

MS. SARAH LYONS (Orcid ID : 0000-0001-7128-2699)

PROF. MAREK LESZEK KOWALSKI (Orcid ID : 0000-0002-8442-2774)

DR. PARASKEVI XEPAPADAKI (Orcid ID : 0000-0001-9204-1923)

Article type : Original Article: Food Allergy and Gastrointestinal Disease

Predicting food allergy: the value of patient history reinforced

Sarah A. Lyons¹, MD, André C. Knulst¹, MD PhD, Peter G.J. Burney², MD PhD, Montserrat Fernandez-Rivas³, MD PhD, Barbara K. Ballmer-Weber^{4,5,6}, MD PhD, Laura Barreales⁷, MD, Christian Bieli⁸, MD PhD, Michael Clausen⁹, MD, Ruta Dubakiene¹⁰, MD PhD, Cristina Fernandez-Perez⁷, MD PhD, Monika Jedrzejczak-Czechowicz¹¹, MD PhD, Marek L. Kowalski¹¹, MD PhD, Ischa Kummeling², Tanya Kralimarkova¹², MD PhD, Tihomir B. Mustakov¹², MD, Harmieke van Os-Medendorp^{1,13}, PhD, Nikolaos G. Papadopoulos^{14,15}, MD, Todor A. Popov¹⁶, MD PhD, James Potts², BSc, Serge A. Versteeg¹⁷, BSc, Paraskevi Xepapadaki¹⁴, MD, Paco M.J. Welsing¹⁸, PhD, E. N. Clare Mills¹⁹, PhD, Ronald van Ree^{17,20}, PhD, Thuy-My Le¹, MD PhD

¹ Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, The Netherlands

² National Heart and Lung Institute, Imperial College London, London, United Kingdom

³ Allergy Department, Hospital Clinico San Carlos, IdISSC, ARADyAL, RD16/0006/0009, Madrid,

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.14583](https://doi.org/10.1111/ALL.14583)

This article is protected by copyright. All rights reserved

Spain

⁴ Allergy Unit, Department of Dermatology, University Hospital of Zürich, Zürich, Switzerland

⁵ Faculty of Medicine, University of Zürich, Zürich, Switzerland

⁶ Clinic for Dermatology and Allergology, Kantonsspital St. Gallen, St. Gallen, Switzerland

⁷ Clinical Epidemiology Unit, Preventive Medicine Department, Hospital Clinico San Carlos, IdISSC, Madrid, Spain

⁸ Department of Paediatric Pulmonology, University Children's Hospital, Zürich, Switzerland

⁹ Children's Hospital, Landspítali University Hospital, Reykjavik, Iceland

¹⁰ Medical Faculty, Vilnius University, Vilnius, Lithuania

¹¹ Department of Immunology, Rheumatology and Allergy, Faculty of Medicine, Medical University of Lodz, Lodz, Poland

¹² Clinical Centre of Allergology of the Alexandrovska Hospital, Medical University of Sofia, Sofia, Bulgaria

¹³ Saxion University of Applied Sciences, Deventer, the Netherlands

¹⁴ Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece

¹⁵ Division of infection, Immunity and Respiratory Medicine, University of Manchester, Manchester, United Kingdom

¹⁶ University Hospital Sv. Ivan Rilski, Sofia, Bulgaria

¹⁷ Department of Experimental Immunology, Amsterdam University Medical Center, Amsterdam, The Netherlands

¹⁸ Division of Internal Medicine and Dermatology, University Medical Center Utrecht, Utrecht University, The Netherlands

¹⁹ Division of Infection, Immunity and Respiratory Medicine, Manchester Institute of Biotechnology & Lydia Becker Institute of Immunology and Inflammation, University of Manchester, Manchester, United Kingdom

²⁰ Department of Otorhinolaryngology, Amsterdam University Medical Center, Amsterdam, The Netherlands

Correspondence to:

Sarah A. Lyons

Department of Dermatology and Allergology, University Medical Centre Utrecht
Heidelberglaan 100, 3584 CX, UTRECHT, The Netherlands
Phone: +31 88 757 4749; Fax: Not available
Email: s.a.lyons-2@umcutrecht.nl

Acknowledgements: We would like to thank all the patients for their participation in the study. We acknowledge the support of the EuroPrevall project by the EU (grant FP6-FOOD-CT-2005-514000).

Conflicts of interest: Outside of submitted work: Dr. Papadopoulos reports personal fees from Novartis, Nutricia, HAL Allergy, Menarine/Faes Farma, Sanofi, Mylan/Meda, Biomay, AstraZeneca, GSK, MSD, ASIT Biotech, Boehringer Ingelheim; and grants from Gerolymatos International SA, and Capricare. Dr. Fernández-Rivas reports grants from Aimmune and Diater, and personal fees from Aimmune, Diater, ALK, DBV, Allergy Therapeutics, GSK, HAL Allergy, ThermoFisher Scientific and SPRIM. Dr. Ballmer-Weber reports personal fees from ThermoFisher Scientific. Dr. Xepapadaki reports personal fees from Uriach, Novartis, Nestle, and Nutricia. Dr. Mills reports grants from Reacta Biotech; and is shareholder of Reacta Biotech Ltd. Dr. Van Ree reports personal fees from HAL Allergy BV, Citeq BV, Angany Inc., and ThermoFisher Scientific. The other authors declare that they have no relevant conflicts of interest.

Word count: 2974

AUTHOR ABBREVIATIONS

Name	Abbreviation
Sarah A. Lyons	SAL
André C. Knulst	ACK
Peter G.J. Burney	PGJB
Montserrat Fernandez-Rivas	MFR
Barbara K. Ballmer-Weber	BBW
Laura Barreales	LB
Christian Bieli	CB
Michael Clausen	MC
Ruta Dubakiene	RD
Cristina Fernández Perez	CFP
Monika Jedrzejczak-Czechowicz	MJC
Marek L. Kowalski	MLK
Tanya Kralimarkova	TK
Ischa Kummeling	IK
Tihomir B. Mustakov	TBM
Harmieke van Os-Medendorp	HvOM
Nikolaos G. Papadopoulos	NGP
Todor A. Popov	TAP
James Potts	JP
Paco M.J. Welsing	PMJW
Paraskevi Xepapadaki	PX
Serge A. Versteeg	SAV
E.N. Clare Mills	ENCM
Ronald van Ree	RvR
Thuy-My Le	TML

		AUTHOR CONTRIBUTIONS
Name	Abbreviation	
PGJB, MFR, IK, JP, ENCM	Epidemiological design	
ACK, MFR, BBW, MC, MLK, RD, NGP, TAP	Study coordination	
ACK, MFR, BBW, LB, CB, MC, RD, CFP, MJC, MLK, TK, TBM, NGP, TAP, PX, TML	Recruitment and clinical investigation of the patients	
SAV	ImmunoCAP IgE testing	
PB, IK, JP	Database design	
IK, JP, SAL	Data cleaning	
SAL	Statistical data analyses and writing of the manuscript	
PMJW, TML, ACK, RvR	Supervision of the statistical data analyses and writing of the manuscript	
ACK, PGJB, MFR, BBW, LB, CB, MC, RD, CFP, MJC, MLK, TK, IK, TBM, HvOM, NGP, TAP, JP, PMJW, PX, SAV, ENCM, RvR, TML	Critical review of the manuscript	

ABSTRACT

Background: EAACI guidelines emphasise the importance of patient history in diagnosing food allergy (FA), and the need for studies investigating its value, using standardised allergy-focused questionnaires.

Objective: To determine the contribution of reaction characteristics, allergic comorbidities, and demographics, in predicting FA in individuals experiencing food-related adverse reactions.

Methods: Adult and school-age participants in the standardised EuroPrevall population surveys, with self-reported FA, were included. Penalised multivariable regression was used to assess the association of patient history determinants with 'probable' FA, defined as a food-specific case history supported by relevant IgE sensitisation.

Results: In adults (N=844), reproducibility of reaction (OR 1.35 [95% CI 1.29-1.41]), oral allergy symptoms (OAS) (4.46 [4.19-4.75]), allergic rhinitis (AR) comorbidity (2.82 [2.68-2.95]), asthma comorbidity (1.38 [1.30-1.46]), and male sex (1.50 [1.41-1.59]), were positively associated with probable FA. Gastrointestinal symptoms (0.88 [0.85-0.91]) made probable FA less likely. The AUC of a model combining all selected predictors was 0.85 after cross-validation. In children (N=670), OAS (2.26 [2.09-2.44]) and AR comorbidity (1.47 [CI 1.39-1.55]) contributed most to prediction of probable FA, with a combined cross-validation-based AUC of 0.73. When focusing on plant foods, the dominant source of FA in adults, the paediatric model also included gastrointestinal symptoms (inverse association), and the AUC increased to 0.81.

Conclusions: In both adults and school-age children from the general population, reporting of OAS, and AR comorbidity, appear to be the strongest predictors of probable FA. Patient history particularly allows for good discrimination between presence and absence of probable plant FA.

Word count abstract: 245 words

Key words: food allergy, food sensitisation, patient history, prediction, Europe

ABBREVIATIONS

AD	-	atopic dermatitis
AR	-	allergic rhinitis
CI	-	confidence interval
FA	-	food allergy
GI	-	gastrointestinal
OAS	-	oral allergy syndrome
OR	-	odds ratio

INTRODUCTION

Typical food allergies (FAs) are IgE-mediated. In some parts of Europe, the prevalence of self-reported FA to commonly incriminated foods is as high as 19% in adults and 25% in school-age children from the general population.^{1, 2} The majority of these self-reported adverse reactions to foods are however not attributed to IgE: the prevalence of probable FA, defined as a food-specific case history supported by relevant IgE sensitisation, is much lower than the prevalence of self-reported FA.¹⁻³

A key tool available to all physicians for assessing the likelihood of FA, is patient history. FA guidelines from the European Academy of Allergy and Clinical Immunology (EAACI) acknowledge the importance of patient history in the diagnosis of FA, but also highlight that studies evaluating the accuracy of predictions using standardised allergy-focused history questionnaires are lacking, as well as studies modelling the use of history to predict FA.⁴ Current evidence is based on expert opinion.^{4, 5} Therefore, the EAACI guidelines have assigned high priority to clinical studies investigating this knowledge gap.⁴

The data collected using well-standardised questionnaires in the EU-funded multicentre EuroPrevall project, designed to evaluate FA across Europe, provide a unique opportunity to investigate the value of information available from patient history for predicting FA. The objective of this study was to ascertain which reaction characteristics, allergic comorbidities, and demographic factors, contribute to prediction of probable FA in adults and school-age children reporting food-related symptoms.

METHODS

Study design, setting and subjects

As part of the EuroPrevall project, data were collected between 2005 and 2009 from 20- to 54-year-old and 7- to 10-year-old randomly sampled individuals from the general population of socio-economically and climatically different regions in Europe. The detailed methodology of this study is described elsewhere.^{2, 3, 6} The study population for the current study consisted of subjects with self-reported FA from Athens (Greece), Lodz (Poland), Madrid (Spain), Reykjavik (Iceland), Utrecht (the Netherlands), Vilnius (Lithuania), and Zurich (Switzerland). Subjects responded to a short screening questionnaire on adverse reactions to food, symptoms, and incriminated foods, in phase I of the EuroPrevall study. Subjects were further evaluated in phase II if they indicated that they had symptoms to one of 24 foods frequently consumed or commonly implicated in food allergic reactions across Europe (so-called *priority foods*: hen's egg, cow's milk, fish, shrimp, peanut, hazelnut, peach, apple, celery, walnut, soy, wheat, buckwheat, kiwi fruit, corn, carrot, tomato, melon, banana, lentils, sesame seed, mustard seed, sunflower seed, and poppy seed). Phase II consisted of an extensive questionnaire and blood sampling to test for presence of IgE against priority foods. All subjects with self-reported symptoms to one of the 24 priority foods, a completed phase II questionnaire, and IgE serology testing, were included in this study.^{2, 3}

The local ethical committees of all participating centres approved this study, and informed consent was obtained from all participants.

Data collection

The outcome, probable FA, was considered present in subjects with IgE sensitisation corresponding to a self-reported adverse reaction to at least one of the 24 priority foods. Commercially available ImmunoCAP tests (Phadia, *currently ThermoFisher Scientific*, Uppsala, Sweden) were used to measure serum sIgE levels, and a value ≥ 0.35 kU_A/l was considered positive. All serology testing was performed at a single laboratory in the Amsterdam University Medical Center (Location AMC, Amsterdam, The Netherlands).

Evaluated predictors were: reaction characteristics (time until onset, reproducibility of the reaction, oral allergy symptoms [OAS], skin symptoms, gastrointestinal symptoms, rhinoconjunctivitis, respiratory symptoms, and cardiovascular symptoms); allergic comorbidities (asthma, allergic rhinitis [AR], atopic dermatitis [AD]); demographic factors (age, sex, [parental] level of education); and (parental) smoking. The predictor information was obtained from both the phase I and phase II questionnaires, which were enriched versions of well-standardised allergy questionnaires,⁷ with a specific focus on reactions to the priority foods. The phase I questionnaire was self-administered, while the phase II questionnaire was conducted by trained interviewers.

Data analysis

Analyses were performed separately for adults and children. Differences between subjects with and without probable FA were described, and analysed using the chi-square test, two-sample T-test or Mann-Whitney U test, as appropriate for the variable's distribution. After obtaining crude odds ratios (ORs) for each of the evaluated predictors through univariable logistic regression, multivariable logistic regression was performed with all predictors to determine adjusted ORs. Because the probability of probable FA is known to differ per centre,^{2, 3} centre was included as a covariate in the analysis. The Lithuanian site Vilnius was only included in the paediatric population, as very few (N=4) Lithuanian adults with self-reported FA participated in phase II.³

In order to present a parsimonious model with the most discriminative combination of the evaluated predictors for probable FA, and to avoid overfitting, Least Absolute Shrinkage and Selection Operator (Lasso) regression was applied. Lasso regression is a form of penalised regression, in which only the most contributive variables are selected, and shrinkage of regression coefficients is applied through cross-validation, to arrive at a more generalisable model.⁸ The area under the curve (AUC) of the receiver-operating characteristic (ROC) was calculated to evaluate the diagnostic value of both the full and penalised model.

We know from previous research that probable FA to plant source foods dominates in adults,³ but that both plant and animal source probable FA play important roles in school-age children.² Because the presentation of FA may depend on the type of food eliciting the reaction, patient history determinants

of children with only plant source probable FA and of children with only animal source probable FA were compared univariably in an extra explorative analysis. The Lasso regression was then repeated in the source population of children with self-reported FA to plant source foods, and the outcome plant source probable FA was evaluated, as this concerned the largest group of children, and improved comparability to the adult population.

Analyses were conducted with SPSS version 25 and R version 3.4.1.

RESULTS

Adults

Of 862 adult subjects reporting symptoms to priority foods and completing phase II,³ the 844 with available serology were evaluated in this study. Positive IgE serology matching the food reported to cause symptoms was identified in 207/844 (25%) subjects, who were classified as having probable FA. Table 1 shows the population characteristics of these subjects. Most adults had probable FA to hazelnut, followed by apple, peach, kiwi, carrot and walnut (Table E1).

Complete data on the predictor variables, as required for multivariable analyses, was available for 807 subjects. There were no significant differences in demographics, allergic comorbidities, or reaction characteristics between the subjects with complete data (N=807) and the subjects with missing data on food serology or predictor variables (N=55), except that subjects from certain centres were more likely to have complete data (Table E2).

Univariable analysis revealed that shorter time until onset of the reaction, reproducibility of the reaction, and reporting of OAS, rhinoconjunctivitis or respiratory symptoms in response to the culprit food, were statistically significantly ($p<0.05$) associated with probable FA, as were allergic comorbidities AR and asthma, and demographic factors younger age and male sex (table 1 and 2). Reporting of gastrointestinal (GI) symptoms and potential cardiovascular symptoms (i.e. fainting or dizziness) were associated with not having probable FA.

In multivariable analyses, the combination of all predictor variables resulted in an AUC of 0.86 (95%-CI 0.83-0.89), implying good discriminative ability. Seven patient history predictors (reaction time, reproducibility of the reaction, OAS, GI symptoms, asthma, AR, and sex) were found to independently and statistically significantly contribute to differentiation between presence or absence of probable FA (table 2). The strongest of these predictors were reporting of OAS and AR comorbidity, with respective OR's of 5.62 (95%-CI 3.61-8.93) and 4.44 (95%-CI 2.52-8.26).

The results from Lasso regression are presented in figure 1. The same seven patient history variables were selected to optimally predict probable FA (figure 1), though the ORs were less extreme and the

AUC of this parsimonious model (based on cross validation) was lower (0.85 (95%-CI 0.82-0.87)), as expected.

Children

As regards the population of school-age children, 702 subjects with self-reported FA completed phase II,² and 670 underwent food serology testing. A total of 136/670 (20%) children were found to have probable FA (table 1). Children were mostly allergic to cow's milk, hen's egg, hazelnut, peanut, apple, kiwi, peach and walnut (Table E1).

Multivariable analyses could be performed in 593 children with complete data on predictor variables. As seen in table E2, the population characteristics of the children with complete data (N=593) were not significantly different to those of children with missing data on food serology or predictor variables (N=109).

Similarly to adults in univariable analyses, reporting of shorter time until onset of the reaction, OAS, rhinoconjunctivitis or respiratory symptoms, or having comorbid AR or asthma, was significantly associated with probable FA, and subjects reporting GI symptoms were less likely to have probable FA (table 1 and 2). In contrast to adults, reporting skin symptoms and having comorbid atopic dermatitis, were positively and significantly associated with probable FA in children, and reproducibility of the reaction, although not statistically significant, was inversely associated with probable FA. None of the demographic factors age, sex, or level of education predicted probable FA in children.

All patient history variables combined in multivariable analysis, yielded a full model with an AUC of 0.76 (0.71-0.82). Two variables, which were also the strongest predictors in adults, were statistically significant for prediction of probable FA in children: OAS (OR 2.94 [95%-CI 1.75-4.97]) and AR comorbidity (OR 3.39 [95%-CI 1.98-5.91]) (table 2). These two variables were also selected in the Lasso regression (figure 1), which again resulted in less extreme ORs, and a lower cross-validation based AUC of 0.73 (95% CI 0.68-0.78).

Plant *versus* animal source causative foods in children

Whereas the vast majority of adults with probable FA were allergic to plant source foods (188/207, 91%), probable FA in children was frequently caused by animal source foods (62/136, 46%) as well as by plant source foods (92/136, 68%) (Table E1).

Table 3 shows that children with probable FA to only plant source foods (N=74) reported OAS and AR comorbidity more often than children with probable FA to only animal source foods (N=44). Furthermore, 58% of children with probable FA to animal source foods reported GI-symptoms, compared to only 13% of children with probable FA to plant source foods.

When probable FA to plant source foods rather than all priority foods was taken as the outcome of interest, in a source population of children with self-reported FA to plant source foods, Lasso regression selected OAS (OR 1.69, 95% CI 1.57-1.82), rhinoconjunctivitis symptoms (OR 1.08, 95% CI 1.04-1.13), GI-symptoms (OR 0.63, 95% CI 0.59-0.66), and AR comorbidity (OR 3.10, 95% CI 2.86-3.37), as contributive predictors. The cross-validation based AUC of this LASSO model focused on plant source probable FA, 0.81 (95% CI 0.75-0.89), was more comparable to adults, than the AUC of the LASSO model for predicting probable FA due to any priority food.

DISCUSSION

Experts describe patient history as the most important single test for diagnosing FA.⁹ To our knowledge, the current study is the first to quantify the value of specific reported reaction characteristics (reaction time, reproducibility of reaction, symptoms) alongside allergic comorbidities and demographic factors, for predicting IgE sensitisation corresponding to the culprit food, making FA probable. We also found that combining seven independent predictors (reaction time, reproducibility of reaction, OAS, GI symptoms, AR comorbidity, asthma comorbidity, and sex) in a prediction model, allowed for good discrimination between presence and absence of probable FA in adults, with an AUC after cross-validation of 0.85. For school-age children, OAS and AR comorbidity was found to be the most discriminative combination of predictors for probable FA, with a comparatively lower AUC of 0.73, but which tended to improve when focusing solely on plant source causative foods, the main source of FA in adults.

Based on expert opinion, current guidelines state that timing, reproducibility, symptoms and co-existing allergic diseases should be addressed in patient history for FA.^{4, 5, 10} Our findings lend scientific evidence in support of these recommendations. A shorter time until onset of a reaction, reporting of OAS, rhinoconjunctivitis or respiratory symptoms upon ingestion of the culprit food, and AR or asthma comorbidity, were positively associated with probable FA in both adults and children. However, predictors of probable FA in children contrasted with those in adults in that time until onset and reproducibility of the reaction were not independently associated with probable FA in the paediatric multivariable analyses, and that skin symptoms tended to be more strongly associated with probable FA in children than in adults. An explanation for this could be that parents may not pick up on their child's reaction until later, when objective symptoms (i.e. skin symptoms) appear. Parents are also likely to ensure strict avoidance of a food after a child experiences a single adverse reaction, whereas adults may retry a food in case of mild symptoms, leading to reproducible reactions in adults and not in children. Another important difference between adults and children that affects which patient history determinants are associated with probable FA, is that adults are mainly allergic to plant source foods, whereas children are also likely to be allergic to animal source foods. Probable FAs to plant source foods rarely present with GI symptoms, whereas GI symptoms are often reported in

relation to probable FA to animal source foods (table 3). This observation explains why GI symptoms were inversely associated with probable FA in adults, but this association was only found in children when the analyses focused on plant source probable FA.

The strongest predictor of probable FA in both the adult and paediatric population, was reporting of OAS. Clinical experience teaches that this clearly identifiable symptom is generally the first symptom that subjects with an IgE-mediated FA experience,^{11, 12} though it is particularly associated with pollen-related FA. Pollen-related FA is a very common cause of FA in European adults and adolescents, and generally presents with mild OAS in reaction to raw fruits, vegetables and nuts that cross-react with pollen allergens to which the symptomatic individual is sensitised (most often PR10 proteins found in birch, or profilin found in all pollen).^{13, 14} The majority of subjects in our study were from birch endemic regions in Central and Northern Europe. In order to evaluate the relative importance of OAS independently of, and the modification of its predictive effect by, birch pollen sensitisation, we performed an additional analysis. We added IgE-sensitisation to major birch pollen allergen Bet v 1,¹³ and an interaction between OAS and IgE-sensitisation to Bet v 1, to the full multivariable model. As expected, there was a statistically significant interaction between reporting of OAS and Bet v 1 sensitisation in adults ($p = 0.02$). OAS was particularly predictive of FA in those with Bet v 1 sensitisation (OR 11.8 [95% CI 3.9-37.6]), and a less strong predictor in those without Bet v 1 sensitisation (OR 2.6 [95% CI 1.4-4.9]). Nonetheless, OAS remained a statistically significant independent predictor of probable FA in adults. As birch-pollen related FA is not yet as common in 7- to 10-year-old children as in adults, it was not surprising that a similar interaction was not observed in children.

Although it goes beyond the scope of this paper to delve into geographical variation in the likelihood of probable FA, as this topic was extensively discussed in previous publications,^{2, 3} it is worth noting that the effect of centre on probable FA in adults in multivariable analysis was strongest in countries known for high level of birch pollen sensitisation (Switzerland, Poland and The Netherlands). The effect of centre was no longer statistically significant after adjustment for Bet v 1 sensitisation in the full model. In Lasso regression analysis, only Switzerland, the EuroPrevall country with the most birch pollen sensitisation,³ was selected as predictive of probable FA in adults. In the paediatric

multivariable models, centre was not a statistically significant predictor in the full model with all covariates included, nor was it selected during Lasso regression. Apparently, most of the variation between centres in the paediatric population is explained by the other covariates included in the model (table 2).

Previous studies taking the predictive value of patient history into account, tend to focus only on severity of reported symptoms. In a paediatric outpatient population selected for food challenge in Ireland and the UK, DunnGalvin *et al.* found that increasing severity of reported symptoms increased the likelihood of challenge-confirmed peanut, milk and egg allergy.¹⁵ In a Dutch adult outpatient population, Klemans *et al.* observed no statistically significant association between reported symptom severity and challenge-confirmed peanut allergy.¹⁶ For comparative purposes, we graded reported symptoms according to the severity classification used by DunnGalvin *et al.*, in an additional analysis (Table E3).¹⁵ Similarly to DunnGalvin *et al.*, the likelihood of probable FA tended to increase with increasing symptom severity in children in our study, though the trend was less clear in adults. Interestingly, our model with specific symptoms included independently (table 2) rather than grouped in severity classifications (table E3), was significantly better at discriminating between presence and absence of probable FA, specifically in adults (AUC = 0.86 [95% CI 0.83-0.89] *vs.* 0.81 [0.78-0.84], *p* *De Long's test* <0.001 in adults; and AUC 0.76 [0.71-0.82] *vs.* 0.73 [0.68-0.79], *p* *De Long's test* = 0.43 in children).

The high predictive ability of our multivariable models for probable FA in adults, which combine reaction time, reproducibility of reaction, OAS, GI symptoms, AR comorbidity, asthma comorbidity, and sex, may be useful in clinical practice. Our parsimonious model corrected for overfitting (Figure 1) aimed to be more generalisable to the general population of patients with food-related complaints (Table 2). Details for the prediction formula and accuracy measures corresponding to specific cut-offs of the formula's outcome score are available in table E4 and table E5. Of particular interest is the high negative predictive value of the prediction formula. If all adults with a prediction score smaller than 0.17 (= 46% of the population) were to be classified as not having probable FA, 95% of these adults would indeed not have a probable FA. This might be of interest to GPs for identifying adults in whom

to conduct further IgE sensitisation testing, although formal validation of this formula should probably be performed before it can be used as such.

Although there were no food challenge outcomes available to assess the diagnostic value of patient history by comparing it to the reference standard for diagnosis of FA, our findings from prediction analyses yield essential evidence on the value of patient history in support of clinical practice. Our findings for probable FA are in line with expectations from expert opinion, according to which timing, reproducibility, symptoms and co-existing allergic diseases should be addressed in patient history for FA.^{4, 5, 10} The individual weights provided for these patient history determinants of probable FA in the current study, may in the future inform physicians' decision-making in daily practice, i.e. to help avoid unnecessary IgE-testing in adults reporting adverse reaction to (mainly plant source) foods. All in all, our findings reinforce the value of patient history in the diagnostic work-up of FA.

		Adults			Children		
		Probable FA	No probable FA	p-value*	Probable FA	No probable FA	p-value*
		<i>N</i> = 207	<i>N</i> = 637		<i>N</i> = 136	<i>N</i> = 534	
Age, mean (SD)		35.9 (9.0)	37.8 (9.5)	0.012	9.02 (0.99)	8.88 (0.95)	0.138
Sex, <i>N</i>(%)	Male	93 (44.9)	198 (31.1)	<0.001	68 (50.0)	254 (47.6)	0.612
	Female	114 (55.1)	439 (68.9)		68 (50.0)	280 (52.4)	
Level of education^a, <i>N</i>(%)	Low	69 (33.3)	208 (32.7)	0.856	82 (60.3)	297 (55.6)	0.326
	High	138 (66.7)	429 (67.3)		54 (39.7)	237 (44.4)	
(Parental) smoking^b, <i>N</i>(%)		106 (51.2)	321 (50.4)	0.838	78 (57.4)	258 (48.4)	0.062
Allergic comorbidities, <i>N</i>(%)	Allergic rhinitis	190 (91.8)	376 (59.0)	<0.001	101 (74.3)	234 (43.8)	<0.001
	Asthma	81 (39.1)	119 (18.7)	<0.001	54 (39.7)	145 (27.2)	0.004
	Atopic dermatitis	55 (26.6)	179 (28.1)	0.669	89 (65.4)	288 (53.9)	0.016
Reproducibility of reaction^c, <i>N</i>(%)		195 (95.6)	547 (88.1)	0.002	120 (90.9)	481 (92.3)	0.592
Time onset in minutes, median (Q1-Q3)		5 (1-15)	30 (10-120)	<0.001	5 (1.0-60.0)	60.0 (5.0-240.0)	<0.001
Symptoms^d, <i>N</i>(%)	Oral allergy	169 (81.6)	214 (33.6)	<0.001	75 (55.1)	112 (21.0)	<0.001
	Skin	79 (38.2)	259 (40.7)	0.524	108 (79.4)	345 (64.6)	0.001
	Gastrointestinal	52 (25.1)	286 (44.9)	<0.001	38 (27.9)	205 (38.4)	0.024
	Rhinoconjunctivitis	61 (29.5)	142 (22.3)	0.036	55 (40.4)	133 (24.9)	<0.001
	Respiratory	44 (21.3)	71 (11.1)	<0.001	27 (19.9)	47 (8.8)	<0.001
	Cardiovascular	15 (7.2)	79 (12.4)	0.041	6 (4.4)	18 (3.4)	0.560
Centre, <i>N</i>(%)	Athens	5 (2.4)	17 (2.7)	<0.001	7 (5.1)	17 (3.2)	0.003

Lodz	26 (12.6)	88 (13.8)	30 (22.1)	174 (32.6)
Madrid	19 (9.2)	63 (9.9)	22 (16.2)	43 (8.1)
Reykjavik	21 (10.1)	189 (29.7)	26 (19.1)	128 (24.0)
Utrecht	60 (29.0)	139 (21.8)	28 (20.6)	78 (14.6)
Zurich	76 (36.7)	141 (22.1)	17 (12.5)	48 (9.0)
Vilnius	-	-	6 (4.4)	46 (8.6)

Table 1. Population characteristics

Table 1 Legend:

^aLow level of education: None, primary school only, secondary school only or lower level vocational training. High level of education: higher level vocational training, university or full-time student. For children, the highest level of education of the best educated parent was taken into account.

^bFor adults: “Ever smoked for at least one year?” For children: “Has either parent smoked at least 1 cigarette (or alternative) a day since the birth of the child?”

^cReproducibility of reaction: the reaction occurred more than once (*reference = once*).

^dOral allergy symptoms = itching, tingling or swelling of the mouth, lips or throat; Skin symptoms = rash, nettle sting or itchy skin; Rhinoconjunctivitis = runny or stuffy nose or red, sore or running eyes; Gastrointestinal symptoms = diarrhoea or vomiting; Respiratory symptoms = breathlessness; Cardiovascular symptoms = fainting or dizziness.

* The p-values pertain to the comparison of the two preceding columns using the chi-square test, two-sample T-test or Mann-Whitney U test as appropriate for the variable’s distribution.

Table 2. Associations between reaction characteristics, allergic comorbidities, and demographic factors, and probable FA in individuals reporting food-related symptoms

	Adults				Children			
	Crude ORⁱ	95%-CI	Adjusted ORⁱⁱ	95%-CI	Crude ORⁱ	95%-CI	Adjusted ORⁱⁱ	95%-CI
Reaction characteristics								
Time until onset (per 30 mins)	0.94	0.90 - 0.96	0.96	0.93 - 0.99	0.99	0.98-1.00	1.00	0.99-1.00
Reproducibility of reaction	2.93	1.52 - 6.39	3.24	1.41 - 8.33	0.83	0.44-1.70	0.75	0.34-1.72
Oral allergy symptoms	8.79	6.02 - 13.12	5.62	3.61 - 8.93	4.63	3.12-6.91	3.43	2.07-5.71
Skin symptoms	0.90	0.65- 1.24	0.92	0.59 - 1.42	2.11	1.36-3.37	1.67	0.96-2.96
Gastrointestinal symptoms	0.41	0.29 - 0.58	0.59	0.38 - 0.90	0.62	0.41-0.93	0.86	0.52-1.42
Rhinoconjunctivitis	1.46	1.02 - 2.07	1.11	0.69 - 1.77	2.05	1.38-3.03	1.43	0.85-2.38
Respiratory symptoms	2.15	1.41- 3.25	1.41	0.82 - 2.41	2.57	1.52-4.28	1.01	0.50-1.98
Cardiovascular symptoms	0.55	0.30 - 0.95	0.63	0.30 - 1.25	1.32	0.44-3.23	1.39	0.40-3.82
Allergic comorbidities								
Allergic rhinitis	7.76	4.74 -13.52	4.44	2.52 - 8.26	3.70	2.45-5.70	3.13	1.87-5.33
Asthma	2.80	1.98 - 3.94	1.88	1.21 – 2.95	1.77	1.19-2.61	1.20	0.71-2.02
Atopic dermatitis	0.93	0.65 - 1.31	0.74	0.47-1.16	1.62	1.10-2.41	1.36	0.85-2.22
Demographic factors								
Age	0.98	0.96 - 1.00	0.98	0.96 - 1.00	1.16	0.95-1.42	0.99	0.78-1.26
Male sex	1.81	1.31 - 2.49	2.34	1.55 - 3.57	1.10	0.76-1.61	1.03	0.65-1.61
High level of education	0.97	0.70 - 1.36	1.01	0.64 - 1.59	0.83	0.56-1.21	0.93	0.57-1.50

(Parental) smoking	1.03	0.75 - 1.41	1.43	0.95 - 2.16	1.43	0.98-2.10	1.22	0.77-1.96
<i>AUC</i>			0.86				0.76	
			(0.83-0.89)				(0.71-0.82)	

Table 2 Legend: OR: Odds ratio, CI: confidence interval; AUC: area under the receiver operating characteristic curve. **Bold print:** significant at $p < 0.05$. ⁱ Unadjusted OR, results of univariable logistic regression analysis. ⁱⁱ Adjusted OR, results of multivariable logistic regression analysis with all covariates included, i.e. the full model. Model coefficients were adjusted for centre.

Table 3. Population characteristics for plant vs. animal source probable FA

		Children		
		Plant source probable FA	Animal source probable FA	p-value*
		N = 74	N = 44	
Age, mean (SD)		9.2 (1.02)	8.7 (0.85)	0.017
Sex, N(%)	Male	37 (50.0)	22 (50.0)	>0.99
	Female	37 (50.0)	22 (50.0)	
Level of education parents, N(%)	Low	49 (66.2)	26 (59.1)	0.437
	High	25 (33.8)	18 (40.9)	
Parental smoking, N(%)		43 (58.1)	27 (61.4)	0.728
Allergic comorbidities, N(%)	Allergic rhinitis	62 (83.8)	23 (52.3)	<0.001
	Asthma	27 (36.5)	17 (38.6)	0.815
	Atopic dermatitis	44 (59.5)	29 (65.9)	0.485
Reproducibility of reaction, N(%)		61 (87.1)	41 (93.2)	0.306
Time onset in minutes, median (Q1-Q3)		5.0 (1.0-120.0)	15.0 (3.0-90.0)	0.404
Symptoms, N(%)	Oral allergy	45 (60.8)	15 (34.1)	0.005
	Skin	60 (81.1)	32 (72.7)	0.290
	Gastrointestinal	9 (12.2)	23 (52.3)	<0.001
	Rhinoconjunctivitis	33 (44.6)	13 (29.5)	0.105
	Respiratory	11 (14.9)	8 (18.2)	0.635
	Cardiovascular	5 (6.8)	0 (0.0)	0.078
Centre, N(%)	Athens	3 (4.1)	1 (2.3)	0.002
	Lodz	16 (21.6)	11 (25.0)	
	Madrid	13 (17.6)	6 (13.6)	
	Reykjavik	7 (9.5)	16 (36.4)	
	Utrecht	15 (20.3)	8 (18.2)	
	Zurich	16 (31.6)	0 (0.0)	
	Vilnius	4 (5.4)	2 (4.5)	

Table 3 Legend: In 18/136 children, both animal and plant source foods caused probable FA (table E1). These subjects are excluded in this table. * The p-values pertain to the comparison of the two

preceding columns using the chi-square test, two-sample T-test or Mann-Whitney U test as appropriate for the variables distribution. Exploratory analyses, not corrected for multiple testing.

Figure 1. Independent predictors of probable FA in individuals reporting food-related symptoms, results from Lasso regression analysis

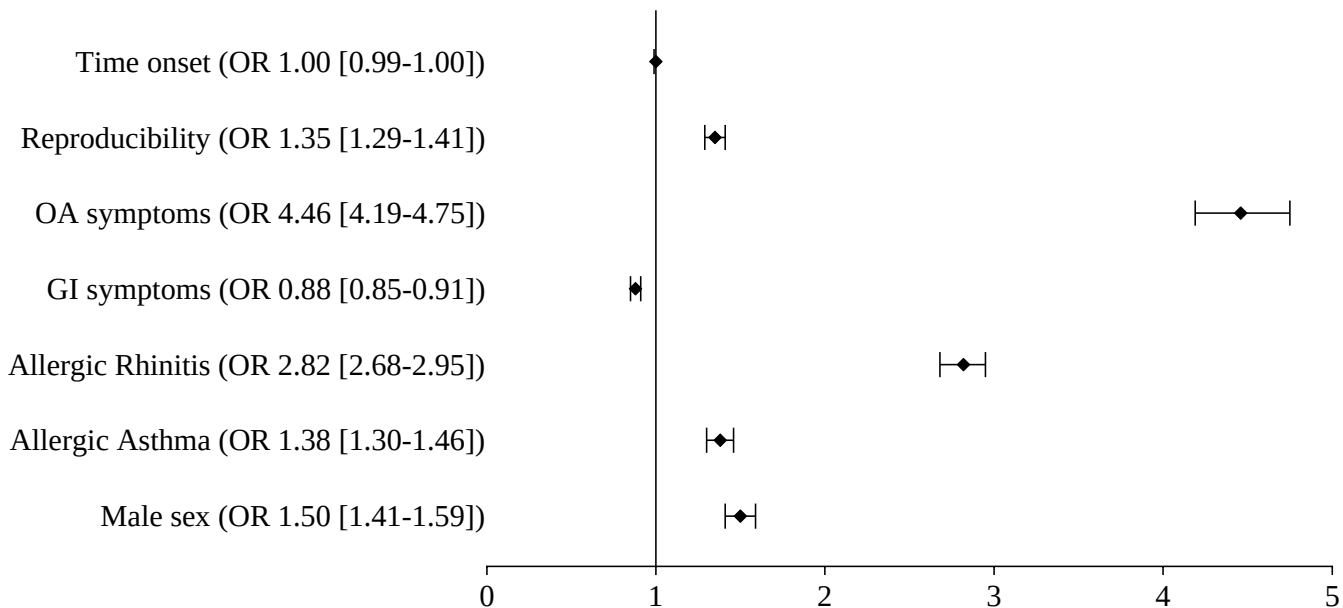
Figure 1 Legend: Odds ratios for independent predictors of food allergy in adults and children as selected and determined by LASSO regression. 95% confidence intervals were calculated from standard errors obtained through 1000 bootstrap samples. OA = oral allergy; GI = gastro-intestinal.

REFERENCES

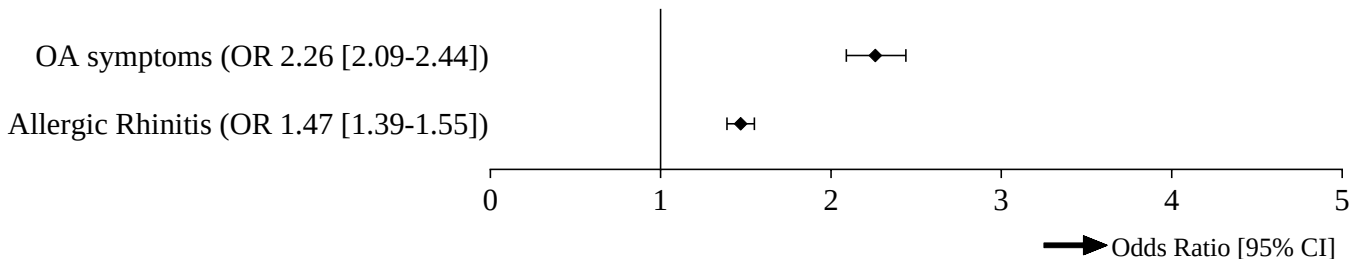
1. Burney PG, Potts J, Kummeling I, Mills EN, Clausen M, Dubakiene R, et al. The prevalence and distribution of food sensitization in European adults. *Allergy*. 2014;69(3):365-71.
2. Lyons SA, Clausen M, Knulst AC, Ballmer-Weber BK, Fernandez-Rivas M, Barreales L, et al. Prevalence of Food Sensitization and Food Allergy in Children across Europe. *J Allergy Clin Immunol Pract*. 2020.
3. Lyons SA, Burney PGJ, Ballmer-Weber BK, Fernandez-Rivas M, Barreales L, Clausen M, et al. Food Allergy in Adults: Substantial Variation in Prevalence and Causative Foods Across Europe. *J Allergy Clin Immunol Pract*. 2019;7(6):1920-8 e11.
4. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy*. 2014;69(8):1008-25.
5. Skypala IJ, Venter C, Meyer R, deJong NW, Fox AT, Groetch M, et al. The development of a standardised diet history tool to support the diagnosis of food allergy. *Clin Transl Allergy*. 2015;5:7.
6. Kummeling I, Mills EN, Clausen M, Dubakiene R, Perez CF, Fernandez-Rivas M, et al. The EuroPrevall surveys on the prevalence of food allergies in children and adults: background and study methodology. *Allergy*. 2009;64(10):1493-7.
7. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J*. 1994;7(5):954-60.
8. Tibshirani R. Regression Shrinkage and Selection via the Lasso. *J Roy Stat Soc B*. 1996;58(1):267-88.
9. Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol*. 2018;141(1):41-58.
10. Sampson HA. Food allergy--accurately identifying clinical reactivity. *Allergy*. 2005;60 Suppl 79:19-24.
11. Turner PJ, Baumert JL, Beyer K, Boyle RJ, Chan CH, Clark AT, et al. Can we identify patients at risk of life-threatening allergic reactions to food? *Allergy*. 2016;71(9):1241-55.
12. Amlot PL, Kemeny DM, Zachary C, Parkes P, Lessof MH. Oral allergy syndrome (OAS): symptoms of IgE-mediated hypersensitivity to foods. *Clin Allergy*. 1987;17(1):33-42.

- Accepted Article
13. Werfel T, Asero R, Ballmer-Weber BK, Beyer K, Enrique E, Knulst AC, et al. Position paper of the EAACI: food allergy due to immunological cross-reactions with common inhalant allergens. *Allergy*. 2015;70(9):1079-90.
 14. Lyons SA, Dijk AMV, Knulst AC, Alquati E, Le TM, Os-Medendorp HV. Dietary Interventions in Pollen-Related Food Allergy. *Nutrients*. 2018;10(10).
 15. DunnGalvin A, Daly D, Cullinane C, Stenke E, Keeton D, Erlewyn-Lajeunesse M, et al. Highly accurate prediction of food challenge outcome using routinely available clinical data. *J Allergy Clin Immunol*. 2011;127(3):633-9 e1-3.
 16. Klemans RJ, Broekman HC, Knol EF, Bruijnzeel-Koomen CA, Otten HG, Pasmans SG, et al. Ara h 2 is the best predictor for peanut allergy in adults. *J Allergy Clin Immunol Pract*. 2013;1(6):632-8 e1.

Adults (AUC 0.85 [95%CI 0.82-0.87])



Children (AUC 0.73 [95%CI 0.68-0.78])



**PATIENT HISTORY CAN ACCURATELY PREDICT PROBABLE FOOD ALLERGY –
SUPPLEMENTARY FILES**

Table E1. Types of foods causing probable food allergy

Food causing probable FA	Adults		Children	
	N	%	N	%
Any	207		136	
Animal source food only	19	9.2	44	32.4
Plant source food only	179	86.5	74	54.4
Both animal and plant source foods	9	4.3	18	13.2
Animal source foods				
Cow's milk	2	1.0	35	25.7
Hen's egg	8	3.9	26	19.1
Fish	7	3.4	8	5.9
Shrimp	18	8.7	9	6.6
Plant source foods				
Hazelnut	102	49.3	26	19.1
Walnut	25	12.1	14	10.3
Apple	81	39.1	22	16.2
Peach	70	33.8	16	11.8
Kiwi	34	16.4	19	14.0
Banana	7	3.4	12	8.8
Melon	14	6.8	1	0.7
Tomato	13	6.3	10	7.4
Carrot	30	14.5	10	7.4
Celery	8	3.9	8	5.9
Peanut	11	5.3	26	19.1
Soybean	2	1.0	6	4.4
Lentil	1	0.5	5	3.7
Wheat	9	4.3	5	3.7
Buckwheat	1	0.5	2	1.5
Corn	2	1.0	1	0.7
Sesame seed	0	0.0	2	1.5
Sunflower seed	2	1.0	3	2.2
Mustard seed	0	0.0	0	0.0
Poppy seed	0	0.0	0	0.0

Table E1 Legend: This table shows the causative foods in subjects with probable FA. Subjects could be allergic to more than one food. A total of 447 probable FA's were identified in 207 adults, and 266 probable FA's in 136 children.

Table E2. Comparison of subjects with complete data for multivariable analyses to subjects with missing data

		Adults			Children		
		Complete data on food serology and predictors	Missing data on food serology or predictors	p-value	Complete data on food serology and predictors	Missing data on food serology or predictors	p-value
		<i>N</i> = 807	<i>N</i> =55		<i>N</i> = 593	<i>N</i> =109	
Probable FA		201 (24.9)	6 (16.2)*	0.230	126 (21.2)	10 (13.0)*	0.090
Age, mean (SD)		37.3 (9.4)	37.3 (10.1)	0.986	8.9 (0.96)	8.9 (0.92)	0.721
Sex, <i>N</i> (%)	Male	276 (34.2)	20 (36.4)	0.744	283 (47.7)	52 (47.7)	0.997
	Female	531 (65.8)	35 (63.6)		310 (52.3)	57 (52.3)	
Level of education ^a , <i>N</i> (%)	Low	267 (33.1)	17 (30.9)	0.740	338 (57.0)	55 (50.5)	0.206
	High	540 (66.9)	38 (69.1)		255 (43.0)	54 (49.5)	
(Parental) smoking ^b , <i>N</i> (%)		410 (50.8)	28 (50.9)	0.988	302 (50.9)	47 (43.5)	0.157
Allergic comorbidities, <i>N</i> (%)	Allergic rhinitis	543 (67.3)	38 (69.1)	0.782	304 (51.3)	48 (44.0)	0.165
	Asthma	191 (23.7)	13 (23.6)	0.996	184 (31.0)	26 (23.9)	0.133
	Atopic dermatitis	229 (28.4)	10 (18.2)	0.102	342 (57.7)	58 (53.2)	0.387
Reproducibility of reaction ^c , <i>N</i> (%)		728 (90.2)	31 (86.1)	0.422	545 (91.9)	86 (93.5)	0.602
Time onset in minutes, median (Q1-Q3)		20.0 (5.0-120.0)	10.0 (2.0-60.0)	0.069	30.0 (5.0-180.0)	12.5 (2.0-240.0)	0.264
Symptoms ^d , <i>N</i> (%)	Oral allergy	370 (45.8)	21 (38.2)	0.269	170 (28.7)	30 (27.5)	0.808
	Skin	324 (40.1)	24 (43.6)	0.610	397 (66.9)	78 (71.6)	0.344
	Gastrointestinal	326 (40.4)	17 (30.9)	0.164	212 (35.8)	38 (34.9)	0.859
	Rhinoconjunctivitis	194 (24.0)	13 (23.6)	0.946	171 (28.8)	26 (23.9)	0.287
	Respiratory	110 (13.6)	8 (14.5)	0.849	69 (11.6)	8 (7.3)	0.187
	Cardiovascular	370 (45.8)	4 (7.3)	0.505	24 (4.0)	1 (0.9)	0.156
Centre, <i>N</i> (%)	Athens	22 (2.7)	1 (1.8)	<0.001	21 (3.5)	5 (4.6)	<0.001
	Lodz	112 (13.9)	5 (9.1)		183 (30.9)	23 (21.1)	
	Madrid	77 (9.5)	6 (10.9)		61 (10.3)	8 (7.3)	
	Reykjavik	198 (24.5)	12 (21.8)		141 (23.8)	14 (12.8)	
	Utrecht	197 (24.4)	2 (3.6)		101 (17.0)	16 (14.7)	
	Zurich	201 (24.9)	29 (52.7)		56 (9.4)	15 (13.8)	
	Vilnius	-	-		30 (5.1)	28 (25.7)	

Table E2 Legend:

^aLow level of education: None, primary school only, secondary school only or lower level vocational training. High level of education: higher level vocational training, university or full-time student. For children, the highest level of education of the best educated parent was taken into account.

^bFor adults: “Ever smoked for at least one year?” For children: “Has either parent smoked at least 1 cigarette (or alternative) a day since the birth of the child?”

^cReproducibility of reaction: the reaction occurred more than once (*reference = once*).

^dOral allergy symptoms = itching, tingling or swelling of the mouth, lips or throat; Skin symptoms = rash, nettle sting or itchy skin; Rhinoconjunctivitis = runny or stuffy nose or red, sore or running eyes; Gastrointestinal symptoms = diarrhoea or vomiting; Respiratory symptoms = breathlessness; Cardiovascular symptoms = fainting or dizziness.

* Probable FA could only be determined in those subjects with available serology

Table E3. Full logistic regression model with reaction severity rather than individual symptoms as covariates

	Adults				Children			
	Crude OR ⁱ	95%-CI	Adjusted OR ⁱⁱ	95%-CI	Crude OR ⁱ	95%-CI	Adjusted OR ⁱⁱ	95%-CI
Reaction characteristics								
Time until onset (per 30 mins)	0.94	0.90 - 0.96	0.95	0.92-0.97	0.99	0.98-1.00	1.00	0.99-1.00
Reproducibility of reaction	2.93	1.52 - 6.39	3.56	1.56-9.33	0.83	0.44-1.70	0.64	0.30-1.44
Symptom severity*	<i>Reference</i>				<i>Reference</i>			
Grade I								
Grade II	1.58	1.04-2.40	1.37	0.84-2.24	1.78	1.10-2.89	1.74	1.01-3.01
Grade III	2.73	1.79-4.19	2.54	1.50-4.32	2.83	1.70-4.71	2.19	1.21-3.96
Grade IV	0.90	0.51-1.51	0.94	0.50-1.73	3.19	1.54-6.42	2.95	1.31-6.55
Allergic comorbidities								
Allergic rhinitis	7.76	4.74 -13.52	4.74	2.74-8.70	3.70	2.45-5.70	3.94	2.37-6.70
Asthma	2.80	1.98 - 3.94	1.92	1.24-2.98	1.77	1.19-2.61	1.11	0.68-1.80
Atopic dermatitis	0.93	0.65 - 1.31	0.73	0.47-1.11	1.62	1.10-2.41	1.43	0.90-2.30
Demographic factors								
Age	0.98	0.96 - 1.00	0.98	0.96-1.00	1.16	0.95-1.42	1.00	0.80-1.27
Male sex	1.81	1.31 - 2.49	2.18	1.47-3.25	1.10	0.76-1.61	1.03	0.66-1.60
High level of education	0.97	0.70 - 1.36	0.91	0.59-1.41	0.83	0.56-1.21	0.90	0.55-1.45
(Parental) smoking	1.03	0.75 - 1.41	1.24	0.84-1.85	1.43	0.98-2.10	1.15	0.73-1.82
AUC			0.81				0.73	
			(0.78-0.84)				(0.68-0.79)	

Table E3 Legend:OR: Odds ratio, CI: confidence interval; AUC: area under the receiver operating characteristic curve.* Symptom severity was classified similarly to DunnGalvinet al: I. oral allergy or skin or gastrointestinal or rhinoconjunctivitis symptoms only; II. 2 systems; III. lower respiratory symptoms or 3 systems; IV. cardiovascular symptoms or 4 systems.¹ⁱ Unadjusted OR, results of univariable logistic regression analysis. ⁱⁱ Adjusted OR, results of multivariable logistic regression analysis with all covariates included, i.e. the full model. Model coefficients were adjusted for centre. **Bold print:** significant at p<0.05

Table E4. Combination of determinants for optimal prediction of probable FA in adults from the general population with food-related symptoms

	Adults		
	Beta	OR	95%-CI
Reaction characteristics			
Time until onset (per 30 mins)	-0.005	1.00	0.99-1.00
Reproducibility of reaction	0.30	1.35	1.29-1.41
Oral allergy symptoms (<i>OAS</i>)	1.49	4.46	4.19-4.75
Gastrointestinal symptoms (<i>GI</i>)	-0.13	0.88	0.85-0.91
Allergic comorbidities			
Allergic rhinitis (<i>AR</i>)	1.04	2.82	2.68-2.95
Asthma (<i>A</i>)	0.32	1.38	1.30-1.46
Demographic factors			
Male sex (<i>MS</i>)	0.40	1.50	1.41-1.59
<i>Intercept</i>	-3.09		

Table E4 Legend: Above table shows the coefficients corresponding with the odds ratios (OR; =Exp(beta)) presented for adults in figure 1. The coefficients from LASSO regression are used rather than those from the full logistic regression model, as the LASSO model is expected to be more generalisable. Regarding centre, only Zurich was found to have an effect on the likelihood of FA compared to other centres (beta = 0.20). The corresponding prediction score can be calculated as follows:

$$1/(1+(e^{(-3.09 + (\text{Time} * -0.005) + (\text{Reproducibility} * 0.30) + (\text{OAS} * 1.49) + (\text{GI} * -0.13) + (\text{AR} * 1.04) + (\text{A} + 0.32) + \text{MS} * 0.40) + (\text{Zurich} * 0.20)})))).$$

Relevant information on accuracy and positivity thresholds is presented in table E5.

Table E5. Accuracy measures for the combination of determinants for optimal prediction of probable FA in adults from the general population with food-related symptoms in table E4.

Accuracy measure	Maximum value of accuracy measure	Cut-off on prediction score*		PFA	No PFA	Sensitivity	Specificity	PPV	NPV
-	-	0.5	<	119	557	41 (34-48)	92 (90-94)	63 (54-70)	82 (79-85)
			≥	82	49				
Sens	100%	0.05	<	0	83	100 (98-100)	14 (11-17)	28 (25-31)	100 (96-100)
			≥	201	523				
	95%	0.15	<	10	299	95 (91-97)	49 (45-53)	38 (34-43)	97 (94-98)
			≥	191	307				
Spec	100%	0.61	<	189	603	6 (3-10)	100 (99-100)	80 (55-93)	76 (72-78)
			≥	12	3				
	95%	0.52	<	134	576	33 (27-40)	95 (93-97)	69 (59-77)	81 (78-84)
			≥	67	30				
PPV	80%	0.54	<	157	595	22 (17-28)	98 (97-99)	80 (68-88)	79 (76-82)
			≥	44	11				
NPV	100%	0.05	<	0	83	100 (98-100)	14 (11-17)	28 (25-31)	100 (96-100)
			≥	201	523				
	95%	0.17	<	18	356	91 (86-94)	59 (55-63)	42 (38-47)	95 (93-97)
			≥	183	250				
Youden		0.24	<	39	452	81 (75-86)	75 (71-78)	51 (46-57)	92 (89-94)
			≥	162	154				
PPV + NPV		0.54	<	157	595	22 (17-28)	98 (97-99)	80 (68-88)	79 (76-82)
			≥	44	11				

Table E5 Legend:*For prediction score, see table E4. This table shows the sensitivity (sens), specificity (spec), positive predictive value (PPV), and negative predictive value (NPV) corresponding with a cut-off on the prediction score of 0.5 (i.e. risk of 50%), and alternative cut-offs on the prediction score corresponding with optimal sens, spec, PPV, NPV, Youden's index = maximum [sensitivity+specificity-1]², and maximum [PPV+NPV].

REFERENCES SUPPLEMENTARY FILES

1. DunnGalvin A, Daly D, Cullinane C, Stenke E, Keeton D, Erlewyn-Lajeunesse M, et al. Highly accurate prediction of food challenge outcome using routinely available clinical data. *J Allergy Clin Immunol*. 2011;127(3):633-9 e1-3.
2. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3(1):32-5.