eicosanoid profiles is probably a helpful diagnostic tool for pediatric asthma. However, the assessment of serum eicosanoids does not yet seem to be practically applicable in routine clinical workup because of the limited availability of expensive equipment. Instead, it might be a nice approach for early warning of asthmatic risk, as well as the progress of asthma.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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To the Editor,

As an alternative to the costly, time-consuming and possibly stressful double-blind, placebo-controlled challenge (DBPCFC) test, a model to predict the risk of cashew nut allergy was studied incorporating patient characteristics, standard diagnostic parameters (specific IgE [sIgE] and Skin prick test [SPT]) as well as component-resolved diagnosis (CRD). We previously demonstrated that sIgE to the components Ana o 1, 2 and 3 discriminated better between cashew nut allergic and tolerant children sensitized to cashew nut than the current testing methods (SPT and sIgE to cashew nut).[1] The aim of this study was to develop a prediction model for cashew nut allergy.

Results of children who participated in the IDEAL study (trial number NTR3572) were analysed. The study protocol and inclusion criteria were previously described.[2] Briefly, 179 children sensitized to cashew nut (sIgE and/or SPT) and with a history of previous positive reaction to cashew nut or with no (known) history of cashew nut ingestion were included from three tertiary care centres in the period May 2012 to March 2015. SIgE to cashew nut and to Ana o 1, 2 and 3 was measured,

Abbreviations: AUC, area under the curve; C-index, concordance index; CRD, component-resolved diagnosis; DBPCFC, double-blind, placebo-controlled food challenge; LR, likelihood ratio; OR, odds ratio; ROC, receiver operator characteristics; sIgE, specific IgE; SPT, skin prick test.

a SPT with cashew nut extract was performed, and all patients underwent a DBPCFC test. Cashew nut allergens Ana o 1, 2 and 3 were purified specifically for this study,[3] and sIgE to these purified allergens was measured by the standardized Siemens IMMULITE procedure.

The DBPCFC test consisted of an eight-step incremental dose regime of validated and standardized food challenge material.[4] The cumulative dose was 3180 mg cashew nut protein (approximately 22 cashew nuts) when all eight-dose steps were consumed.

Univariate and multivariable logistic regression analysis was used to assess the contribution of potential predictors to cashew allergy. The odds ratios (ORs) for continuous variables were scaled in a way that they corresponded to a change in one standard deviation of the predictor distribution. The model building process followed the usual order in a diagnostic work-up. We used a relatively high p-value ($P<.5$) in the backward selection procedure, because of the limited number of non-events.[5] We also applied the "sign OK" rule.[6] Discriminative ability of the models was assessed with the concordance index (c-index). Internal validity was assessed with bootstrapping.[7] The regression coefficients in the final model were multiplied with a shrinkage factor. Without shrinkage, predictions are generally too extreme. The prediction models were transformed into score charts for use the use in clinical practice.

TABLE 1 Univariate logistic regression of patient characteristics for a positive challenge test with cashew nut

	Positive DBPCFC		Negative DBPCFC			
Variables	**N=137**	**79%**	**N=36**	**21%**	**OR**	**95% CI**
History						
Gender (girl)	60	86%	10	14%	2.0	0.9-4.5
Age, y[a]	9.0	Range 2 to 7	9.5	Range 2-17	1.0	0.9-1.0
History of cashew nut allergy	92	86%	15	14%	2.9	1.4-6.0
Atopic features[b]	102	81%	24	19%	1.5	0.7-3.2
Standard diagnostics						
Median sIgE to cashew nut, kU/L[a]	5.8	Range 0 to ≥100	1.2	Range 0-17.1	2.9	2.1-4.0
SPT with cashew nut extract (mean wheal diameter)	11.0	Range 2.5 to 26.0	5.0	Range 0-14.5	7.1	6.2-8.2
Components						
Median sIgE to Ana o 1, kU/L[a]	2.0	Range 0 to ≥100	0.2	Range 0-6.7	8.6	5.4-13.8
Median sIgE to Ana o 2, kU/L[a]	6.3	Range 0 to ≥100	1.2	Range 0-8.4	5.4	3.6-8.1
Median sIgE to Ana o 3, kU/L[a]	13.0	Range 0 to ≥100	0.6	Range 0-30.9	8.6	5.8-12.7

OR, odds ratio; SPT, skin prick test; sIgE, specific IgE.
[a]For continuous variables, OR is given for a change in standard deviation of the predictor distribution.
[b]Symptoms reported of hay fever, eczema or asthma.

TABLE 2 Multivariate models with demographics and history, standard diagnostics (sIgE to cashew nut and SPT) and sIgE to Ana o 3

	Demographics and history Model A		+Standard diagnostics Model B				+Component Ana o 3 Model C			
			Without SPT		With SPT		Without SPT		With SPT	
Variables	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Gender (girl)	1.8	0.8-4.2	2.4	1.0-6.0	3.1	1.0-9.2	2.1	0.7-6.3	2.7	0.8-8.5
History of cashew nut allergy	2.9	1.4-6.4	3.5	1.5-8.1	2.2	0.7-6.7				
Atopic features[a]	1.8	0.8-4.1	1.6	0.6-3.9	2.2	0.8-6.2				
sIgE to cashew nut (kU/L)[b]			3.2	2.3-4.4	2.1	1.5-3.0				
SPT with cashew nut extract (mean wheal diameter)[b]					5.9	5.0-6.9			4.6	3.1-6.9
sIgE to Ana o 3 (kU/L)[b]							8.7	5.9-12.8	3.3	2.8-3.9
C-index (optimism corrected)	0.66		0.80		0.87		0.89		0.91	

OR, odds ratio; SPT, skin prick test; sIgE, specific IgE.
[a]Symptoms reported of hay fever, eczema or asthma.
[b]For continuous variables, OR is given for a change in standard deviation of the predictor distribution.

The median age of the total study group was 9.0 years (range 2-17 years), with 106 boys (59%) and 73 girls (41%). The children were included from three participating medical research centres and came from all over the Netherlands. Atopy was reported by 126 (72%) children, for example eczema N=70 (39%), asthma N=55 (31%) and 94 children (53%) had symptoms consistent with hay fever. Hundred and seven children (62%) had a positive history of cashew nut allergy. The majority of the children reacted to cashew nuts as a single food ingested and not incorporated in other foods and to an amount equivalent to approximately one cashew nut.

The DBPCFC with cashew nut was positive in 137 (79%) patients and negative in 36 (21%) patients. Six patients had an uncertain DBPCFC test outcome with cashew nut and were considered as undetermined (eg children who did not complete the test). These children were excluded from the analysis.

The predictors gender (girl), history of cashew nut allergy and atopic features were associated with a positive challenge test of which the history of cashew nut allergy (62%) gave the highest OR (2.9, 95% CI 1.4-6.0).

sIgE to the cashew nut components Ana o 1, 2 and 3 was strongly associated with a positive challenge test (ORs of 8.6 (95% CI 5.4-13.8), 5.4 (95% CI 3.6-8.1) and 8.6 (95% CI 5.8-12.7), respectively) (Table 1). Furthermore, chi-square statistics were used to assess the strength of the different predictors. SPT (LR 61.25) was statistically significantly a stronger predictor than the allergen molecules of cashew Ana o 1, 2 and 3 (LR 45.63, 47.44 and 56.02, respectively). Less strong predictors were history (LR 7.65) and sIgE cashew (LR 24.7).

The discriminative ability of the model including gender, history of cashew nut allergy and atopic features was relatively low after correction for optimism (c-index=0.66). Adding sIgE to cashew nut increased the c-index to 0.80 and further increased when SPT was also included (c-index=0.87). When CRD was included, only gender and SPT remained in the models after backward selection. Using the CRD in the work-up resulted in the highest discriminative ability with a c-index of 0.89 for Ana o 3 plus gender and a c-index of 0.91, when SPT is also considered (Table 2). As a result of the liberal *P*-value, 95% confidence limits for ORs can include the value 1. Internal validity was satisfactory with shrinkage factors of 0.82 0.88, 0.89, 0.89 and 0.94 for the five models.

An easy to use format of the prediction model is based on gender, sIgE to Ana o 3 and the SPT (Figure 1) and facilitates calculation of the predictive risk of a positive challenge test in cashew nut sensitized children. Based on this score chart, 71 of the 173 (41%) children in our study had a score of ≥8 corresponding to ≥97% chance of a positive challenge test outcome. In 70 of these 71 (99%) children, the cashew nut allergy was established with the DBPCFC test. There was nothing of note in this patient with an unexpected negative challenge outcome.

Of the 102 children with a probability score of <8 corresponding to a <97% chance of a positive challenge test outcome, 67 children (66%) had a positive and 35 (34%) had a negative DBPCFC test outcome. Thus, the majority of the group have a score of <8 in the prediction model, which does not allow for a meaningful prediction of clinical allergy, and for these children, oral challenge will still be required for accurate diagnosis.

We developed and internally validated diagnostic model for cashew nut allergy in sensitized children. In situations where there is limited availability of double-blind testing, the use of the model and scoring system presented here may be useful for identifying children who have ≥97% chance of having a positive challenge test result and in whom such testing is thus less likely to influence management. In our present series, this pertains to a substantial number of patients (71, 41%).

The specificity of the scoring system may be negatively influenced by several factors, including cross-reacting allergens. Currently, there is no data on allergens cross-reacting with cashew nut, for example PR-10 allergens. More research in this area is needed.

Predictor	**Value**	**Score**
Gender(girl)		1
Ana o 3(kU/l)	0 - 0.1	0
	0.11 - 0.5	1
	0.51 - 1.5	2
	1.51 - 5	3
	5.01 - 19	4
	19.01 - 60	5
	60.01 - 100	6
SPT(meandiameter(mm))	0 - 2	0
	2.01 - 5.5	1
	5.51 - 9.5	2
	9.51 - 13	3
	13.01 – 17	4
	17.01 – 21	5
	21.01 – 23	6
	24+	7
Total sum score		…….

Total	0	1	2	3	4	5	6	7	8	9	10	11+
%*	3	6	12	26	50	67	84	92	97	98	99	100

* % chanceofapositiveDBPCFC

FIGURE 1 Score chart for the predictive risk of a positive DBPCFC with cashew nut including SPT for cashew nut sensitized children. The score chart facilitates calculation of the predictive risk of a positive challenge outcome and is developed for clinical practice. The score chart is based on the variables gender, sIgE to Ana o 3 and the SPT. The continuous scales of sIgE to Ana o 3 and SPT are divided into small steps. The scores are derived from the prediction model an updated intercept: Lp=−2.025+0.913*Girl+0.778*log(AnaO3+0.1)+0.237*SPT Hypothetical example: a sensitized girl (1 point) with a sIgE to Ana o 3 value of 21 kU/l (5 points) and a SPT of 8.5 (two points) scores eight points and has 97% risk on a positive challenge test

Gender was included in the model, with a higher risk of a positive challenge test for girls. Why sensitization to cashew nut is more often clinically relevant in girls than boys is currently unknown.

Not all medical settings have the opportunity to perform the SPT.[7] Therefore, we developed a model with and without the SPT. If sIgE results to Ana o components are not available, the SPT is second best in the diagnostic model for cashew nut allergy.

A prediction model for cashew nut allergy has never been developed previously, and the final model in this article has higher discriminability (C-index of 0.91) than the individual Ana o 1, 2 and 3 components in our previous report (c-index of 0.87, 0.85 and 0.89, respectively).[1] Our prediction model is very useful in clinical practice; however, the generalizability of this method needs to be established through external validation.

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Relation of infant dietary patterns to allergic outcomes in early childhood

To the Editor,

Allergic disorders result from the complex interplay between genetic predisposition and environmental influences. According to the Developmental Origins of Health and Disease hypothesis, environmental pressures at critical or early periods of development can evoke persisting changes in gene regulation and expression,[1] affecting disease development. Infant nutrition is a major environmental influence in early life as the immature gut is exposed to a variety of food proteins. However, results from studies examining the early introduction of allergenic food and allergic outcomes have been conflicting. In addition, the current literature, describing associations between different types of diet or nutrients and allergic outcomes, consists mainly of either cross-sectional studies or case-control studies that examine children during preschool or school-going ages.[2] Moreover, studies that have examined the contribution of infant nutrition to the development of paediatric allergic outcomes in a prospective birth