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ORIGINAL ARTICLE

Food Allergy and Gastrointestinal Disease

A European-Japanese study on peach allergy: IgE to Pru p 7 associates with severity

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Abbreviations: AUC, Area under the curve; CCD, Cross-reactive carbohydrate determinants; CI, Confidence interval; CRD, Component-resolved diagnostics; GRP, Gibberellin-regulated protein protein; IgE, Immunoglobulin E; LTP, Lipid transfer protein; PR-10, Pathogenesis-related protein family 10; PTP, Prick-to-prick test; ROC, Receiver operating characteristic; SPT, Skin prick test; TLP, Thaumatin-like protein.

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Abstract

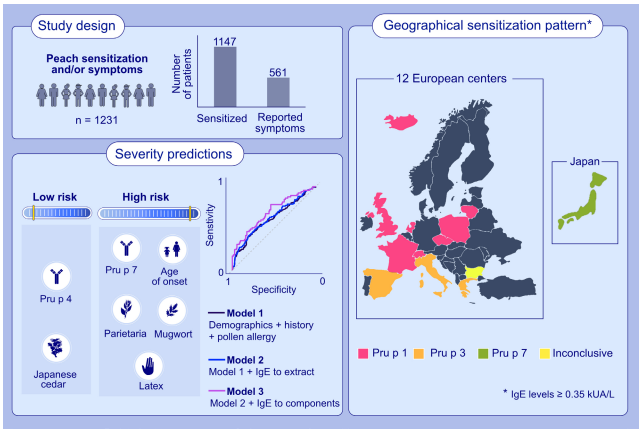
Background: Pru p 3 and Pru p 7 have been implicated as risk factors for severe peach allergy. This study aimed to establish sensitization patterns to five peach components across Europe and in Japan, to explore their relation to pollen and foods and to predict symptom severity.

Methods: In twelve European (EuroPrevall project) and one Japanese outpatient clinic, a standardized clinical evaluation was conducted in 1231 patients who reported symptoms to peach and/or were sensitized to peach. Specific IgE against Pru p 1, 2, 3, 4 and 7 and against Cup s 7 was measured in 474 of them. Univariable and multivariable Lasso regression was applied to identify combinations of parameters predicting severity.

Results: Sensitization to Pru p 3 dominated in Southern Europe but was also quite common in Northern and Central Europe. Sensitization to Pru p 7 was low and variable in the European centers but very dominant in Japan. Severity could be predicted by a model combining age of onset of peach allergy, probable mugwort, *Parietaria* pollen and latex allergy, and sensitization to Japanese cedar pollen, Pru p 4 and Pru p 7 which resulted in an AUC of 0.73 (95% CI 0.73–0.74). Pru p 3 tended to be a risk factor in South Europe only.

Conclusions: Pru p 7 was confirmed as a significant risk factor for severe peach allergy in Europe and Japan. Combining outcomes from clinical and demographic background with serology resulted in a model that could better predict severity than CRD alone.

KEYWORDS
Peach allergy, prediction, Pru p 3, Pru p 7, severity



GRAPHICAL ABSTRACT

This study analyzed sensitization patterns to five peach components across Europe and in Japan, to explore their relation to pollen and foods and to predict symptom severity. A severity prediction model combining clinical and demographic outcomes with component-resolved diagnostic (CRD) performs better than CRD alone. Geographic differences were identified, confirming and extending earlier reports: PR-10 (Pru p 1) dominant in Northern/Central Europe, lipid transfer protein (LTP) (Pru p 3) in Southern Europe and GRP (Pru p 7) in Japan. Pru p 7 is associated with severe reactions.

Abbreviations: CRD, component-resolved diagnostic; IgE, immunoglobulin E; kUA/L, kilounits of allergen-specific IgE per liter; LTP, lipid transfer protein

1 | INTRODUCTION

Peach is among the most prevalent plant food allergies in Europe and Japan.[1,2] The prevalence of sensitization in adults increased from 5.4% in 2010[3] to 7.9% in 2013.[4] In adults, the EuroPrevall study showed a mean prevalence of probable peach allergy (reported symptoms plus matching IgE sensitization) of 0.80%.[5]

Component-resolved diagnostics (CRD) defines sensitization profiles of patients at the molecular level.[6] Five food allergen components from peach are listed in the IUIS/WHO allergen database: Pru p 1 (Bet v 1-like protein [PR-10]), Pru p 2 (thaumatin-like protein [TLP]), Pru p 3 (lipid transfer protein [LTP]), Pru p 4 (profilin), and Pru p 7 (gibberellin-regulated protein [GRP]).[7]

In Northern and Central Europe, patients are dominantly sensitized to Pru p 1 and in Mediterranean countries to Pru p 3.[8–10] Sensitization to Pru p 4 is less regionally determined.[8,9,11] Recently, sensitization to Pru p 7 (peamaclein), a gibberellin-regulated protein (GRP) was reported.[12] It is thought to originate from primary sensitization to GRPs in pollen of *Cupressaceae* trees as cypress[13] and Japanese cedar.[14]

CRD could help to better estimate the risk of severe reactions to peach.[15] In smaller studies in Southern Europe, Pru p 3 was a marker for severe peach allergy,[16] and also, Pru p 7 was associated with more severe reactions, both in Japan[1] and in Southern Europe.[13] It remains difficult to compare these results because study designs vary. The EuroPrevall project used study protocols across Europe with standardized case-record forms (CRFs), centralized serum testing and identical challenge protocols.[17] We added data from a clinical center from Japan where it was expected that sensitization to Pru p 7 is more common due to the importance of allergy to Japanese cedar pollen, using the EuroPrevall CRF.

Our aims were to (1) identify differences in sensitization pattern to peach components across Europe and Japan; (2) assess relationships between IgE to peach components and pollen and foods, providing insight into possible primary sensitizers; and (3) develop a model to predict severity of peach allergy.

2 | METHODS

2.1 | Study design, setting and patients

Patients from twelve European centers and one Japanese center were included. The European patients were enrolled in the outpatient clinic survey of the EuroPrevall project[18] of which the methodology was published previously.[17] Patients from the EuroPrevall study were selected for this study if they had a reported adverse reaction within 2 h of ingestion of peach and/or were sensitized to peach (positive IgE to peach extract/component, positive SPT or prick-to-prick test [PTP] to peach).

In Japan, patients were included if they reported adverse reactions within 2 h of ingestion of peach and had an IgE to peach extract ≥0.10 kU_A/L. Patients with only oral allergy symptoms to peach were excluded.

To gain more insight into the molecular sensitization patterns of the sensitized patients with and without symptoms, in the European centers peach sensitized patients with and without symptoms were included and in the Japanese center this was only possible for patients with symptoms to peach.

Ethical approval and informed consent were obtained in each center and from each participating patient.

2.2 | Data collection

In the EuroPrevall study, clinical data were collected using a detailed standardized CRF.[17] Skin prick tests were performed with peach extract (ALK). Total IgE, specific IgE to latex, 12 inhalant allergen sources, peach, and 23 other foods commonly implicated in food allergy across Europe were measured in serum (ImmunoCAP, ThermoFisher Scientific).[17] Prick-to-prick testing (PTP) with fresh peach peel or pulp was performed in case of negative SPT with peach extract, as indicated by local practice. In addition, in the course of the present study, IgE against Japanese cedar (*Cryptomeria japonica*) pollen was determined for the EuroPrevall patients to allow comparison to the Japanese patients. In the CRD analysis, specific IgE against rPru p 1, rPru p 2, rPru p 3, rPru p 4, rPru p 7, and rCup s 7 (GRP protein of cypress) was measured. Due to restricted availability of the custom-made peach component ImmunoCAP tests (rPru p 2, rPru p 7 and rCup s 7), analysis was only performed in a selection of patients (37%) (for detailed description see Appendix S1). A double-blind placebo-controlled food challenge (DBPCFC) for peach was performed in all consenting patients who reported symptoms except for patients with a history of severe life-threatening anaphylaxis.[17]

In Japan, the same standardized EuroPrevall CRF was retrospectively filled out. IgE to peach extract, Japanese cedar pollen and cypress pollen, and the same CRD analysis as for the European patients was performed.

The validated oFASS-3 scoring was used to classify the severity; oFASS-3 grade 1 (mild: isolated oropharyngeal symptoms), grade 2 (moderate: grade 1 symptoms and/or symptoms of the skin, eye, upper airways and/or digestive system), and grade 3 (severe: grade 1 and/or 2 symptoms and/or symptoms of the lower airways, cardiovascular and/or nervous system).[19]

2.3 | Definitions

Probable peach allergy was defined as a combination of reported symptoms upon ingestion of peach and matching IgE sensitization (positive SPT, PTP, and/or IgE against peach and/or any components). SPT results were expressed as allergen/histamine wheal ratios. A wheal ratio ≥0.5 and IgE levels ≥0.35 kU_A/L were considered positive for both the EuroPrevall and Japanese's patients.

Probable allergy to inhalant allergen sources and latex was defined as reported symptoms and matching IgE sensitization in SPT and/or ImmunoCAP. Since allergic symptoms to cat and dog were collected as symptoms to epithelia and not as single outcomes, and symptoms to Japanese cedar pollen were only collected in Japan, sensitization to cat, dog and Japanese cedar pollen was used instead.

2.4 | Statistical analyses

Patients' demographical characteristics, clinical history, and symptom severity were described using means with standard deviation (SD) or medians with interquartile range (Q1, Q3) for, respectively, normally or non-normally distributed continuous variables and frequency and proportions for categorical variables. Proportions of patients reporting symptoms to peach and/or sensitized to peach were explored overall and for each participating center separately. Differences between centers were tested using ANOVAs, Kruskal–Wallis tests, or chi-square tests, respectively.

Spearman rho coefficients were calculated to assess relationships between levels of IgE to peach components, and levels of IgE to foods, inhalants allergens and latex if at least 10 patients with both measured IgE for a peach component and for another extract were present.

For severity prediction, only patients with a probable peach allergy were analyzed. Peach allergy severity was dichotomized as mild to moderate (i.e., oFASS-3 grades 1/2) versus severe (i.e., oFASS-3 grade 3).

First univariable logistic regression analysis was performed followed by multivariable logistic regression using Lasso regression (R package "glmnet"). Missing data were imputed as preprocessing step (Appendix S2).

A 3-step approach to building prediction models was used for patients with probable peach allergy in the Japanese and European centers together and for European centers only. In step 1 (model 1), demographic, clinical history, and inhalant allergy variables were entered as predictors. In step 2 (model 2), both the selected predictors of model 1, and IgE levels to peach extract, cypress pollen and Japanese cedar pollen, and the SPT with peach extract results were used as predictors. In step 3 (model 3), the predictors selected by model 2 and the 10 log IgE levels to peach components were used. A 4th separate model was built with only the peach components as predictors (Appendix S3).

These models were subsequently applied to a subset of European patients that had undergone a DBPCFC together with those who had a history of severe anaphylaxis to peach (oFASS-3 grade 3). When the model fit was evaluated for the patients in this group, for those that underwent a challenge, challenge-reported symptoms were used, for those that reported anaphylaxis, self-reported symptoms were used. Overall, model predictive performance was evaluated using AUC-ROC and sensitivity/specificity with an optimal cutoff determined by the Youden-index.

Analyses were conducted with R version 4.2.1.

3 | RESULTS

3.1 | Population characteristics

In total, 1231 patients were included in this study (Table 1), the mean age was 28.6 (±15.0), and 57.8% were female. There were a few significant differences between centers with respect to the age of patients at inclusion (younger in Prague being a pediatric clinic), age of onset of peach allergy (older in Milan), and severity of reported symptoms (more severe in Sagamihara as expected based on exclusion of oFASS-3 grade 1; Appendix S1). Of the 1231 patients, 561 (45.6%) reported symptoms of which 477 (38.7%) were also sensitized, that is, having probable peach allergy. Almost half of the 561 patients reported mild symptoms (46.9%) and around a quarter moderate or severe symptoms (26.9% and 26.2%, respectively). Most reported were symptoms of the oral cavity (85.4%), skin (33.2%), upper airways (27.8%), digestive system (13.9%), and lower airways (10.5%). Fewer patients reported neurologic symptoms (2.0%), life-threatening anaphylaxis or cardiovascular symptoms (3.0%). In total, 670 patients (54.4%) reported no symptoms of which all were sensitized. There were no patients without symptoms and not sensitized (Appendix S4).

3.2 | Peach sensitization patterns across Europe and Japan

Of the 1231 patients, 1147 patients were sensitized to peach. The mean levels of sensitization were slightly higher in the group with self-reported symptoms compared to the group without symptoms. However, this did not reach significance (Figure 1).

CRD was assessed in 474 sensitized patients with or without symptoms to peach (Table 1; Figure 2). There were significant differences between the 13 centers in the number of patients sensitized to Pru p 3 and to Pru p 7. In Athens, 87.3% was sensitized to Pru p 3, in Sagamihara 14.7%. The percentage sensitized to Pru p 7 was 64.7% in Sagamihara and ranged in Europe from 15.4% in Utrecht to 0% in Prague, Reykjavik and Milan.

Among the European patients sensitized to peach, the most frequently recognized allergen was Pru p 1 (55.2%), followed by Pru p 3 (46.1%), Pru p 4 (19.8%), Pru p 7 (6.1%), and Pru p 2 (4.5%) (Figure 2). In the subgroup of patients with probable peach allergy (218/474), these percentages were similar (Appendix S5). Sensitization to Pru p 1 was most common in Northern and Central Europe (Zürich, Strasbourg, Utrecht, Manchester, Lodz, Prague, and Vilnius). In the Mediterranean area (Madrid, Milan and Athens), sensitization to Pru p 3 dominated (from 66.7% to 100%), but it was also quite common in Northern and Central Europe (from 13% to 60%). Sensitization to Pru p 7 was not often observed in patients from European centers (mostly <10%). In all centers, except for Madrid, Athens, and Reykjavik, sensitization to Pru p 4 was detected at clearly lower frequency than to Pru p 1 and at lower or similar frequency as to Pru p 3. Pru p 2 was hardly recognized in any of the twelve centers.

TABLE 1 Characteristics of patients with peach sensitization and/or peach symptoms.

Characteristics	Total (*N* = 1231)	Zürich (*N* = 204)	Strasbourg (*N* = 119)	Utrecht (*N* = 131)	Manchester (*N* = 56)	Lodz (*N* = 107)	Prague (*N* = 55)
Age, mean (SD)	28.6 ± 15.0	33.1 ± 13.5	32.1 ± 13.1	29.9 ± 12.2	31.3 ± 15.4	29.4 ± 17.7	12.0 ± 11.1
Female sex	712 (57.8%)	123 (60.3%)	81 (68.1%)	83 (63.4%)	35 (62.5%)	70 (65.4%)	25 (45.5%)
Age onset, mean (SD)[a]	21.1 ± 14.0	22.9 ± 11.5	23.5 ± 10.6	21.2 ± 12.3	27.3 ± 16.4	25.0 ± 17.6	13.8 ± 9.47
Severity oFASS-3							
No symptoms	670 (54.4%)	103 (50.5%)	45 (37.8%)	66 (50.4%)	30 (53.6%)	54 (50.5%)	47 (85.5%)
oFASS-3 grade 1	263 (21.4%)	52 (25.5%)	56 (47.1%)	32 (24.4%)	4 (7.1%)	11 (10.3%)	4 (7.3%)
oFASS-3 grade 2	151 (12.3%)	23 (11.3%)	5 (4.2%)	15 (11.5%)	6 (10.7%)	25 (23.4%)	2 (3.6%)
oFASS-3 grade 3	147 (11.9%)	26 (12.7%)	13 (10.9%)	18 (13.7%)	16 (28.6%)	17 (15.9%)	2 (3.6%)
Probable peach allergy	477 (38.7%)	86 (42.2%)	67 (56.3%)	63 (48.1%)	23 (41.1%)	26 (24.3%)	6 (10.9%)
Peach sensitization[b]/[c]							
Positive SPT peach	269 (21.9%)	29 (14.2%)	7 (5.9%)	9 (6.9%)	7 (12.5%)	13 (12.1%)	13 (23.6%)
Positive IgE to peach	957 (77.7%)	151 (74.0%)	105 (88.2%)	73 (55.7%)	49 (87.5%)	74 (69.2%)	52 (94.5%)
CRD performed	474 (38.5%)	61 (29.9%)	32 (26.9%)	39 (29.8%)	22 (39.3%)	50 (46.7%)	20 (36.4%)
Positive Pru p 1	254 (53.6%)	51 (83.6%)	28 (87.5%)	34 (87.2%)	14 (63.6%)	42 (84.0%)	17 (85.0%)
Positive Pru p 2	20 (4.2%)	2 (3.3%)	1 (3.1%)	4 (10.3%)	1 (4.5%)	4 (8.0%)	0 (0%)
Positive Pru p 3	208 (43.9%)	22 (36.1%)	7 (21.9%)	12 (30.8%)	10 (45.5%)	14 (28.0%)	12 (60.0%)
Positive Pru p 4	94 (19.8%)	19 (31.1%)	4 (12.5%)	12 (30.8%)	6 (27.3%)	12 (24.0%)	3 (15.0%)
Positive Pru p 7	49 (10.3%)	3 (4.9%)	1 (3.1%)	6 (15.4%)	1 (4.5%)	5 (10.0%)	0 (0%)
Positive Cup s 7	36 (7.6%)	0 (0%)	0 (0%)	2 (5.1%)	0 (0%)	3 (6.0%)	0 (0%)

Characteristics	Vilnius (*N* = 133)	Sofia (*N* = 34)	Reykjavik (*N* = 32)	Milan (*N* = 95)	Madrid (*N* = 118)	Athens (*N* = 112)	Sagamihara (*N* = 35)	*p*
Age, mean (SD)	27.8 ± 12.9	17.9 ± 12.7	30.1 ± 10.5	39.2 ± 14.7	21.4 ± 13.9	26.7 ± 11.6	19.9 ± 19.9	**<.001**
Female sex	75 (56.4%)	15 (44.1%)	18 (56.3%)	59 (62.1%)	58 (49.2%)	51 (45.5%)	19 (54.3%)	**.006**
Age onset, mean (SD)[a]	13.8 ± 8.04	11.8 ± 8.50	14.4 ± 10.1	27.9 ± 15.8	13.6 ± 10.2	12.9 ± 7.89	19.6 ± 20.0	**<.001**
Severity oFASS-3								
No symptoms	116 (87.2%)	21 (61.8%)	27 (84.4%)	32 (33.7%)	56 (47.5%)	73 (65.2%)	0 (0%)	**<.001**
oFASS-3 grade 1	9 (6.8%)	1 (2.9%)	0 (0%)	42 (44.2%)	35 (29.7%)	17 (15.2%)	0 (0%)	
oFASS-3 grade 2	5 (3.8%)	9 (26.5%)	4 (12.5%)	12 (12.6%)	16 (13.6%)	14 (12.5%)	15 (42.9%)	
oFASS-3 grade 3	3 (2.3%)	3 (8.8%)	1 (3.1%)	9 (9.5%)	11 (9.3%)	8 (7.1%)	20 (57.1%)	
Probable peach allergy	15 (11.3%)	5 (14.7%)	4 (12.5%)	56 (58.9%)	58 (49.2%)	36 (32.1%)	32 (91.4%)	**<.001**
Peach sensitization[b/c]								
Positive SPT peach	18 (13.5%)	11 (32.4%)	8 (25.0%)	25 (26.3%)	46 (39.0%)	83 (74.1%)	0 (0%)	**<.001**
Positive IgE to peach	122 (91.7%)	17 (50.0%)	22 (68.8%)	87 (91.6%)	86 (72.9%)	95 (84.8%)	24 (68.6%)	**<.001**

(Continues)

TABLE 1 (Continued)

Characteristics	Vilnius (N = 133)	Sofia (N = 34)	Reykjavik (N = 32)	Milan (N = 95)	Madrid (N = 118)	Athens (N = 112)	Sagamihara (N = 35)	p
CRD performed	32 (24.1%)	13 (38.2%)	20 (62.5%)	20 (21.1%)	60 (50.8%)	71 (63.4%)	34 (97.1%)	
Positive Pru p 1	26 (81.3%)	4 (30.8%)	9 (45.0%)	7 (35.0%)	7 (11.7%)	4 (5.6%)	11 (32.4%)	**<.001**
Positive Pru p 2	2 (6.3%)	1 (7.7%)	1 (5.0%)	0 (0%)	2 (3.3%)	2 (2.8%)	0 (0%)	.617
Positive Pru p 3	7 (21.9%)	4 (30.8%)	3 (15.0%)	13 (65.0%)	37 (61.7%)	62 (87.3%)	5 (14.7%)	**<.001**
Positive Pru p 4	5 (15.6%)	4 (30.8%)	6 (30.0%)	2 (10.0%)	9 (15.0%)	5 (7.0%)	7 (20.6%)	**.032**
Positive Pru p 7	2 (6.3%)	1 (7.7%)	0 (0%)	0 (0%)	7 (11.7%)	1 (1.4%)	22 (64.7%)	**<.001**
Positive Cup s 7	1 (3.1%)	1 (7.7%)	0 (0%)	0 (0%)	6 (10.0%)	0 (0%)	23 (67.6%)	**<.001**

Note: All measurements are in *N* (%) unless otherwise specified. SPT/PTP was considered positive if allergen/histamine wheal ratios ≥0.5; ImmunoCAP if IgE levels ≥0.35 kU_A/L. *p* values between centers were determined for exploratory purposes (no correction for multiple testing) using the Pearson chi-square test for categorical variables and the ANOVA or Kruskall–Wallis test for continuous variables. Bold values indicates $p < .05$.

Abbreviations: CRD, component-resolved diagnostics; SPT, skin prick test; PTP, prick-to-prick test.

[a]Reported age of onset of symptoms against peach.

[b]The total number differs for the different centers and tests. Not all patients underwent all tests. The percentage given in brackets is the percentage of this variable total number that were tested.

[c]The results show the number and percentage of patients with positive sensitization according to each test.

3.3 | Relationships between IgE to peach components and other allergens in Europe

Correlations between the level of IgE to peach components and to inhalants and foods are shown in Figure 3 (overall) and Appendix S6 (per center). The strongest correlation overall was between IgE to Pru p 1 and to birch pollen ($\rho = .9$), with stronger associations ($\rho > .9$) in most centers with high birch pollen exposure (Northern/Central Europe, except Utrecht) compared to centers with low exposure ($\rho \leq .8$ in Madrid, Athens, and Reykjavik). IgE to Pru p 7 was moderately associated with pollen from all species except birch, but most strongly with IgE to Japanese cedar and cypress pollen (both $\rho = .7$). IgE to profilin (Pru p 4) was associated with all pollen species except birch pollen. IgE to Pru p 3 was hardly associated with sensitization to pollen.

Regarding the correlations between IgE to peach components and foods, the strongest correlation, overall and in most centers, was seen between IgE to Pru p 1 and hazelnut (3 and Appendix S6). IgE to Pru p 3 showed moderate associations with food specific IgE, the highest with walnut and only weakly with apple and peach. Only in Madrid and Athens, strong correlations were found with IgE to apple and peach ($\rho = .9$). For IgE responses against Pru p 4 and Pru p 7, overall, a broad pattern of associations was observed, with no food clearly standing out.

3.4 | Predictors for severity of peach allergy in Europe and Japan

Of the patients with probable peach allergy ($N = 477$), 349 (73.2%) reported mild to moderate symptoms (oFASS-3 grades 1/2) and 128 (26.8%) severe symptoms (oFASS-3 grade 3). Table 2 shows the results of the univariable analyses for factors associated with severe symptoms. Patients with severe peach allergy were significantly more likely to have a higher age of onset of peach allergy and probable mugwort pollen and/or latex allergy. Patients with a severe peach allergy had significantly higher median IgE levels against both GRP allergens, Pru p 7 and Cup s 7.

In Figure 4, the results of the multivariable analyses are presented. In model 1, "age of onset," "symptoms upon skin contact," "mugwort pollen allergy," "*Parietaria* pollen allergy" and "latex allergy" were selected as being positively associated with severity. In model 2, IgE against Japanese cedar pollen was added as a predictor to model 1, and in model 3, these were IgE levels to Pru p 4 and Pru p 7, while, "symptoms upon skin contact" did not have added predictive value anymore and was excluded. Model 4 selected IgE against Pru p 7 (positively associated with severity) and IgE against Pru p 3 and 4 (inversely associated).

The area under the curve (AUC) of model 1 was 0.61 and of model 2 0.63. In model 3, the AUC increased to 0.73. The optimal sensitivity and specificity of the models were for model 1: 0.39 and 0.81, for model 2: 0.53 and 0.67 and for model 3: 0.63 and 0.75. Also, model 4 had a poor predictive performance with an AUC of

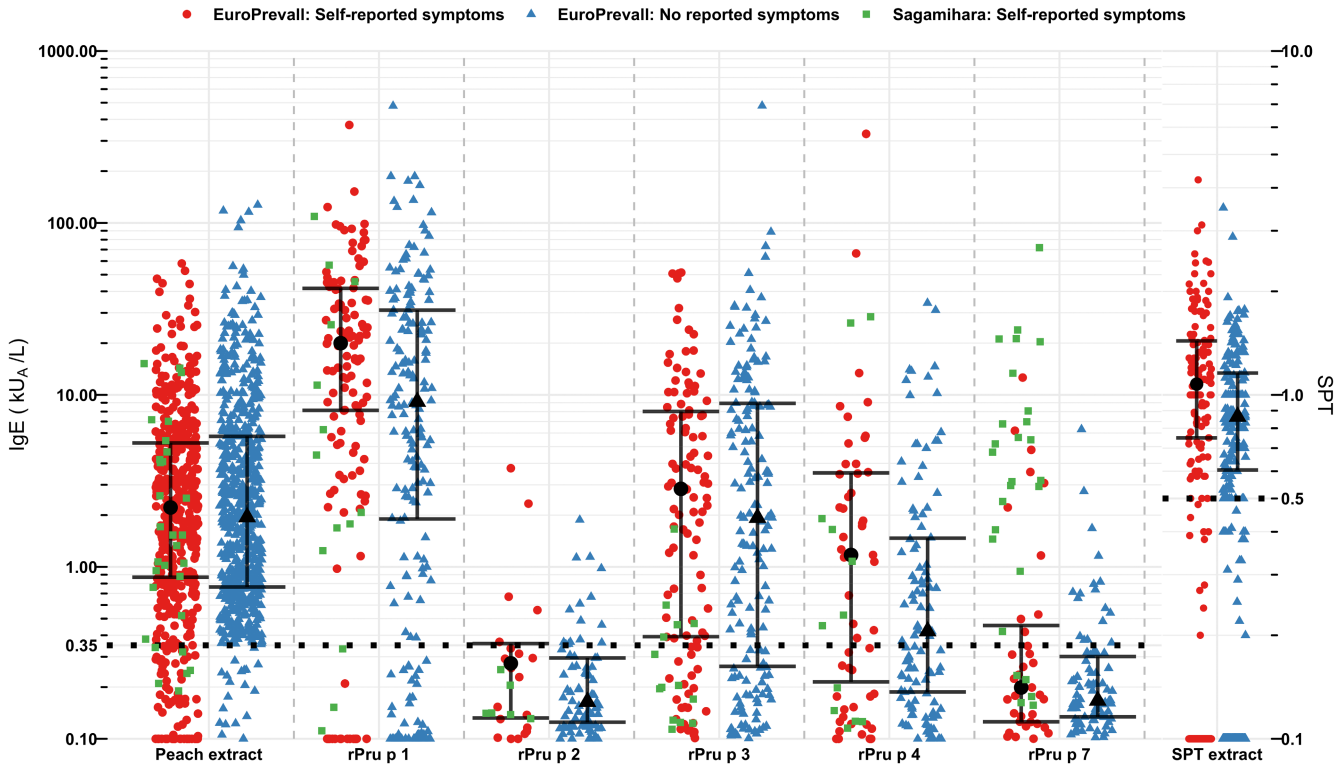


FIGURE 1 IgE to peach extract and peach allergens and size of skin prick test in patients with and without self-reported symptoms in twelve European centers and in patient with self-reported symptoms of Japan. The black symbols and error bars indicate the median IgE response and interquartile ranges of only the EuroPrevall data. SPT, skin prick test.

0.63 (Figure 4) and a sensitivity and specificity of, respectively, 0.58 and 0.66. When the model was built using European data only, very similar results were obtained with comparable AUC's (Appendix S7).

The developed model was then applied to a subset of patients of the EuroPrevall study that had a positive DBPCFC ($N=28$) or had a history of severe anaphylaxis to peach ($N=10$). The AUCs of prediction model 1 were somewhat lower (AUC 0.50) and of model 3 higher (AUC 0.80). The AUCs of model 2 and 4 remained the same (Figure 4).

4 | DISCUSSION

This study is the largest international study on peach allergy to date. Observed were regionally distinct sensitization patterns against peach, and correlations between peach and other allergens across Europe and Japan. A severity prediction model showed an AUC of 0.73 for distinguishing between mild-to-moderate and severe peach allergy.

4.1 | Distribution of (co-)sensitization patterns and correlations

The different sensitization patterns to peach components among geographical areas have similarities with those reported for walnut, hazelnut, and apple across Europe.[20–22] Sensitization to Pru p 1 (PR-10) dominated in birch pollen-exposed Northern and Central Europe and to Pru p 3 (LTP) in Southern Europe, but the latter was also common in Northern and Central Europe.[23] Almost 35% of the patients from Japan were (also) sensitized to Pru p 1. Since birch pollen are uncommon in Japan, this is likely due to sensitization to other tree pollen.[24] Sensitization to Pru p 3 in Japan was low, which might be explained by dietary differences.[25] Sensitization to Pru p 4 was variable but less clearly divided along a North–South axis,[26] while Pru p 2 (TLP) sensitization seems to plays a negligible role in peach allergy, similar to what was reported for apple allergy.[22] Finally, Pru p 7 was barely recognized in the European centers, where exposure to cypress pollen for most centers, with the exception of Madrid and Milan,[27] is generally low. For the Japanese patients, Pru p 7 was the dominant peach allergen, most likely driven by Japanese cedar pollen.[13]

Overall, IgE against Pru p 1 associated strongest with IgE to birch pollen and hazelnut and not so much to peach. Possible reason is that the hazelnut ImmunoCAP is spiked with rCor a 1. IgE against Pru p 3 showed the strongest (though moderate) association with IgE to walnut, followed by corn and lentil, but surprisingly not to peach and apple. Likely, the dominance of birch pollen and PR-10 sensitization has masked this association. When focusing on individual centers, IgE to Pru p 3 was strongly associated with that to peach and apple in Athens and Madrid, as reported by others.[22] Furthermore, these observations are suggestive for a more diverse spectrum of foods associated with LTP and peach sensitization.[28] Asero et al. also reported that IgE levels to peach in peach-allergic

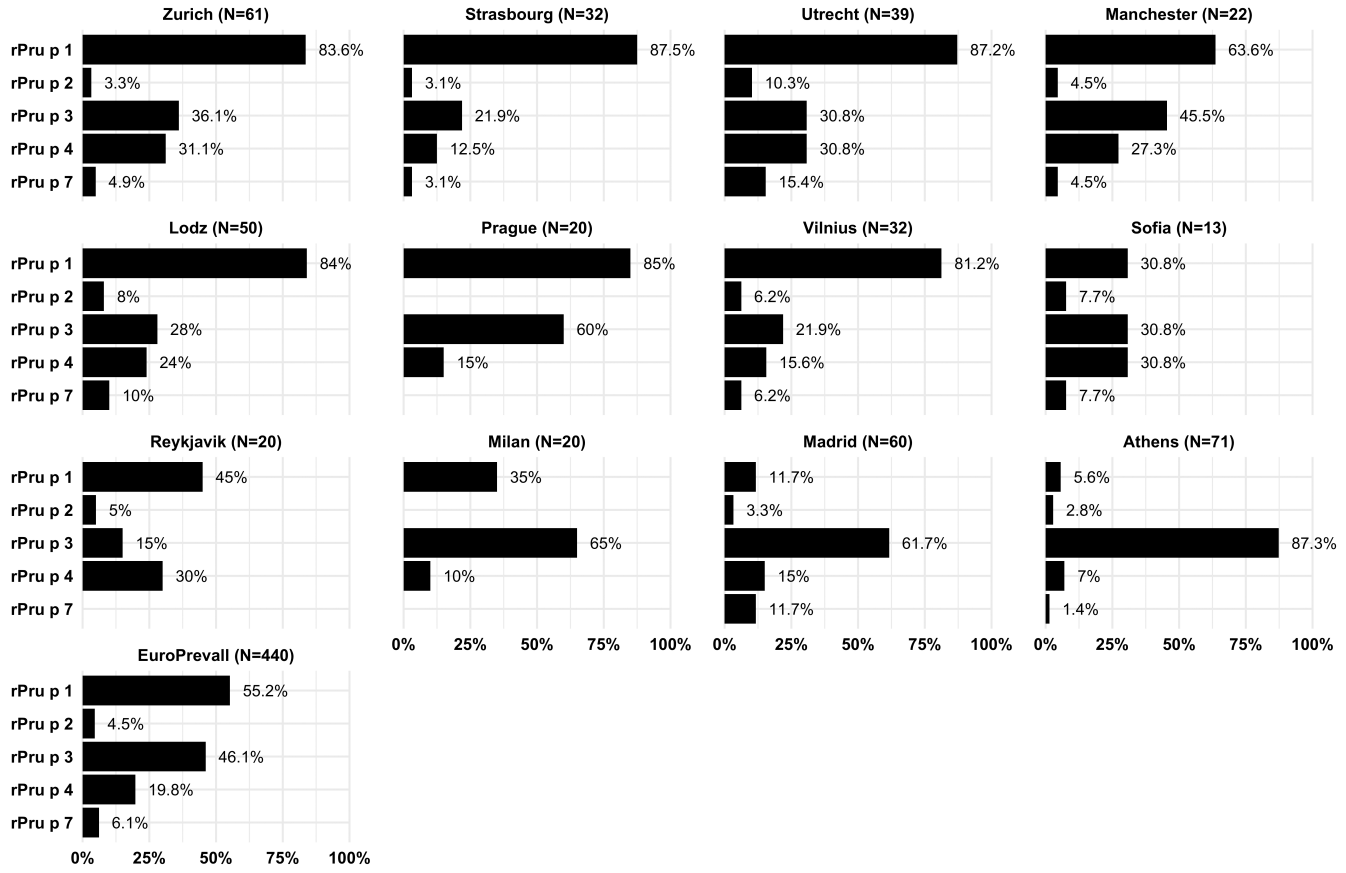


FIGURE 2 IgE to peach components (IgE levels ≥0.35 kU_A/L) across Europe among sensitized patients with or without reported symptoms.

adults mono-sensitized to LTP strongly correlated with sensitization to walnut, hazelnut, lentil and corn.[29]

The GRPs Cry j 7 and Cup s 7 in pollen of Japanese cedar and common cypress, respectively, both members of the *Cupressaceae* family, are considered the primary sensitizers of Pru p 7.[12,13] We observed high correlations between IgE to Pru p 7 and Japanese cedar and cypress pollen. All Japanese peach-allergic patients enrolled in the study were sensitized to Japanese cedar pollen, illustrating the dominant role of this pollen in peach allergy in Japan. Some caution is necessary, because Japanese peach-allergic patients with oral symptoms only were excluded, which may have biased toward Pru p 7 sensitization (Appendix S7). In the European centers, only 5.4% of the patients were sensitized to Pru p 7, which can be explained by low representation of centers with high exposure to cypress pollen.

4.2 | Prediction of severity of peach allergy

A model combining age of onset of peach allergy, having probable mugwort pollen, *Parietaria* pollen and latex allergy together with IgE levels to Pru p 7, Japanese cedar pollen and to Pru p 4 was found to have the highest accuracy for predicting severity of peach allergy in patients with a probable peach allergy. Although it would be preferable to study this in patients with challenge-confirmed peach allergy, this group was too small. Therefore, as second best, the developed model was applied to the subset of patients who had a positive DBPCFC or had severe anaphylaxis resulting in an even higher AUC, possibly supporting the generalizability of the model in peach-allergic patients.

The explanation for IgE to mugwort and *Parietaria* being associated with severity is not really clear but has been reported earlier. Lyons et al. showed that mugwort allergy was the strongest predictor for severity of walnut allergy.[20] It may be that LTPs in weeds contribute to the LTP syndrome by diversifying epitope recognition, but we have not analyzed that at a molecular level. The predictive factor latex allergy has been reported in earlier studies on severity of hazelnut and peanut allergy[30,31] and has been suggested as part of a cluster of skin-related risk factors, also including atopic dermatitis and symptoms upon skin contact.[32] The latter was selected in models 1 and 2 in the present study.

In our study, Pru p 7 was the only peach allergen positively associated with severe peach allergy. The hypothesis that this was only due to the biased Japanese selection could be rejected, because a post hoc analysis showed that this effect was also seen in Northern and Southern Europe (Appendix S7). Pru p 7 is a GRP with high stability to heat and resistance to digestive enzymes. Such properties might be related to the potential to induce severe allergic reactions, as described a.o. for LTP.[33,34] Other studies in Southern France[13]

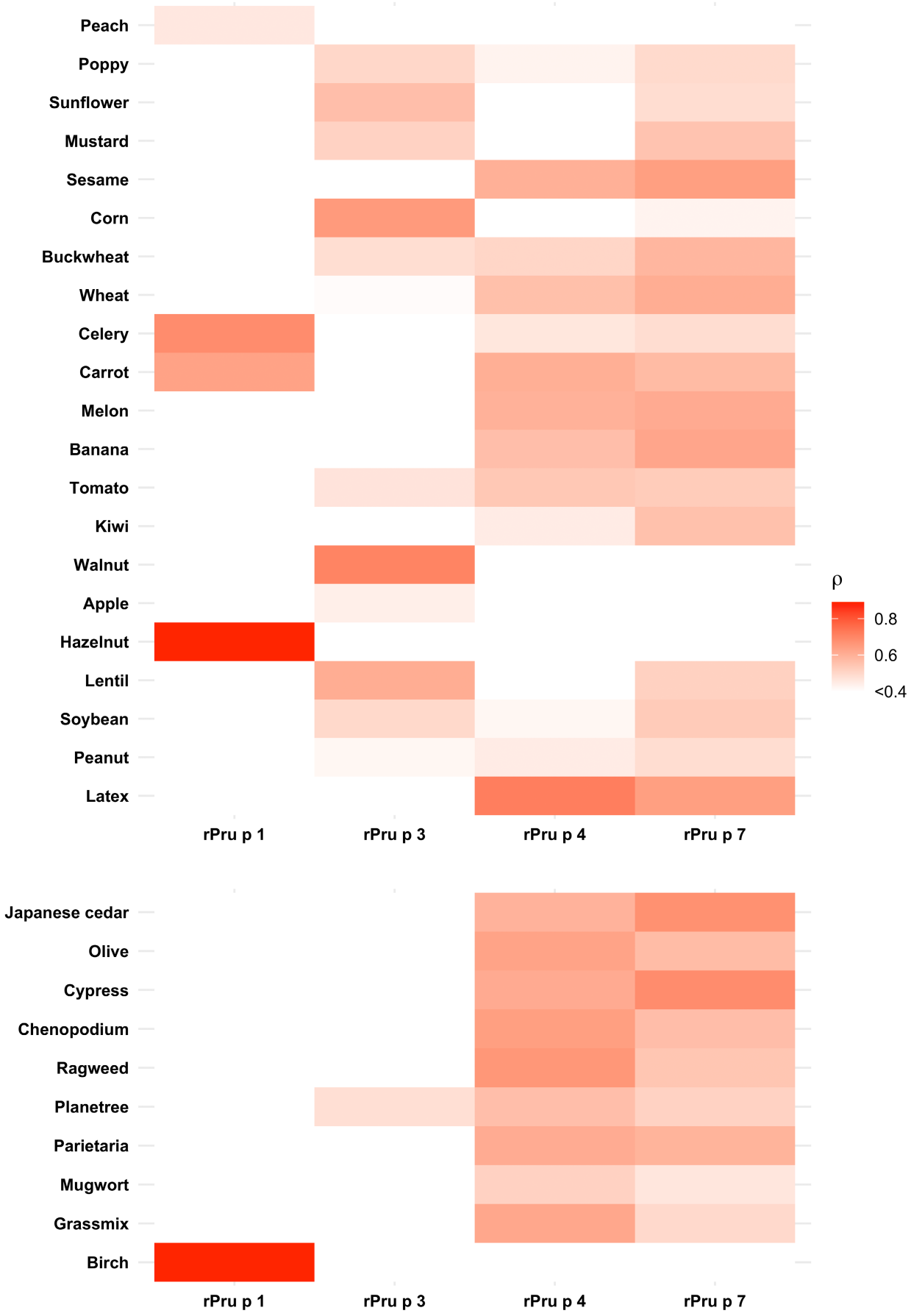


FIGURE 3 Correlation between IgE to peach components and IgE to pollen and foods other than peach across Europe.

TABLE 2 Predictors for severity of peach allergy in patients with probable peach allergy.

	oFASS-3 grades 1 or 2 (*N* = 349)	oFASS-3 grade 3 (*N* = 128)	*p*	Univariable OR (95% CI)
Demographics				
Age of inclusion (*y*) mean (±SD)	29.7 (±13.9)	32.2 (±14.7)	.089	1.01 (1.00–1.03)
Female sex	229 (65.6%)	85 (66.4%)	.872	1.04 (0.68–1.60)
Clinical history				
Age of onset (*y*)	19.6 (±12.8)	22.7 (±13.9)	**.026**	**1.02 (1.00–1.03)**
Family atopy	210 (65.2%)	74 (64.4%)	.867	0.96 (0.62–1.51)
Symptoms upon skin contact	53 (16.4%)	25 (22.7%)	.138	1.50 (0.87–2.54)
Pollen allergies				
Birch	216 (64.3%)	75 (62.5%)	.727	0.93 (0.60–1.43)
Grass	193 (57.4%)	73 (60.8%)	.518	1.15 (0.75–1.77)
Mugwort	30 (8.8%)	20 (16.4%)	**.024**	**2.02 (1.09–3.69)**
Parietaria	12 (3.6%)	9 (7.4%)	.086	2.18 (0.87–5.30)
Plane tree	10 (3.0%)	6 (5.0%)	.309	1.71 (0.57–4.71)
Cypress	10 (2.9%)	6 (5.2%)	.258	1.82 (0.61–5.01)
Olive	35 (10.4%)	10 (8.4%)	.528	0.79 (0.36–1.59)
Ragweed	24 (7.1%)	9 (7.6%)	.855	1.08 (0.46–2.31)
Chenopodium	26 (7.7%)	12 (9.9%)	.447	1.32 (0.62–2.66)
Other				
House dust mite allergy	79 (25.2%)	27 (26.2%)	.844	1.05 (0.63–1.73)
Latex allergy	15 (4.4%)	12 (9.4%)	**.040**	**2.28 (1.02–5.01)**
Cat/dog sensitization	106 (38.4%)	40 (42.6%)	.478	1.19 (0.74–1.81)
Japanese cedar sensitization	55 (41.9%)	16 (32.6%)	.256	0.67 (0.33–1.32)
Peach sensitization, median (Q1–Q3)[a]				
SPT peach extract	0.00 (0.00–0.35)	0.00 (0.00–0.58)	.940	1.01 (0.71–1.41)
IgE level peach extract	2.43 (0.95–5.39)	2.03 (0.91–5.19)	.937	0.91 (0.64–1.31)
IgE level rPru p 1	2.15 (0.01–19.95)	1.69 (0.01–22.21)	.875	1.02 (0.84–1.24)
IgE level rPru p 2	0.03 (0.02–0.06)	0.02 (0.02–0.07)	.766	0.91 (0.50–1.65)
IgE level rPru p 3	0.20 (0.06–3.09)	0.065 (0.04–1.41)	.090	0.77 (0.56–1.04)
IgE level rPru p 4	0.04 (0.01–0.15)	0.03 (0.02–0.08)	.213	0.81 (0.57–1.12)
IgE level rPru p 7	0.04 (0.03–0.09)	0.06 (0.03–0.48)	**.002**	**1.78 (1.24–2.58)**
Cupressaceae sensitization, median (Q1–Q3)[a]				
IgE level cypress pollen extract	0.19 (0.06–0.91)	0.19 (0.07–0.62)	.601	0.93 (0.70–1.23)
IgE level rCup s 7	0.02 (0.01–0.05)	0.03 (0.01–0.15)	**.013**	**1.40 (1.08–1.84)**
IgE level Japanese cedar	0.28 (0.06–1.64)	0.17 (0.04–0.95)	.271	0.81 (0.56–1.17)

Note: Results are given as *N* (%) or median with interquartile range (Q1–Q3), unless otherwise specified. Bold values indicates $p < .05$.

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation; SPT, skin prick test.

[a]For calculating the OR IgE levels to peach components and to *Cupressaceae pollen* sensitization were log-transformed to approximate a normal distribution of these variables.

and Japan[35] also found a relationship between Pru p 7 and severe peach allergy, although not absolute, as was demonstrated in a study from Italy.[36] It would be interesting to study the effect of Pru p 7 in more regions.

In the model, both IgE to Japanese cedar and IgE to Pru p 4 were inversely related to severe peach allergy which is in line with earlier reports.[11] However, the inverse association of IgE to Japanese cedar pollen with severity may seem unexpected, being a primary source of sensitization to Pru p 7. Because exposure to Japanese cedar pollen is virtually absent in Europe, primary sensitization to cypress pollen is likely the basis of the observed (cross-)sensitization to Japanese cedar. Nevertheless, in most cities exposure to cypress pollen is low. Therefore, sensitization to major allergens like Cup s 1 will likely dominate, and significant sensitization to Cup s 7 will only occur in areas with high exposure, as described for olive (Ole e 7 and 9)[37] and mugwort pollen (Art v 3).[38]

	Model 1 Demographics + clinical history + pollen allergy	Model 2 Model 1 + IgE to peach/cypress/ Japanese cedar extract	Model 3 Model 2 + IgE to peach components	Model 4 All peach components
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age onset (y)	1.01 (0.94 - 1.09)	1.01 (0.93 - 1.10)	1.02 (0.94 - 1.12)	
Symptoms upon skin contact	1.35 (0.76 - 2.41)	1.34 (0.71 - 2.53)		
Mugwort pollen allergy	1.44 (0.85 - 2.44)	1.48 (0.83 - 2.63)	1.56 (0.77 - 3.15)	
Parietaria pollen allergy	1.64 (0.79 - 3.39)	1.71 (0.80 - 3.67)	2.08 (0.83 - 5.21)	
Latex allergy	1.51 (0.92 - 2.47)	1.56 (0.82 - 2.99)	2.01 (1.22 - 3.30)	
Japanese cedar		0.88 (0.51 - 1.53)	0.76 (0.46 - 1.26)	
Pru p 4			0.86 (0.62 - 1.21)	0.79 (0.59 - 1.06)
Pru p 7			1.79 (1.18 - 2.70)	1.65 (1.14 - 2.38)
Pru p 3				0.83 (0.68 - 1.02)
AUC	0.61 (0.61 - 0.61)	0.63 (0.62- 0.64)	0.73 (0.73 - 0.74)	0.63 (0.63 - 0.63)
AUC DBPCFC	0.50 (0.47 - 0.54)	0.61 (0.58 - 0.65)	0.80 (0.79 - 0.81)	0.65 (0.64 - 0.65)

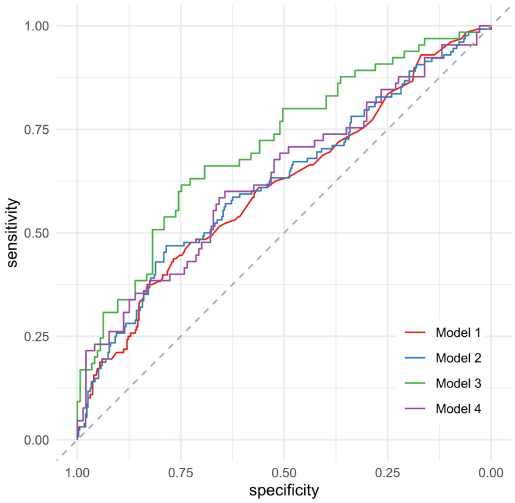


FIGURE 4 Prediction models and ROC curves of the four models for predicting the severity of peach allergy. The area under the curve (95% confidence interval) is presented in the plot legends. For the DBPCFC subgroup, only European patients were included. CI confidence interval; OR, odds ratio.

Another surprising observation was that IgE to Pru p 3 tended to be inversely associated with severity. This may be explained by the regional differences; a univariable logistic regression with regional interaction term showed a trend toward a positive association between the level of IgE to Pru p 3 and severity in Southern Europe while in Northern Europe this tended to be inversely associated (1.05 vs. 0.86, $p = .135$; Appendix S7). The lack of significance can be attributed to the low number of patients in Northern Europe with severe symptoms ($n = 27$). It is unclear why sensitization to Pru p 3 in one area is associated with severity whereas in another area it is inversely associated.

Due to selection, the data in this study could not be generalized to the entire population. However, the aim of this study was to identify serologic, demographic, and clinical risk factors associated with severity of peach allergy to improve diagnosis, and not to provide solid unbiased prevalence data.

5 | CONCLUSION

To conclude we showed that sensitization to Pru p 7 was low and variable in the European centers but dominant in Japan and correlations between IgE to peach components with pollen and foods are similar to those of other plant source foods. A model with reasonable predictive accuracy showed that a higher age of onset of peach allergy, having probable mugwort pollen, *Parietaria* pollen and latex allergy together with sensitization to Japanese cedar, Pru p 4 and Pru p 7 were the best predictors of a severe peach allergy.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to conception, design or data collection of this study and have been involved in drafting or revising the manuscript. All authors have given final approval of the version to be published an agreed to be accountable for all aspects of the work. E. Kallen, A. Revers, and R. van Ree have full access to all the data in the study and take responsibility for the integrity of the data. E. Kallen and A. Revers take full responsibility for the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

M. Fernández-Rivas received grants or contracts from Instituto de Salud Carlos III, Spanish Government, Aimmune Therapeutics, Diater, and Novartis; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Aimmune Therapeutics, Ediciones Mayo S.A., Diater, Ga2LEN, HAL Allergy, GSK, MEDSCAPE, NOVARTIS, and EPG Health; is member of the Data Safety Monitoring Board at DBV and advisory board at Aimmune Therapeutics, Novartis, Reacta Healthcare, and SPRIM. B. Ballmer-Weber received consulting fees from ALK, Allergopharma, Menarini, Sanofi, Novartis, Thermofisher and Aimune and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from ALK, Menarini, Sanofi, Novartis, and Thermofisher. F. De Blay received grants or contract from Aimmune, Stallergenes Greer, GSK, ALK, Chiesi, and Regeneron. Y. Fukutomi received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Thermo Fisher Diagnostics KK. K. Hoffmann-Sommergruber received funding from Danube Allergy Research Cluster funded by the Country of Lower Austria to (P07) KHS; was Member of the EAACI board until 2022/07. J. Lidholm is employee at Thermo Fisher Scientific. E.N.C Mills received grants or has contracts from Food Standards Agency Patterns and prevalence of adult food allergy (FS101174), European Food Safety Authority (ThRAll; allergenicity prediction [with EuroFIR]) and from Innovate (ML for food allergy); has applied for a patent on oral food challenge meal formulations for diagnosis of food allergy; is member of the Advisory Board of Novartis and Advisory Committee on Novel Foods and Processes; and is shareholder of Reacta Healthcare Ltd. N.G. Papadopoulos received grants or contracts from Capricare, Nestle, Numil, Vianex; received consultancy fees from Abbott, Abbvie, Astra Zeneca, GSK, HAL, Medscape, Menarini/Faes Farma, Mylan, Novartis, Nutricia, OM Pharma, and Regeneron/Sanofi. S. Vieths received royalties or licenses from Schattauer Allergologie Handbuch, Elsevier Nahrungsmittelallergien and Intoleranzen and Karger Food Allergy: Molecular Basis and Clinical Practice; support for attending meetings and/or travel as Associate Editor of the Journal of Allergy and Clinical Immunology. R. van Ree received consulting fees from HAL Allergy, Citeq, Angany, Reacta Healthcare, Mission MightyMe, and Ab Enzymes; received payment of honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from HAL Allergy, Thermo Fisher Scientific and ALK; received payment for expert testimony from AB Enzymes; has stock option at Angany. The rest of the authors declare that they have no relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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