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Prediction of the severity of allergic reactions to foods

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Abstract

Background: There is currently considerable uncertainty regarding what the predictors of the severity of diagnostic or accidental food allergic reactions are, and to what extent the severity of such reactions can be predicted.

Objective: To identify predictors for the severity of diagnostic and accidental food allergic reactions and to quantify their impact.

Methods: The study population consisted of children with a double-blind, placebo-controlled food challenge (DBPCFC)–confirmed food allergy to milk, egg, peanut, cashew nut, and/or hazelnut. The data were analyzed using multiple linear regression analysis. Missing values were imputed using multiple imputation techniques. Two scoring systems were used to determine the severity of the reactions.

Results: A total of 734 children were included. Independent predictors for the severity of the DBPCFC reaction were age ($B = 0.04$, $P = .001$), skin prick test ratio ($B = 0.30$, $P < .001$), eliciting dose ($B = -0.09$, $P < .001$), level of specific immunoglobulin E ($B = 0.15$, $P < .001$), reaction time during the DBPCFC ($B = -0.01$, $P = .004$), and severity of accidental reaction ($B = 0.08$, $P = .015$). The total explained variance of this model was 23.5%, and the eliciting dose only contributed 4.4% to the model. Independent predictors for more severe accidental reactions with an explained variance of 7.3% were age ($B = 0.03$, $P = .014$), milk as causative food ($B = 0.77$, $P < .001$), cashew as causative food ($B = 0.54$, $P < .001$), history of atopic dermatitis ($B = -0.47$, $P = .006$), and severity of DBPCFC reaction ($B = 0.12$, $P = .003$).

Conclusions: The severity of DBPCFCs and accidental reactions to food remains largely unpredictable. Clinicians should not use the eliciting dose obtained from a graded food challenge for the purposes of making risk-related management decisions.

KEYWORDS
anaphylaxis, double-blind placebo-controlled food challenge, eliciting dose, food allergy, severity of reaction

1 | INTRODUCTION

Food allergic exposures vary from mild localized reactions to life-threatening anaphylaxis.[1] According to current estimates, approximately 3.1% of all children will experience a severe food allergic reaction.[2] Prediction of the severity of allergic reactions to food is a key issue for medical professionals, patients, policymakers, and the food industry to be able to accurately target treatment and improve management and prevention strategies. Thus, efforts have been made to examine possible predictors of severe and/or life-threatening reactions, and recently, a review has been published by Turner et al[3] on this topic. However, the previous studies used for this review have not quantified the contribution of the predictors to reaction severity and have not established them as statistically independent of one another in this regard. In addition, several studies show conflicting results,[4-15] and thus, much uncertainty still remains about the relationship between potential risk factors and the severity of reactions.

Dose has been considered to be an important factor in the development of severe reactions,[16] although the evidence for this is scant and contradictory. A prior study has suggested that severe reactions during oral food challenges (OFC) tend to occur more frequently with increasing dose levels.[15] Moreover, in a study where the food challenge procedure was allowed to continue after initial mild symptoms, many subjects progressed to anaphylaxis with increasing dose levels.[17] In contrast, Rolinck-Werninghaus et al[4] concluded that severe reactions may occur at any dose during oral food challenges. Additionally, patients with prior anaphylaxis to peanut do not seem to have a lower threshold dose than patients with milder reactions.[14,18,19]

It is currently unknown to what extent the severity of food allergic reactions may be predicted by a combined number of readily available clinical factors, such as age, gender, type of allergenic food, level of specific IgE (sIgE), eliciting dose (ED), previous reactions, and comorbid atopic disease. Furthermore, it remains uncertain whether more severe reactions tend to occur at higher doses and whether limiting exposure would thus preferentially impact severe reactions accordingly. This study aimed at identifying clinically available factors predictive of the severity of reactions in DBPCFCs as well as for the most severe accidental reaction by history. Particular attention was paid to the extent to which the eliciting dose explains the severity of reactions during DBPCFCs.

2 | METHODS

2.1 | Study population

Data of all positive DBPCFCs in children (2002-2017) were extracted from the Food Challenge Unit Database of our tertiary care pediatric allergy department at Beatrix Children's Hospital, University Medical Center Groningen (UMCG). The study population consisted of children referred to our center because of suspected food allergy. No children were excluded due to a history of previous anaphylactic reactions. The medical ethics committee of the UMCG deemed that

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Clinical Implications

Clinicians should not assess a patient's risk of experiencing severe reactions from the eliciting dose obtained from graded food challenges, as eliciting dose only contributes marginally to reaction severity.

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formal medical ethical approval was not required for this study, as all procedures were performed as part of routine clinical care.

Extraction of the data on study patients from the Food Challenge Unit Database was completed using the following inclusion criterion: a positive DBPCFC on the verum test day according to protocol.[20,21] Additionally, to allow for sufficient power for the food-specific analysis, only challenges conducted with the 5 most commonly challenged foods were extracted (cow's milk, hen's egg, peanut, hazelnut, and cashew nut). In children with multiple food challenges, only the first challenge for each food was included.

2.2 | Double-blind, placebo-controlled oral food challenges

The food challenges were double-blind and placebo-controlled with the suspected food and placebo administered on separate days. The food challenges were conducted according to previously published methods and protocols.[20-23] In brief, the suspected allergenic food or placebo was hidden in a food matrix capable of masking sensory detection.[20] The dose of the allergenic food was determined using an incremental scale, specific for the food tested. The doses were given at 30-minute intervals, and the dose steps used are displayed in Table 1. The food challenge was considered to be positive when objective or repeated or persistent subjective allergic symptoms occurred during the verum test day but not on the placebo day. If symptoms occurring on the verum day were significantly more severe than the symptoms on the placebo day, the food challenge was deemed positive. Unblinding of the test occurred 48 hours after the second food challenge day. Information

TABLE 1 Dose schemes used during the DBPCFCs

	UMCG 2002-2017 (milk, egg), mg protein	UMCG 2002-2006 (peanut, tree nuts), mg protein	PRACTALL 2007-2017, mg protein
Dose 1	1.75 mg	1.75 mg	1.0 mg
Dose 2	3.50 mg	3.50 mg	3.0 mg
Dose 3	14 mg	14 mg	10 mg
Dose 4	70 mg	70 mg	30 mg
Dose 5	350 mg	130 mg	100 mg
Dose 6	1750 mg	350 mg	300 mg
Dose 7	-	-	1000 mg
Total	2190 mg	570 mg	1444 mg

on the nature and frequency of previous food allergic reactions was obtained in addition to the general atopic history prior to the DBPCFC.

2.3 | Scoring system for the severity of reaction

A scoring system from Astier et al[24] ranging from 0 to 5 was used for determining the severity of reaction. The symptoms occurring during the verum day of the DBPCFC and of the most severe accidental reaction by history were used to score the severity. Patients were classified according to their most severe symptom and received the corresponding grade. Mild symptoms occurring at home after leaving the hospital after 2 hours of symptom-free observation after the DBPCFC on the verum day were placed in severity grade 0. Children never having consumed the allergic food and thus never having had an accidental reaction to the food were placed in the severity grade 0 for the accidental reaction. As there is currently no clear consensus on the use of scoring systems for the severity of allergic reactions, an additional scoring system [25] ranging from 0 to 12 was used to compare the severity of allergic reactions during the food challenge and the severity of the most severe accidental reaction by history.

2.4 | Measurement of food-specific IgE levels

Serum samples were collected as part of the routine clinical workup for food allergy and were drawn within 6 months of the DBPCFC. The ImmunoCAP system (Thermo Fisher Scientific Inc., Phadia AB, Uppsala, Sweden) was used for determining the level of sIgE. The test was considered positive when a sIgE level of 0.35 kU/L or more was confirmed. Values of >100 kU/L received a designated value of 101 kU/L.

2.5 | Skin prick tests

Skin prick tests (SPTs) were performed with a sterile lancet (ALK-Abelló, Horsholm, Denmark) and food allergen extracts (ALK-Abelló, Horsholm, Denmark). The size of the SPT response was calculated as a mean of the longest diameter and its perpendicular longest diameter measured at 15 minutes. To control for possible intertechnician variability, the ratio of the size of the tested food wheal to the size of the histamine wheal was reported. Any differences in wheal size caused by the device or technician should be similar and thus minimally affect the reported ratio.[26]

2.6 | Statistical analysis

The statistical analysis was performed using the statistics software package IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY). Multiple linear regression analysis was used to study the relationship between the determinants and the severity of reactions during the DBPCFC as well as those following accidental ingestion. The stepwise backward selection method was used for

constructing the prediction model. Alpha was set at 0.05. Only significant factors in the model were considered to be predictors. All assumptions of the tests were met. The determinants were preselected for inclusion in the analysis according to previously reported data as well as factors hypothesized to be of influence on the severity of the outcome by the authors. Dummy variables were created for the categorical variable "Type of food" with hazelnut as reference for the regression analysis. Cumulative dose (CD), ED, and the level of sIgE were logarithmically transformed before being entered into the analysis to comply with the assumptions required for conducting linear regression.

To reduce the probability of bias that might result from excluding missing cases and performing a complete case analysis, missing data were randomly imputed using multiple imputation. A missing-value analysis was performed to rule out missing not at random (MNAR) for the included variables. The missing cases for the included variables were in the range of 1%-20%. The missing data were replaced using a multiple imputation procedure with a conditional specification, predictive mean matching, 20 iterations, and 20 data sets. The use of 20 iterations in the multiple imputation was based on the variable with the highest number of missing cases. The patient characteristics, severity of reaction, and allergic features were included as predictors for the multiple imputation.

3 | RESULTS

3.1 | Descriptives of study population

The initial data extraction identified 864 positive DBPCFCs. In children with multiple food challenges to the same food, only the first challenge for each type of food was included (130 cases excluded). Thus, a total of 734 children with DBPCFC-confirmed food allergy were included in the final analysis. The median age of the children was 6.2 years, with a range of 0.3 to 18.2 years. The study population consisted largely of boys (59.4%). Of the participating children, 87.3% had a doctor's diagnosis of atopic dermatitis, 49.7% asthma, and 36.6% had previously been diagnosed with allergic rhinoconjunctivitis. The DBPCFCs were performed with peanut (38.7%), cow's milk (20.4%), cashew nut (17.3%), hen's egg (12.3%), and hazelnut (11.3%). The level of sIgE ranged from 0.01 to >100.00 kU/L and was positive in 91.7% of the children. The median reaction time during the DBPCFC was 15.0 minutes, with an IQR of 5.0-50.0.

The interquartile range (IQR) of severity of reaction in the DBPCFC ranged from 1.0 to 4.0 with a median severity index of 3.0 using the scoring system of Astier et al. Additional demographics categorized according to the severity of the DBPCFC reaction are shown in Table 2.

The IQR of the severity of the previous accidental reaction by history ranged from 1.0 to 4.0 and had a median severity index of 3.0. The time interval between accidental ingestion of allergen and allergic reaction by history ranged from 0 to 2880 minutes in all children, with an IQR of 1.0-15.0 and a median of 5.0 minutes.

TABLE 2 Characteristics of the study population according to the severity grade of the DBPCFC reaction

	Grade 0 (n = 78)	Grade 1 (n = 160)	Grade 2 (n = 55)	Grade 3 (n = 171)	Grade 4 (n = 270)
Age (y), median (IQR)	(5.78) 2.32-11.44	4.76 (2.00-7.63)	6.24 (4.34-9.52)	5.39 (3.16-8.33)	7.99 (5.29-12.12)
Gender, n (%)					
Female	32 (41.0)	69 (43.1)	22 (40.0)	65 (38.0)	110 (40.7)
Male	46 (59.0)	91 (56.9)	33 (60.0)	106 (62.0)	160 (59.3)
Food, n (%)					
Cashew nut	7 (9.0)	19 (11.9)	15 (27.3)	31 (18.1)	55 (20.4)
Cow's milk	35 (44.9)	45 (28.1)	7 (12.7)	31 (18.1)	32 (11.9)
Hazelnut	11 (14.1)	17 (10.6)	3 (5.5)	10 (5.8)	42 (15.6)
Hen's egg	3 (3.8)	26 (16.3)	8 (14.5)	36 (21.1)	17 (6.3)
Peanut	22 (28.2)	53 (33.1)	22 (40.0)	63 (36.8)	124 (45.9)
sIgE (kU/L), median (IQR)	2.71 (0.30-23.20)	2.99 (0.96-14.08)	8.40 (2.11-40.20)	11.75 (2.48-41.80)	12.10 (2.83-51.10)
SPT wheal ratio, median (IQR)	1.00 (0.00-1.55)	1.30 (0.90-1.88)	1.30 (0.90-2.00)	1.50 (1.10-2.00)	1.70 (1.30-2.20)
Estimation of SPT wheal size (mm), median (IQR)[a]	10.0 (0-15.5)	13.0 (9.0-18.8)	13.0 (9.0-20.0)	15.0 (11.0-20.0)	17 (13.0-22.0)
ED (mg protein), median (IQR)	1750.00 (350.00-1750.00)	98.00 (3.50-350.00)	139.20 (21.00-580.00)	70.00 (14.00-350-00)	58.00 (1.75-307.93)
CD (mg protein), median (IQR)	2189.25 (577.97-2189.25)	141.12 (5.25-577.97)	226.49 (30.80-837.52)	89.25 (19.18-559.58)	83.52 (1.75-433.68)
Reaction time during the DBPCFC (minutes), median (IQR)	55.00 (15.00-60.00)	25.00 (5.50-60.00)	12.50 (5.00-32.50)	20.0 (5.00-45.00)	15.0 (5.0-37.0)
History of asthma, n (%)					
Yes	34 (43.6)	70 (43.8)	28 (50.9)	78 (45.6)	155 (57.4)
No	41 (52.6)	89 (55.6)	24 (43.6)	91 (53.2)	110 (40.7)
History of atopic dermatitis, n (%)					
Yes	60 (76.9)	150 (93.8)	42 (76.4)	157 (91.8)	232 (85.9)
No	17 (21.8)	9 (5.6)	11 (20.0)	13 (7.6)	36 (13.3)
History of rhinoconjunctivitis, n (%)					
Yes	26 (33.3)	45 (28.1)	14 (25.5)	59 (34.5)	125 (46.3)
No	49 (62.8)	110 (68.8)	38 (69.1)	107 (62.6)	138 (51.1)
Severity of most severe accidental reaction, n (%)					
Grade 0	10 (12.8)	34 (21.3)	11 (20.0)	39 (22.8)	48 (17.8)
Grade 1	11 (14.1)	33 (20.6)	6 (10.9)	13 (7.6)	23 (8.50
Grade 2	18 (23.1)	30 (18.8)	10 (18.2)	22 (12.9)	40 (14.8)
Grade 3	13 (16.7)	32 (20.0)	12 (21.8)	40 (23.4)	58 (21.5)
Grade 4	26 (33.3)	31 (19.4)	16 (29.1)	57 (33.3)	101 (37.4)

CD, cumulative dose; DBPCFC, double-blind, placebo-controlled food challenge; ED, eliciting dose; IQR, interquartile range; sIgE, specific immunoglobulin E; SPT, skin prick test.

[a]The estimations of the SPT wheal size were calculated with a histamine wheal size of 10 mm.

Both the CD and the ED were initially included in the analysis. However, these factors showed colinearity during multivariate analysis; thus, the CD was excluded from the multivariate analysis on the basis of the lower explained variance of the model in comparison with the model including the ED (data not shown).

3.2 | Severity of reaction during DBPCFCs

Using the enter method, a significant model for prediction of the severity of reaction in the DBPCFC emerged ($R^2 = 0.235$, $P < .001$). Results from the analyses of the original data and from the pooled data following the multiple imputation procedure are shown in

Table 3. After analysis with multiple linear regression, significant independent predictors for the severity of reaction time during the DBPCFC were increasing age (B = 0.04, P = .001), larger SPT ratio (B = 0.30, P < .001), a lower ED (B = −0.09, P < .001), a higher level of sIgE (B = 0.15, P < .001), a shorter reaction time during the DBPCFC (B = −0.01, P = .004), and a more severe previous accidental reaction (B = 0.08, P = .015). No significant relationship with the severity of reaction in the DBPCFC was found for gender; type of food; history of atopic dermatitis, asthma, or allergic rhinoconjunctivitis; and family history of atopic disease. The total explained variance of this model was 23.5% of the severity of the DBPCFC reaction, and the ED only contributed 4.4% to this explained variance after inclusion in the model (adjusted $R^2_{excluding\ ED}$ = 0.182, adjusted $R^2_{including\ ED}$ = 0.226).

3.3 | Severity of accidental reactions

A significant model was also found for predicting the severity of reactions following accidental ingestion (R^2 = 0.073, P < .001). Results from the analysis of the original data and from the pooled multiple imputation are shown in Table 4. Significant independent predictors for more severe reactions were increasing age (B = 0.03, P = .014), milk as causative food (B = 0.77, P < .001), cashew as causative food (B = 0.54, P < .001), a negative history of atopic dermatitis (B = −0.47, P = .006), and a more severe DBPCFC reaction (B = 0.12, P = .003). Thus, children with a history of atopic dermatitis generally had less severe accidental reactions. Having uncontrolled asthma, defined as having daily symptoms; a clinical history of asthma; or allergic

rhinoconjunctivitis was not predictive of the severity of the accidental reaction. Moreover, age of onset of food allergy; time interval between ingestion and reaction; and a family history of atopic disease were not predictive of the severity of the accidental reaction (data not shown).

3.4 | Subgroup analysis for the severity of reaction per type of food

To examine possible differences between the types of food, the data were analyzed separately for each type of food (see Table 5 and Table 6). This analysis showed that there was a large difference in the ability to predict the severity of cow's milk DBPCFCs compared to peanut DBPCFCs. The severity of cow's milk DBPCFCs was independently predicted by a higher level of sIgE level, a larger SPT ratio, and a family history of atopic dermatitis with an explained variance of 27.0%. In contrast, the model for prediction of the severity of peanut DBPCFC reactions had an explained variance of only 10.9%, and it was independently predicted by a history of rhinoconjunctivitis, a shorter reaction time during the DBPCFC, a lower ED, and a higher level of sIgE. A positive family history of asthma (mother) was predictive of more severe DBPCFC reactions to peanut.

The severity of accidental reactions to cow's milk was predicted by an increasing age and higher ratio of the SPT. A positive history of rhinoconjunctivitis was predictive of the severity of accidental reactions to peanut, while increasing age was predictive of more severe reactions. For the accidental reaction, no predictive factors for the severity of reaction per type of food could be determined for cashew, hazelnut, and hen's egg.

TABLE 3 Independent predictors for the severity of the DBPCFC reaction (Astier)

	Original data (N = 544, R^2=0.235)			Imputed data—pooled (N = 734)		
Predictor	B	95% CI	P-value	B	95% CI	P-value
Age	0.06	0.04 to 0.09	<.001	0.04	0.02 to 0.06	.001
SPT	0.33	0.18 to 0.47	<.001	0.30	0.17 to 0.43	<.001
ED[a]	−0.07	−0.13 to −0.02	.007	−0.09	−0.14 to −0.04	<.001
sIgE[a]	0.17	0.09 to 0.27	<.001	0.15	0.07 to 0.24	<.001
Reaction time during the DBPCFC	−0.004	−0.01 to 0.00	.037	−0.005	−0.01 to −0.00	.004
Severity of accidental reaction	0.10	0.03 to 0.17	.005	0.08	0.02 to 0.06	.015

CI, confidence interval; DBPCFC, double-blind, placebo-controlled food challenge; sIgE, specific immunoglobulin E; R^2, explained variance.
[a]Back-transformed values.

TABLE 4 Predictors for the severity of the most severe, accidental reaction by history (Astier), displaying significant independent factors

	Original data (N = 727, R^2=0.073)			Imputed data—pooled (N = 734)		
Predictor	B	95% CI	P-value	B	95% CI	P-value
Age	0.03	0.01 to 0.06	.016	0.03	0.01 to 0.06	.014
Milk	0.77	0.47 to 1.06	<.001	0.77	0.48 to 1.06	<.001
Cashew	0.58	0.29 to 0.87	<.001	0.54	0.40 to 0.69	<.001
History of atopic dermatitis	−0.48	−0.81 to −0.15	.005	−0.47	−0.80 to −0.14	.006
Severity of DBPCFC reaction	0.12	0.04 to 0.19	.003	0.12	0.04 to 0.19	.003

CI, confidence interval; DBPCFC, double-blind, placebo-controlled food challenge; R^2, explained variance.

TABLE 5 Prediction of the severity of DBPCFC reaction (Astier) per type of food

Food	Predictor	Original data					Imputed analysis—pooled			
		R^2	N	B	95% CI	P-value	N	B	95% CI	P-value
Cashew	Age	0.149	125	0.07	0.01 to 0.12	.018	127	0.07	0.01 to 0.12	.016
	Severity of accidental reaction			0.17	0.03 to 0.32	.019		0.17	0.03 to 0.31	.017
	Family history of asthma (father)			−1.08	−1.71 to −0.45	.001		−1.06	−1.68 to −0.44	.001
Cow's milk	sIgE[a]	0.270	130	0.18	−0.03 to 0.44	.091	150	0.26	0.04 to 0.52	.017
	SPT			0.72	0.32 to 1.13	.001		0.66	0.25 to 1.07	.002
	Family history of atopic dermatitis (mother)			0.47	0.01 to 0.93	.045		0.46	0.03 to 0.89	.036
Hazelnut	ED[a]	0.195	77	−0.26	−0.45 to −0.09	.002	83	−0.30	−0.50 to −0.14	<.001
	Family history of atopic dermatitis (father)			−0.98	−1.75 to −0.22	.012		−0.98	−1.74 to −0.23	.010
	Family history of asthma (father)			1.03	0.04 to 2.02	.041		1.15	0.13 to 2.16	.027
Hen's egg	SPT	0.128	77	0.46	0.06 to 0.87	.025	90	0.44	0.07 to 0.81	.020
	Family history of food allergy (mother)			−0.95	−1.86 to −0.05	.040		−0.91	−1.72 to −0.10	.028
Peanut	History of rhinoconjunctivitis	0.109	234	0.33	0.01 to 0.65	.045	284	0.31	0.003 to 0.62	.048
	Reaction time during the DBPCFC			−0.004	−0.01 to 0.001	.124		−0.01	−0.01 to 0.00	.035
	ED[a]			−0.10	−0.20 to −0.02	.021		−0.18	−0.28 to −0.09	<.001
	sIgE[a]			0.19	0.06 to 0.33	.004		0.12	0.001 to 0.26	.048
	Family history of asthma (mother)			−0.43	−0.85 to −0.01	.045		−0.41	−0.81 to −0.02	.042

CI, confidence interval; DBPCFC, double-blind, placebo-controlled food challenge; ED, eliciting dose; sIgE, specific immunoglobulin E; R^2, explained variance; SPT, skin prick test.
[a]Back-transformed values.

TABLE 6 Prediction of the severity of accidental reactions (Astier) per type of food

Food	Predictor	Original data					Imputed analysis—pooled			
		R^2	N	B	95% CI	P-value	N	B	95% CI	P-value
Cashew	None	-	127	-	-	-	-	-	-	-
Cow's milk	Age	0.063	137	0.04	−0.01 to 0.10	.120	150	0.06	0.01 to 0.11	.033
	SPT			0.33	0.07 to 0.60	.014	150	0.30	0.03 to 0.57	.032
Hazelnut	None	-	83	-	-	-	-	-	-	-
Hen's egg	None	-	90	-	-	-	-	-	-	-
Peanut	History of rhinoconjunctivitis	0.050	278	−0.42	−0.82 to −0.02	.041	284	−0.43	−0.84 to −0.03	.034
	Age (y)			0.09	0.04 to 0.14	<.001		0.08	0.04 to 0.13	<.001

CI, confidence interval; R^2, explained variance; SPT, skin prick test.

3.5 | Sensitivity analysis scoring systems

The analysis was repeated using the scoring system from van der Zee et al to compare the results with the scoring system from Astier et al. Independent predictors for the severity of the DBPCFC reaction were a higher SPT ratio (B = 0.31, P < .006), a higher ED (B = 0.09, P = .026), a higher level of sIgE (B = 0.31, P < .001), a more severe accidental reaction (B = 0.07, P = .003), a history of rhinoconjunctivitis (B = 0.35, P = .034), and cashew as causative food (B = 0.71, P = .002). The total explained variance of this model was 10.5%, and the ED only contributed 2.0% to the model.

Independent predictors for the severity of accidental reactions with an explained variance of 5.7% were increasing age (B = 0.06,

P = .041), milk as causative food (B = 1.37, P < .001), cashew as causative food (B = 1.41, P < .001), a lower reaction time for the accidental reaction (B = −0.002, P = .005), and a higher level of sIgE (B = 0.32, P = .004). The complete case analysis and the pooled multiple imputation analysis for the sensitivity analysis are displayed in Table E1 and Table E2 (Supplemental Material).

4 | DISCUSSION

Prediction of the severity of reactions is important to be able to accurately target the management of food allergic reactions, for example, with the prescription of epinephrine auto-injectors. However, with the

risk factors identified in our study, we were only able to predict 23.5% of the severity of reactions during DBPCFC and 7.3% of the severity of the most severe accidental reaction by history. Moreover, the results of this study show that the ED only contributes 4.4% to the variance of the severity of DBPCFC reactions, and are in agreement with most of the previously published work on predictive factors for severe reactions. Here, we add to those previous results and show to what degree eliciting dose and other factors independently contribute to the severity of DBPCFC reactions.

The result of this study also substantiates the statement by Turner et al[3] that dose sensitivity and severity of reaction should be considered as different entities in the risk assessment of food allergic reactions. Therefore, our findings indicate that clinicians should not make decisions regarding prescription of epinephrine auto-injectors or give advice about the level of stringency of allergen avoidance based on the eliciting dose obtained from graded food challenges, as eliciting dose only contributes marginally to reaction severity. The ED as obtained from the DBPCFC was not predictive of the severity of the accidental reaction. Two studies have provided evidence suggesting that ED is a determinant of the frequency of accidental reactions.[19,27] Thus, even though the number of accidental reactions may be reduced by reducing the dose in accidental exposures by means of public health measures, this is not likely to result in proportionally fewer severe reactions. The total number of accidental reactions may decrease, but the proportion of mild, moderate, and severe reactions will remain largely unchanged. From a public health perspective, limiting dose exposure is one of the few measures possible in efforts to control severe allergic reactions. However, our results suggest that the impact of dose limitation as a public health measure is unlikely to reduce severe reactions significantly more than milder ones.

The assessment of the severity of the food allergic reaction is a matter of debate. We show that our results are quite consistent when 2 different scoring systems are used. The difference in these 2 scoring systems is to be found in the severe end of the range, which is reached more quickly as symptoms increase with the Astier scoring system than with that of van der Zee. Factors related to severity which have a distribution similar to the severity scores generated by one or the other of these scoring systems will give differences in their ability to predict the outcome. This may even give conflicting results within the same data set, as was the case in our study, where a lower ED was seen to predict greater severity using the scoring system of Astier, but a lower severity using that of van der Zee. This underlines the need for analyses using different scoring systems to identify factors which are sensitive to the scoring system used. Conversely, such an approach may also identify factors which are not sensitive to such differences, hence reflecting the robustness of such factors. Our current data showed that higher SPT ratio, a higher level of sIgE, and a more severe accidental reaction were in the latter category and thus were independent predictors of the severity of challenge reactions for both scoring systems. For the severity of the accidental reaction, independent predictors for both scoring systems were increasing age and reactions to milk and cashew.

The severity of cow's milk DBPCFC reactions could be predicted by the level of sIgE, SPT ratio, and a family history of atopic dermatitis with an explained variance of 27.0%. This is higher than for the whole combined group (23.5%) and for the peanut DBPCFC reactions (5.3%). This result suggests that different factors might be more relevant for predicting the severity of reaction for each type of food, including factors which are currently unknown.

Age has previously been examined as a predictor for the severity of reactions. Adolescents and young adults have a higher risk of severe OFC and accidental reactions than younger children.[28,29] The results of the current study also confirm increasing age as a predictor for the severity of DBPCFC reactions and for accidental reactions in a pediatric population.

Our data show no significant difference in the severity of DBPCFC reactions by type of food. This could be because the severity of DBPCFC reactions are deliberately kept at a minimum, and thus could show less difference in severity by type of food. Moreover, there are currently very limited data on individual allergen protein concentrations as compared to whole food protein thresholds. It is possible that differences in severity between different types of foods could become more apparent if data on individual allergen protein concentrations eliciting clinical reactions in sensitized patients were used in the comparison.

However, our data also show that for our population, accidental reactions to cashew and milk are generally more severe than reactions to hazelnut independent of age, sIgE level, and severity of the DBPCFC reaction. These results are partly in agreement with Johnson et al,[30] who have previously reported cashew and peanut anaphylaxis to be more severe than anaphylaxis to hazelnut in a pediatric population. However, in our population accidental reactions to peanut were not more severe than those to hazelnut. A possible explanation for this could be that many of the previously published studies have not corrected for other factors, such as age, possibly confounding the relationship between type of food and severity of reaction.

The inverse relationship between the length of the time interval between ingestion of the allergen and the onset of the reaction and the severity of reaction is a phenomenon often thought to be important in clinical practice. In other words, severe reactions tend to occur quickly. Our data thus confirm, for the first time, that more severe DBPCFC reactions tend to be rapid in onset.

The role of the level of sIgE in the severity of reactions is not clear. Various studies have shown that the level of sensitization (sIgE and SPT) and previous severe accidental reactions are predictive of more severe food challenge reactions.[4,6,7,11,17,29,31,32] However, other studies present conflicting results.[8,10] Our results show that the contribution of the level of sIgE and SPT to the severity of reactions is present, but small, and therefore, based on our results, as well as previous studies, we conclude that SPT and the level of sIgE are not particularly useful on their own in clinical practice for predicting more severe reactions in individual patients. Therefore, the use of absolute values with cutoffs would be very unlikely to reveal any useful cutoff values for clinical practice.

Our data show that previous more severe accidental reactions are weakly predictive of the severity of oral food challenge reactions and vice versa. Even though this effect is small, and not particularly useful in clinical practice, this suggests that individual patients may have a certain, to date unidentified, intrinsic severity component.

Asthma has been proposed to be a risk factor for severe reactions.[9] However, our results show that asthma is not a significant predictor for the severity of reaction during DBPCFC after correcting for age. Additionally, no relationship between asthma and the severity of accidental reactions was found. This could be because asthma is generally well controlled during the food challenges in our center and therefore contributes very little to the severity of reactions. Furthermore, as has been pointed out by others,[3] although asthma is common in patients with fatal or near-fatal reactions, the vast majority of food-allergic patients with asthma will never experience such reactions. Thus, asthma does not seem to independently be a strong predictor for the severity of reactions.

Our data show that more severe reactions during DBPCFCs tend to occur more frequently at lower dose levels using the scoring system of Astier et al. However, this effect was weak and severe reactions were not limited to low doses. The analysis per type of food showed that ED is a predictor for the severity of reaction for peanut and hazelnut, but not for milk, cashew, or egg. For the latter 3 foods, the contribution of ED to the severity of reaction could be much smaller than for peanut and hazelnut, and therefore, it is possible that this potential effect was not shown. This is an argument for further studies with larger groups.

The weak association between the eliciting dose and the severity of the DBPCFC reaction has been proposed to be at least partly due to interpatient variability of the accumulation of doses during the DBPCFC,[33] which could confound the relationship between the eliciting dose and the severity of reactions during oral food challenges on the population level. Blumchen et al[19] have previously shown that most of the study population reacted at a time interval greater than the standard dose interval of 30 minutes in a modified oral food challenge procedure. In this modified oral food challenge, doses were given with a 2-hour interval. This suggests that some patients do indeed accumulate doses during oral food challenges. However, no relationship between the severity of clinical reactions during the OFC and the ED could be shown by Blumchen et al. This is surprising, as the relationship between the ED and the severity of symptoms would be expected to be stronger during the modified OFC, due to the longer dose interval, compared to a standard food challenge procedure. The Blumchen study therefore suggests that the limited effect of the ED on the severity of the DBPCFC reaction in the current study is probably not due to accumulation of doses in some patients.

There are several strengths of this study: Firstly, the diagnosis of food allergy was confirmed by DBPCFCs, and children with a history of previous anaphylaxis were included in the analysis. More importantly, this study gives statistically underpinned evidence for the identified factors, independently of the other determinants. Some of the factors have, for the first time, been shown to be independent predictors for the severity of reactions, and the quantification of these factors is important to be able to allow for an accurate assessment of the risk of developing such reactions. Nonetheless, there are some limitations that should be considered in interpretation of the results of this study. Firstly, the generalizability of the conclusions needs to be externally validated in other studies using this prediction model in other settings. The inclusion of low-dose nut DBPCFCs performed before 2007 did not impact the relationship between the ED and the severity of the DBPCFC reaction (including DBPCFC before 2007 (n = 734, B = −0.14, P < .001, CI: -0.19 to -0.10), excluding DBPCFC before 2007 (n = 558, B = −0.15, P < .001, CI: -0.20 to -0.10)).Therefore, we believe that these data are representative of the wider nut-allergic population. However, this needs to be validated in further studies. Because of the protocol used, graded food challenges may influence the ED and severity of reaction, and these parameters may therefore differ from those relevant to single exposures, such as occurs in accidental reactions. Moreover, severe reactions can be halted by prompt treatment and may therefore be more difficult to predict because treatment modifies the outcome independently of severity. It is reasonable to conclude that this occurs during the food challenge setting, where patients are observed at all times and treated relatively quickly.

In conclusion, the severity of reactions during DBPCFCs and accidental reactions to foods is determined by numerous factors, most of which currently seem to be unknown. Thus, the severity of food allergic reactions remains largely unpredictable. The use of different severity scoring systems may give different or even contradictory results depending on the distribution of the data in a particular population. Sensitivity analysis may reveal the robustness of the conclusions based on the data in this regard. Interestingly, the severity of milk DBPCFC reactions may be predicted to a greater extent than the severity of peanut DBPCFC reactions. The ED did not predict the severity of the accidental reaction. This suggests that dose limitation as a public health measure is unlikely to reduce severe reactions more than milder ones. Finally, clinicians should not use the eliciting dose obtained from a graded food challenge for the purposes of making risk-related management decisions such as the need for stringent avoidance of allergenic foods or the prescription of self-injectable epinephrine. Studies using methodology more comparable to real-life situations than the DBPCFC are required to further examine the influence of dose on the severity of reactions. Single-dose challenges could be used for examining this relationship in future research.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors fulfill the ICMJE authorship criteria.

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