Original Article

Prevalence of Food Sensitization and Food Allergy in Children Across Europe

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What is already known about this topic? For adults, standardized data collection all across Europe has yielded prevalence estimates of food sensitization (FS) and of food allergy (FA) defined as symptoms plus IgE sensitization, that can be validly compared internationally. For children, such estimates are lacking.

What does this article add to our knowledge? Using methodology identical to that in adults, prevalence estimates of FS and FA, respectively ranging from 11.0% to 28.7% and from 1.0% to 5.6%, were found in school-age children across Europe. Both primary and cross-reactive FS and FA occurred frequently at this age.

How does this study impact current management guidelines? This study reveals the substantial geographical variation in the prevalence of FS and FA in school-age children across Europe, provides prevalence estimates for 24 commonly implicated foods in multiple countries, and facilitates valuable comparison with adults.

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This work was funded by the European Union through EuroPrevall (grant no. FP6-FOOD-CT-2005-514000).
Conflicts of interest: B. K. Ballmer-Weber reports personal fees from Thermo Fisher Scientific. M. Fernandez-Rivas reports grants and personal fees from Aimmune Therapeutics and Diater and personal fees from DBV, Allergy Therapeutics, HAL Allergy, Novartis, Thermo Fisher Scientific, and SPRIM. N. G. Papadopoulos reports personal fees from Novartis, Nutricia, HAL Allergy, Menarini/Faes Farma, Sanofi, Mylan/Meda, Biomay, AstraZeneca, GlaxoSmithKline (GSK), MSD, ASIT Biotech, and Boehringer Ingelheim and grants from Gerolymatos International SA and Capricare. P. Xepapadaki reports personal fees from Nutricia, Nestle, Friesland, Uriach, Novartis Pharma AG, and GSK. E. N. C. Mills reports grants from and is shareholder in Reacta Biotech. R. van Ree reports personal fees from HAL Allergy BV, Citeq BV, Angany Inc., and Thermo Fisher Scientific. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication January 8, 2020; revised March 5, 2020; accepted for publication April 6, 2020.
Available online April 21, 2020.
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2213-2198

https://doi.org/10.1016/j.jaip.2020.04.020

Abbreviations used
CCD- Cross-reactive carbohydrate determinant
DBPCFC- Double-blind placebo-controlled food challenge
FA- Food allergy
FS- Food sensitization
PR-10- Pathogenesis-related protein family 10

BACKGROUND: For adults, prevalence estimates of food sensitization (FS) and food allergy (FA) have been obtained in a standardized manner across Europe. For children, such estimates are lacking.
OBJECTIVES: To determine the prevalence of self-reported FA, FS, probable FA (symptoms plus IgE sensitization), and challenge-confirmed FA in European school-age children.
METHODS: Data on self-reported FA were collected through a screening questionnaire sent to a random sample of the general population of 7- to 10-year-old children in 8 European centers in phase I of the EuroPrevall study. Data on FS and probable FA were obtained in phase II, comprising an extensive questionnaire on reactions to 24 commonly implicated foods, and serology testing. Food challenge was performed in phase III.
RESULTS: Prevalence (95% CI) of self-reported FA ranged from 6.5% (5.4-7.6) in Athens to 24.6% (22.8-26.5) in Lodz; prevalence of FS ranged from 11.0% (9.7-12.3) in Reykjavik to 28.7% (26.9-30.6) in Zurich; and prevalence of probable FA ranged from 1.9% (0.8-3.5) in Reykjavik to 5.6% (3.6-8.1) in Lodz. In all centers, most food-sensitized subjects had primary (non−cross-reactive) FS. However, FS due to birch pollen related cross-reactivity was also common in Central-Northern Europe. Probable FA to milk and egg occurred frequently throughout Europe; to fish and shrimp mainly in the Mediterranean and Reykjavik. Peach, kiwi, and peanut were prominent sources of plant FA in most countries, along with notably hazelnut, apple, carrot, and celery in Central-Northern Europe and lentils and walnut in the Mediterranean.
CONCLUSIONS: There are large geograhical differences in the prevalence of FS and FA in school-age children across Europe. Both primary and cross-reactive FS and FA occur frequently. **(J Allergy Clin Immunol Pract 2020;8:2736-46)**

Key words: *Food allergy; Food sensitization; Prevalence; Causative foods; Cross-reactivity; Europe; Children*

INTRODUCTION

Prevalence of food allergy (FA) in children from European countries has been evaluated in several studies, using various study designs and outcome definitions. Studies published between 2000 and 2012 reveal estimates ranging from 5.7% to 41.8% for lifetime prevalence of *self-reported FA*, and from 1.6% to 24.4% for point prevalence of *self-reported FA* in 6- to 10-year-old European children.[1] Point prevalence of *food sensitization* (FS), which entails the presence of IgE antibodies against specific foods, and is a prerequisite for IgE-mediated FA, varies between 4.1% and 52.0% in the same age group.[1] The combination of typical clinical symptoms and IgE sensitization to the same food, which is required for FA diagnosis, is consensually termed *probable FA* by the European Academy of Allergy and Clinical Immunology.[2] The point prevalence of *probable FA* was found to be 4.6% in children of any age in a German study.[1,3] *Confirmed FA*, based on open or double-blind placebo-controlled food challenge (DBPCFC), is reported to occur in 0.4% to 4.2% of 6- to 10-year-old children in Europe.[1]

It is clear that reported prevalence estimates vary considerably, even between studies using the same definition of FA in similar age groups. A likely explanation is that there are geographical differences in prevalence and causative foods across Europe. However, the extent of these differences remains unclear due to methodological heterogeneity among studies conducted in different countries (eg, sampling methods and evaluated foods).

In adults, data from the well-standardized pan-European EuroPrevall project have permitted valid comparisons of FA prevalence estimates in multiple European countries. Analyses of these data have revealed the true geographical variation in the prevalence of FA in the European general adult population, and the foods involved.[4,5] Prevalence of self-reported FA in adults was found to range from around 1.0% to 18.9% for commonly implicated foods; prevalence of FS from 6.6% to 23.6%; and prevalence of probable FA from 0.3% to 5.6%, with plant-source foods dominating as causative foods.

In the current study, data collected during the EuroPrevall project from the general population of 7- to 10-year-old European children were evaluated, to provide prevalence estimates of self-reported FA, FS, probable FA and confirmed FA, and corresponding symptoms and causative foods. A distinction was made between animal- and plant-source foods, because pollen-related cross-reactivity may play a role in the latter.

METHODS

Study design

The 3 phases of the multicenter cross-sectional EuroPrevall study were described in detail previously.[6,7] Briefly, in phase I, a screening questionnaire (see "Food Allergy Screening Questionnaire for Children" in this article's Online Repository at www.jaci-inpractice.org) was distributed to randomly sampled 7- to 10-year-old children from the general population of Zurich (Switzerland), Madrid (Spain), Athens (Greece), Sofia (Bulgaria), Lodz (Poland), Vilnius (Lithuania), Reykjavik (Iceland), and Utrecht (The Netherlands). Twenty-four foods commonly incriminated in FA, or often consumed in participating countries, were deemed so-called *priority foods:* hen's egg, cow's milk, fish, shrimp, peanut, hazelnut, walnut, peach, apple, kiwi, melon, banana, tomato, celery, carrot, corn, lentils, soy, wheat, buckwheat, sesame seed, mustard seed, sunflower seed, and poppy seed. In phase II, responders reporting symptoms to 1 or more of these priority foods (cases) and a random sample of responders who did not report symptoms to any of the priority foods (controls) answered a more extensive questionnaire and underwent blood sampling to test for IgE against priority foods and common inhalant allergens. In phase III, DBPCFC was offered to subjects with self-reported symptoms and matching IgE against 1 of 9 priority foods selected for challenge testing (cow's milk, hen's egg, fish, shrimp, peanut, hazelnut, apple, peach, and celery).

All participating centers obtained local ethical approval, and all participants provided informed consent. All phase I, II, and III evaluations were completed between 2007 and 2009, with a median time interval of 5 months between phase I and II and 7 months between phase II and III.

Outcome definitions

The prevalence of the following FA definitions was explored:

1. *Self-reported FA:* symptoms ever reported to any food, and to any priority food.
2. *FS:* positive IgE serology (IgE $\geq$ 0.35 kU_A/L) for at least 1 of the 24 priority foods. FS was considered primary FS if positive IgE serology was not due to cross-reactivity with pollen (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Prevalence of primary FS was also established.
3. *Probable FA:* self-reported FA in combination with matching positive IgE serology (IgE $\geq$ 0.35 kU_A/L) for at least 1 of the 24 priority foods.
4. *Confirmed FA:* DBPCFC-confirmed FA to at least 1 of the 9 foods selected for challenge testing.

Further information on data collection is described in the "Supplementary Methods on Data Collection" section in this article's Online Repository at www.jaci-inpractice.org.

Statistical analysis

Based on data from phase I, the prevalence of self-reported FA was calculated as the percentage of responders reporting symptoms to any food, and to at least 1 priority food.

Data from phase II were used to estimate the prevalence of FS and probable FA. The percentages of subjects with these outcomes were weighted back according to the sampling scheme in each center (see "Weighting Procedure Prevalence Calculations" section in this article's Online Repository at www.jaci-inpractice.org; also see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Only subjects with available food serology were included. Subjects with discrepancies in the clinical questionnaires of phase I and II were excluded for calculation of probable FA (because of uncertainties regarding symptomatology), but were included in the study population for the calculation of FS. The Bulgarian site Sofia was excluded from analysis beyond phase I, because very few subjects participated in phase II (only 16 cases and 9 controls) to result in valid prevalence estimations.

Further exploration included examination of cross-reactivity in subjects sensitized to plant-source foods, where a distinction was made between subjects with only primary sensitization, likely pathogenesis-related protein family 10 (PR-10) cross-reactivity, likely profilin/cross-reactive carbohydrate determinant (CCD) cross-reactivity, or a combination of such sensitization patterns (Figure E1).

Regarding confirmed FA, phase III data yielded the number and percentage of subjects challenged with each of the 9 selected foods and the frequency of positive challenge test results. No prevalence estimates could be obtained because of the low number of challenges.

Analyses were conducted with SPSS version 25 (IBM Corporation, Armonk, NY) and R version 3.4.1 (R Core Team, Vienna, Austria).

RESULTS

Phase I—Self-reported FA

As shown in Figure 1, 16,935 subjects (59.2%) responded to the phase I screening questionnaire. Participating subjects had a mean age of 8.9 years, and 50.1% were males.

The prevalence of self-reported FA varied considerably between centers, ranging from 13.1% to 47.5% for any food and from 6.5% to 24.6% for priority foods (Figure 2, *A* and *B*). Prevalence was lowest in Athens, and notably high in Vilnius and Lodz.

The priority foods most commonly reported for self-reported FA in the overall population were cow's milk (20.3%), hen's egg (9.9%), tomato (5.2%), fish (3.6%), kiwi (2.9%), apple (2.1%), peanut (1.9%), wheat (1.7%), carrot (1.1%), and banana (1.1%). Self-reported FA to nonpriority foods, of which chocolate (13.0%), strawberry (5.8%), and orange (4.4%) were most often specified as causative foods, was particularly common in Vilnius and Lodz.

In both subjects with self-reported FA to any food and self-reported FA to priority foods, skin symptoms (61.6% and 70.2%, respectively) and gastrointestinal symptoms (39.5% and 37.3%, respectively) were reported most frequently (Table I). Notably, oral allergy symptoms, which are generally the first symptoms subjects with an IgE-mediated FA experience,[8,9] were only rarely reported in relation to self-reported FA in North-Eastern Europe (Vilnius, Lodz), that is, 5.8% to 6.5% for any food compared with 16.3% on average over all centers, and 8.1% to 9.2% for priority foods compared with 23.4% on average.

Phase II—FS

Prevalence of FS was estimated through evaluation of 2196 subjects with available food serology participating in phase II.

Figure 2, *C*, shows that prevalence estimates of FS ranged from 11.0% in Reykjavik to 28.7% in Zurich. Although prevalence estimates for each specific food varied substantially between centers, there was considerable overlap in the most common causative foods, as seen in Figure 3. The foods most frequently causing FS in the different centers included animal-source foods cow's milk and hen's egg and plant-source foods banana, wheat, hazelnut, apple, peach, kiwi, tomato, celery, carrot, sesame seed, and peanut. Prevalence estimates of FS for all priority foods are available in Table E1 in this article's Online Repository at www.jaci-inpractice.org. Fish was one of the least common sensitizers in all countries.

Prevalence of primary FS to all food types (both animal- and plant-source) in the total study population ranged from 8.6% in Reykjavik to 21.7% in Madrid (Table E1). On the basis of component-resolved diagnostics (Figure E1), most food-sensitized children in all centers had primary FS (78.7% of those sensitized), with the highest percentage in Athens (92.5%), followed by Madrid (85.4%), Reykjavik (84.4%), Vilnius (83.3%), Utrecht (76.2%), Lodz (74.4%), and Zurich (67.7%). Relatively, animal-source FS was most common in Athens (70.0% of those sensitized) and Reykjavik (60.9%), and least common in Madrid (48.8%) and Zurich (44.1%).

Focusing on subjects with plant-source FS, 63.2% of subjects had primary plant-source FS, 40.9% plant-source FS based on PR-10 cross-reactivity, and 28.5% plant-source FS based on profilin or CCD cross-reactivity. Figure 4 shows the overlap between primary plant-source FS and cross-reactive plant-source FS per center. Primary plant-source FS was most common in Madrid and Athens, PR-10 cross-reactivity occurred most frequently in Utrecht, Zurich, Lodz, and Vilnius, and profilin or CCD cross-reactivity occurred in 21.7% to 32.5% of plant-source food sensitized subjects in all centers.

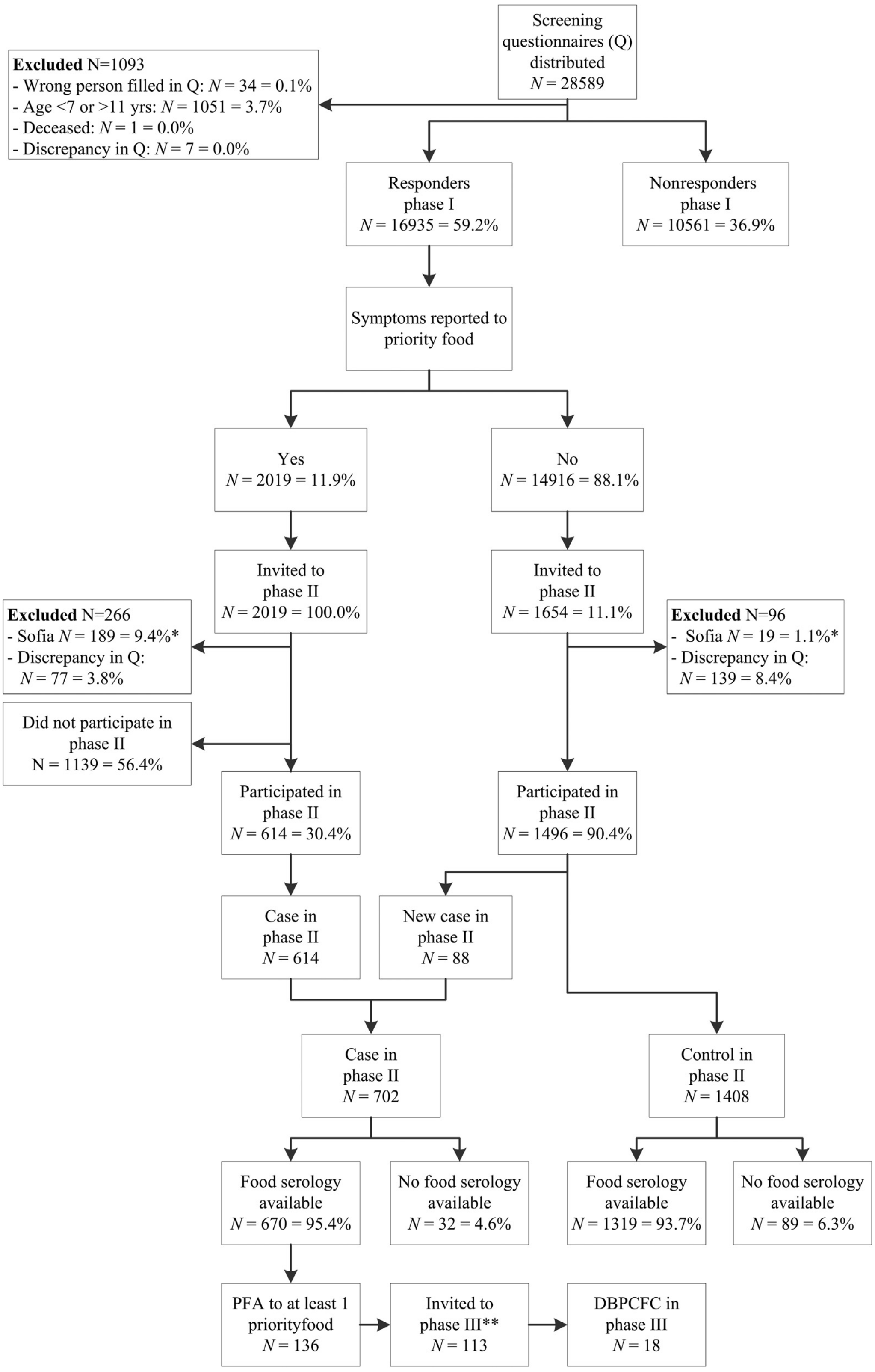

FIGURE 1. Flowchart. Case: subject self-reporting symptoms to at least 1 priority food; Control: subject not reporting symptoms to any priority food; New case: subjects who reported symptoms to priority foods in phase II, but symptoms to only nonpriority foods in phase I, most likely due to the maximum of 3 foods that could be reported in phase I (see "Food Allergy Screening Questionnaire for Children" in this article's Online Repository). *Sofia was excluded from calculation of probable FA prevalence because of lack of cases participating in phase I. **Probable FA to cow's milk, hen's egg, fish, shrimp, peanut, hazelnut, apple, peach, or celery. *PFA*, Probable food allergy.

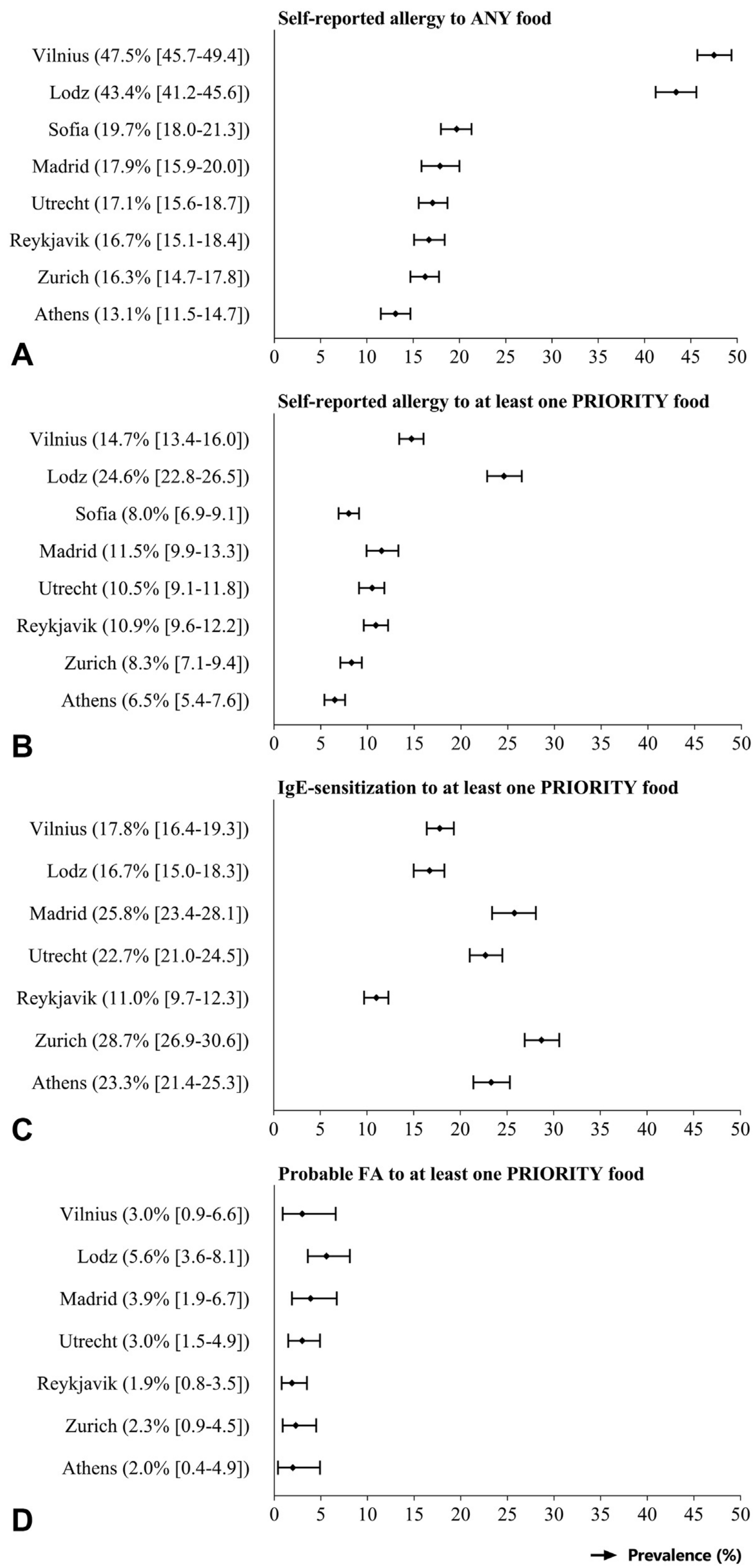

FIGURE 2. Prevalence of probable FA vs prevalence of self-reported FA and FS. (**A**) Self-reported allergy to any food. (**B**) Self-reported allergy to at least 1 priority food. (**C**) IgE sensitization to at least 1 priority food. (**D**) Probable FA to at least 1 priority food.

TABLE I. Reported symptoms for self-reported and probable FA

Characteristics and symptoms	Self-reported FA to any food (N = 4265)	Self-reported FA to priority food (N = 2019)	Probable FA to priority food (N = 136)
Age (y), mean ± SD	8.89 ± 1.01	8.85 ± 1.01	9.02 ± 0.99
Male sex	2116 (49.7)	1014 (50.3)	68 (50.0)
Oral allergy symptoms	631 (16.3)	438 (23.4)	75 (56.0)
Isolated oral allergy symptoms	122 (3.2)	89 (4.7)	7 (5.2)
Skin symptoms	2456 (61.6)	1344 (70.2)	108 (80.6)
Rhinoconjunctivitis	959 (24.7)	534 (28.6)	55 (42.0)
Gastrointestinal symptoms	1567 (39.5)	711 (37.3)	38 (29.5)
Difficulty swallowing	200 (5.2)	110 (5.9)	25 (19.2)
Respiratory symptoms	290 (7.5)	186 (10.0)	27 (20.8)
Cardiovascular symptoms	111 (2.9)	48 (2.6)	6 (4.6)
Other symptoms	1224 (31.4)	624 (33.4)	48 (37.2)
Lifetime frequency of reactions			
1×	986 (24.4)	276 (14.1)	12 (9.1)
2-4×	1315 (32.6)	540 (27.6)	38 (28.8)
>4×	1738 (43.0)	1137 (58.2)	82 (62.1)
Previous doctor diagnosis of FA	1671 (40.2)	1128 (56.9)	94 (70.1)

Values are n (%) unless otherwise indicated.
Oral allergy symptoms: itching/tingling/swelling of the mouth/lips/throat; Skin symptoms: rash/nettle sting/itchy skin; Rhinoconjunctivitis: runny/stuffy nose or red/sore/running eyes; Gastrointestinal symptoms: diarrhea/vomiting; Respiratory symptoms: breathlessness; Cardiovascular symptoms: fainting/dizziness; Other: stiffness in joints or headaches or other symptoms.

Phase II—Probable FA

Prevalence of probable FA was determined using the 670 cases with available food serology participating in phase II (Figure 1).

Overall, matching food serology was found in 17.2% of all self-reported FAs (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Probable FA to at least 1 priority food was established in 136 subjects. The prevalence of probable FA was much lower than the prevalence of self-reported FA and of FS, and was found to range from 1.9% in Reykjavik, to 2.0% in Athens, 2.3% in Zurich, 3.0% in Utrecht and Vilnius, 3.9% in Madrid, and 5.6% in Lodz (Figure 2, *D*).

Cow's milk, hen's egg, hazelnut, walnut, peanut, lentil, apple, peach, kiwi, banana, carrot, and celery were among the foods most often causing probable FA in the participating centers (Figure 5). Probable FA to cow's milk or to hen's egg was relatively common in all centers besides Zurich, where these 2 causative foods were not observed. Hazelnut, apple, carrot, and celery probable FAs were prominent in Central and Northern Europe (Zurich, Utrecht, Lodz, and Vilnius). Peach and kiwi were important causative foods in most countries, but were particularly dominant in Madrid. Probable FA to peanut was observed everywhere except Vilnius, and made the top 3 in Madrid and Reykjavik. In Athens, unique top causative foods were found compared with the rest of Europe, with walnut, lentils, and banana as some of the most common elicitors. Shrimp and fish were important causes of probable FA in Madrid (shrimp and fish), Athens (fish), and Reykjavik (shrimp and fish), but not in the rest of Europe.

Regarding symptoms, skin symptoms (80.6%) and oral allergy symptoms (56.0%) were most frequently reported by subjects with probable FA (Table I). Skin, oral allergy, rhinoconjunctivitis, laryngeal, respiratory, and cardiovascular symptoms were reported more often, and reactions occurred more frequently, in subjects with probable FA than in subjects with self-reported FA. Gastrointestinal symptoms were less common in subjects with probable FA.

Phase III—Confirmed FA

DBPCFC was performed in 18 subjects (Figure 1). Table II presents the results from challenge testing. Most challenges were performed with shrimp, peanut, hazelnut, and apple (N = 3 for each food). Overall, 7 of the challenges (38.9%) were positive, 6 (33.3%) negative, and 5 (27.8%) subjects were placebo reactors. The number of challenges performed was too small to obtain reliable values for prevalence of confirmed FA and corresponding symptomatology.

DISCUSSION

Summary of findings

The present study reviews the largest available data collection on FA and FS in European school-age children from the general population. It is the first to provide prevalence estimates obtained by uniform methods from socially and climatically varied regions all across Europe. Apparently, 6.5% to 24.6% of 7- to 10-year-old children across Europe report symptoms to at least 1 of 24 foods often implicated in FA (priority foods). A remarkable 11.0% to 28.7% of 7- to 10-year-old children are IgE-sensitized to at least 1 such food. The frequency with which symptoms and IgE sensitization coincide (ie, probable FA) is considerably lower, but still impressive at 1.9% to 5.6%. Cow's milk, hen's egg, hazelnut, walnut, peanut, lentil, apple, peach, kiwi, banana, carrot, and celery were top causative foods for probable FA in the participating countries.

Self-reported FA

With lifetime prevalence estimates of self-reported FA ranging from 13.1% to 45.6% for any food and from 6.5% to 24.6% for priority foods, the current study reveals considerable variation due to geographical location and evaluated foods. The wide range is similar to the 5.7% to 41.8% determined in a systematic review of European studies including children aged 6 to 10 years.[1]

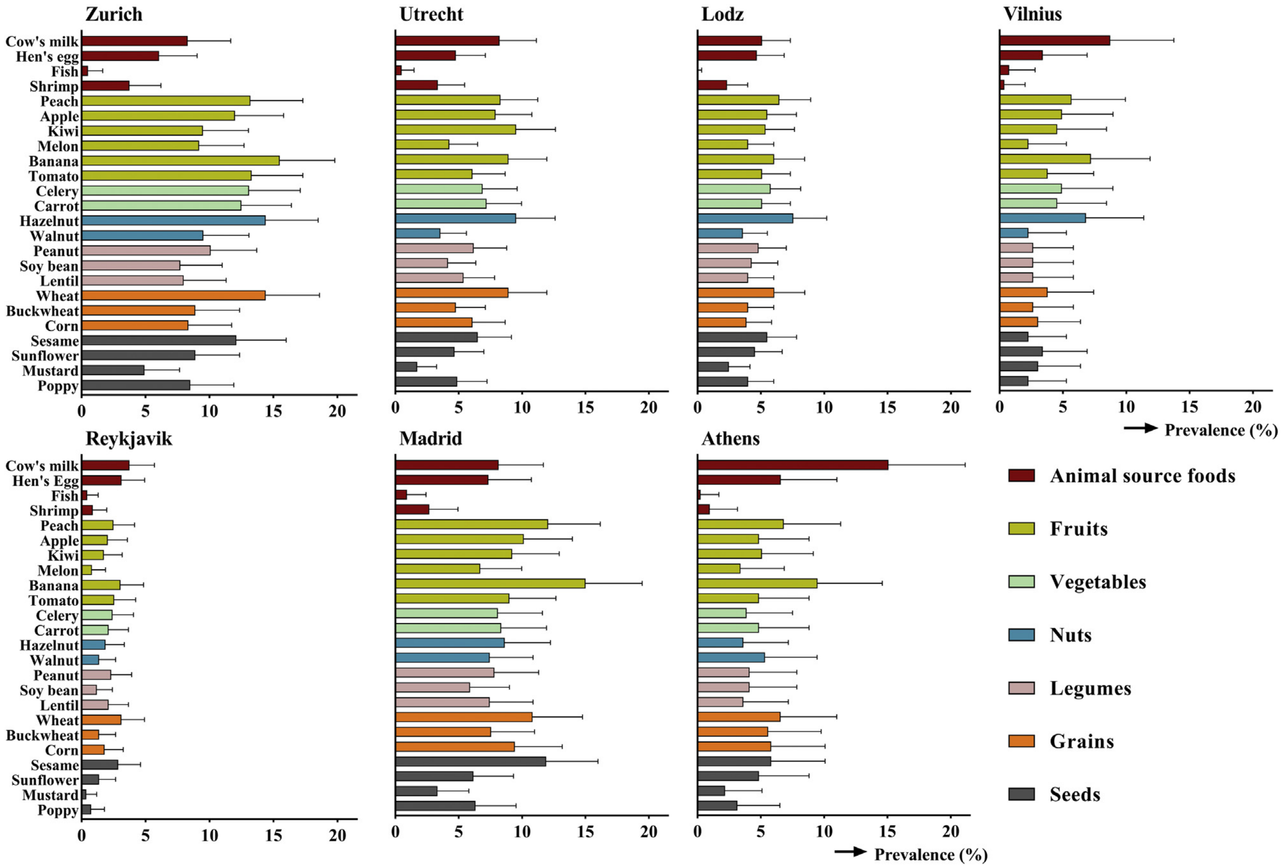

FIGURE 3. FS across Europe. This figure displays the prevalence of FS for each priority food in each center, and the upper limit of the 95% CIs. For numeric prevalence estimates of FS, view Table E1 in this article's Online Repository at www.jaci-inpractice.org. Foods are sorted according to food group. The birch-endemic centers are displayed in the top row.

Also comparable between our study and previous literature is that lifetime prevalence of self-reported FA in children appears highest in North-Eastern Europe (Lithuania, Poland) and lowest in South-Eastern Europe (Greece, Turkey)[1]; that, overall, cow's milk, fruits, and hen's egg are the most commonly reported foods[10]; and that skin-related and gastrointestinal symptoms are reported most frequently.[10]

Compared with other countries, North-Eastern European countries were found to have particularly high occurrence of self-reported FA to foods not selected as priority foods. Closer inspection of the data revealed that the nonpriority foods most often specified to cause FA were foods with suggested histamine-releasing capacities, such as chocolate, strawberry, and orange.[11]

Food sensitization

Regarding FS in school-age children, the standardized approach in the current study likely allowed us to obtain more homogeneous prevalence estimates from different European regions than a previous systematic review: 11.0% to 28.7% compared with 4.1% to 52.0%.[1] The observed FS patterns in our study correspond with transition from early childhood to adulthood FS patterns. On one hand, cow's milk and hen's egg sensitization, sources of FA most common in young children,[1] were some of the most prevalent causes of FS in the 7- to 10-year-old children in the current study. On the other hand, nonprimary FS based on cross-reactivity with pollen, which is the dominant source of FS in European adults, was also prominent in this age group (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org).[4,5]

Especially the major PR-10 protein in birch pollen, Bet v 1, is renowned for cross-reacting with certain food allergens in tree nuts, Rosacea fruits, and Apiaceae vegetables.[12,13] PR-10 cross-reactivity likely explains why hazelnut, apple, peach, kiwi, carrot, and celery were some of the most common sensitizing foods in the birch-endemic countries, Switzerland, the Netherlands, Poland, and Lithuania. PR-10 sensitization was found in 47.8% to 52.2% of plant-source food-sensitized children in these countries. In Greece and Spain, only 7.7% and 14.9% of plant-source food sensitized subjects had PR-10 sensitization. Sensitization to plant-source foods such as peach, apple, and kiwi in the Mediterranean is more likely due to primary sensitization, and partly through lipid transfer protein.[12,13]

FS based on cross-reactivity with profilin or CCD protein components in pollen (in birch, but also grass, mugwort, and *Parietaria*) was found in 21.7% to 32.5% of food-sensitized subjects. Such cross-reactivity with profilin/CCD goes some

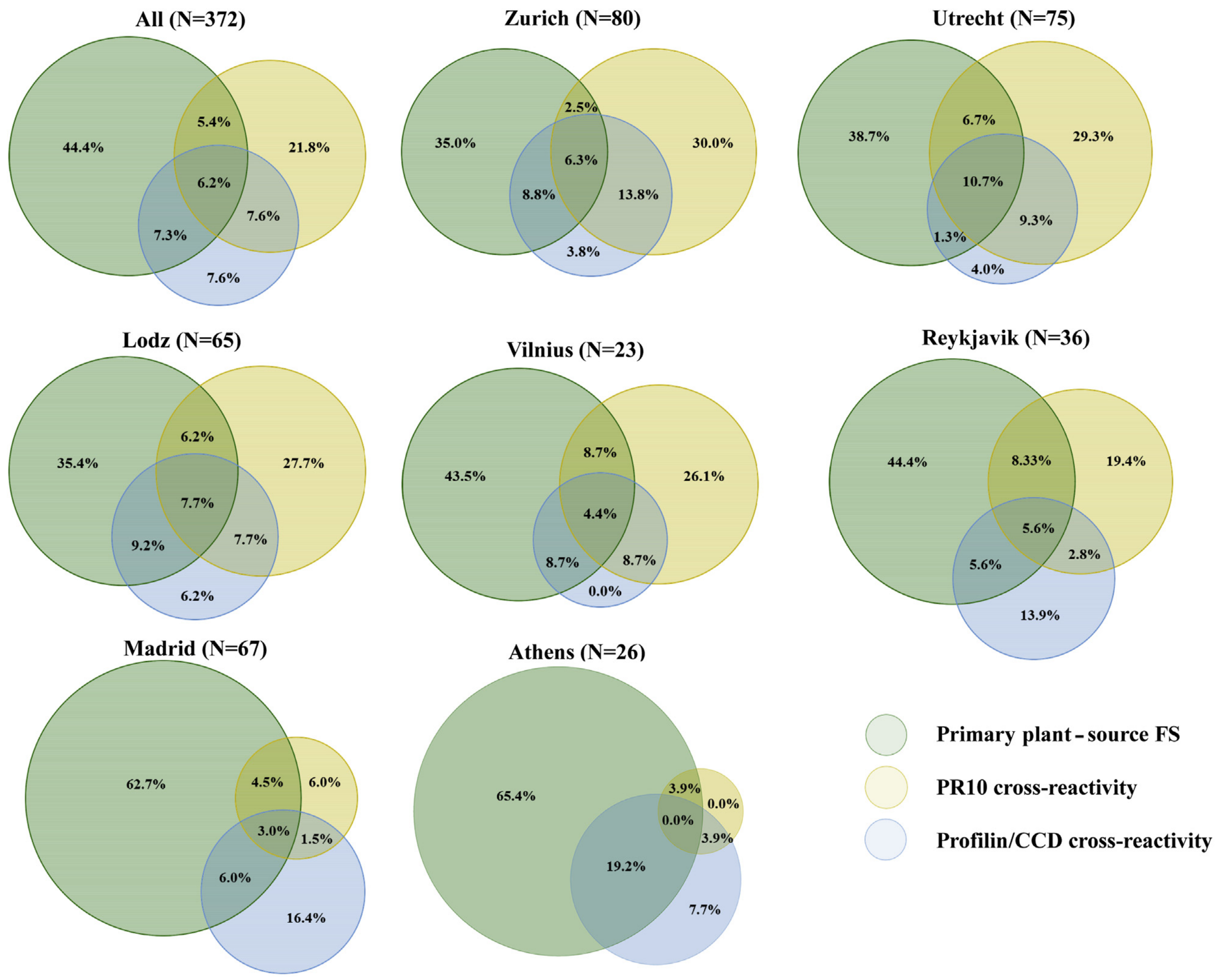

FIGURE 4. Plant-source FS: primary sensitization and cross-reactivity in children. For classification of primary sensitization, PR-10, CCD, and profilin cross-reactivity, view Figure E1. Only subjects with sensitization to plant-source foods are included in this figure.

way toward explaining the high levels of banana and wheat sensitization throughout Europe. Of subjects with FS to banana and wheat, respectively 77% and 92% were sensitized to grass, mugwort, *Parietaria*, or Bet v 2. Profilin and CCD are known to cause broader cross-reactivity than PR-10 proteins with plant-source foods,[14] but FS through profilin does not correspond with symptoms as consistently as FS through PR-10 protein, and CCD sensitization is generally thought to be clinically irrelevant.[15,16] This could help explain the low levels of probable FA to banana and wheat, in contrast to the high levels of FS.

Probable FA

In fact, most food-sensitized subjects did not have concurrent symptoms, and most subjects with self-reported FA appeared not to have an IgE-mediated FA (as viewed in Table E2). Overall, 1.9% to 5.6% of children across Europe were found to have a probable FA. We identified only 1 previous study providing a prevalence estimate for probable FA, defined as symptoms and matching IgE sensitization, in 1 country: 4.6% in 0- to 17-year old children from an unselected pediatric population in Germany.[1,3] This lack of evidence is rather surprising, because the prevalence of probable FA is a key prevalence estimate in FA epidemiology. Because patients in daily practice tend to decline the time-consuming and burdensome criterion standard of diagnostic testing, oral food challenge, probable FA is often the best attainable end point. This was clearly observed in our study, where too few subjects agreed to undergo DBPCFC to reliably determine the prevalence of challenge-confirmed FA.

Some notably common causes of probable FA were cow's milk, hen's egg, hazelnut, peanut, apple, peach, kiwi, and carrot. Birch pollen−related FA can explain the high prevalence of hazelnut, apple, peach, kiwi, and carrot probable FA in countries such as Switzerland, the Netherlands, Poland, and Lithuania. In the countries where birch pollen is not a key source of FA (Greece, Spain, and Iceland), animal-source foods and other plant-source foods appear higher up in the hierarchy of foods most commonly causing probable FA. The low prevalence of

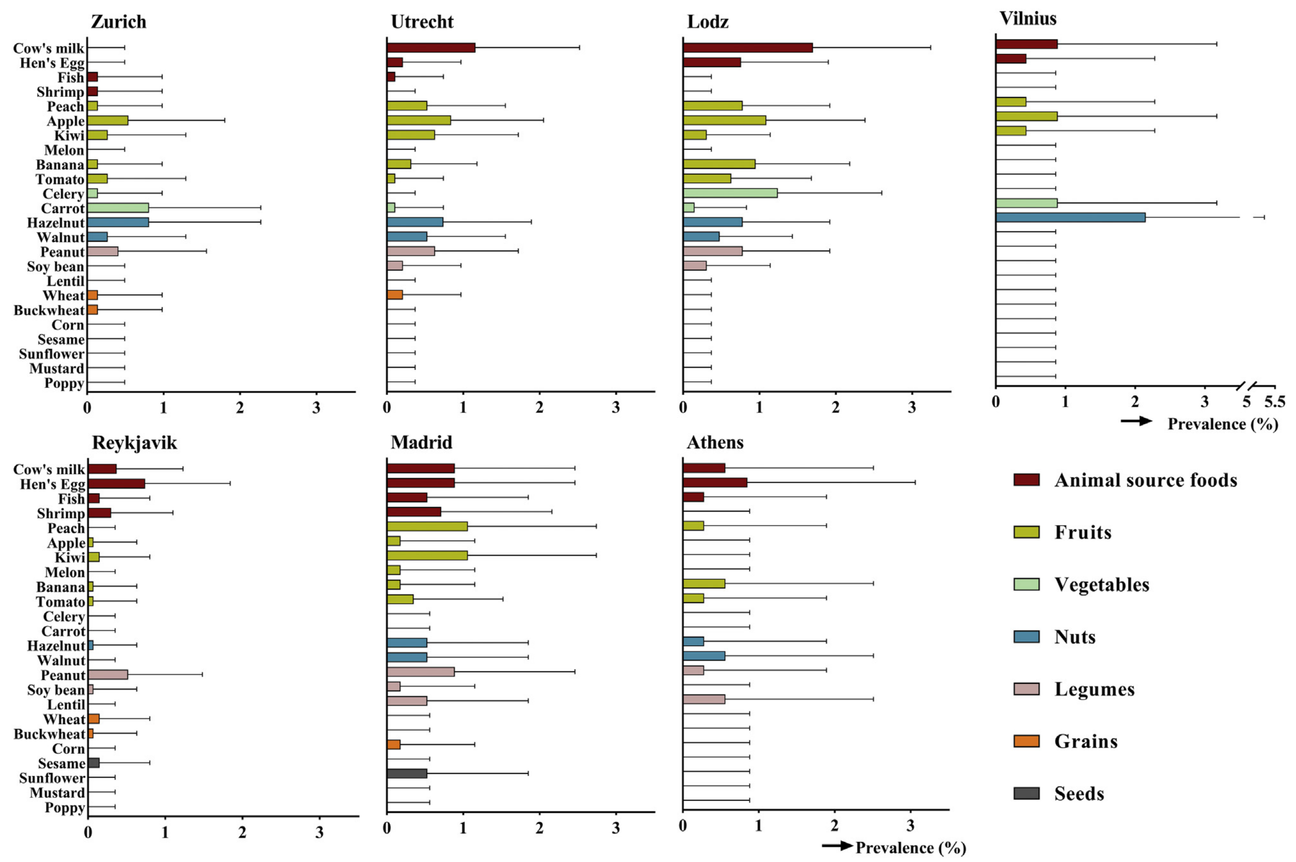

FIGURE 5. Probable FA across Europe. This figure displays the prevalence of probable FA for each priority food in each center, and the upper limit of the 95%CIs. For numeric prevalence estimates of probable FA, view Table E3 in this article's Online Repository at www.jaci-inpractice.org. Foods are sorted according to food group. The birch endemic centers are displayed in the top row.

cow's milk and hen's egg probable FA in Switzerland was a remarkable finding for which no clear explanation is apparent.

Interestingly, fish and shrimp were the least common sensitizing foods across Europe, but they were definitely not the least common causes of probable FA. In literature, fish and shellfish are 2 of the 8 foods suggested to cause most food-allergic reactions.[17] Apparently, subjects with fish and shrimp sensitization are likely to have concurrent symptoms. Fish and shrimp were among the top foods causing probable FA in Spain, Greece (for fish), and Iceland. This observation suggests that levels of exposure and frequency of consumption may increase the likelihood of probable FA for certain foods, because seafood consumption is highest in Southern and Northern Europe.[18]

Comparison to adults

The EuroPrevall population study was also conducted in 20- to 54-year-old adults during the same time period, in which the same study design was applied,[6] and the same food and outcome measures were investigated.[4,5]

One of the major differences between children and adults is observed on comparison of Figure 4 and Figure E3, which show patterns of cross-reactivity in respectively children and adults sensitized to plant-source foods. Where primary FS explains most plant-source FS in children, plant-source FS due to cross-reactivity dominates in adults, mainly due to birch pollen cross-reactivity in Switzerland, the Netherlands, and Poland.

Despite the relatively more frequent occurrence of cross-reactive FS in adults, overall FS was more prevalent in children

TABLE II. Challenge-confirmed FA

Food	No. of challenges*	Reactive	Tolerant	Placebo reactive
Cow's milk	2	0	2	0
Hen's egg	1	1	0	0
Fish	1	0	1	0
Shrimp	3	1	0	2
Peanut	3	2	0	1
Hazelnut	3	2	1	0
Apple	3	0	1	2
Peach	2	1	1	0
Celery	0	0	0	0
Total	18	7	6	5

*Three subjects were challenged in Zurich, 1 in Madrid, 1 in Athens, 5 in Utrecht, 1 in Lodz, 7 in Reykjavik, 0 in Vilnius. No challenges were performed with celery. None of the subjects underwent more than 1 challenge.

than in adults in all countries where both pediatric and adult populations were evaluated (Switzerland, the Netherlands, Spain, Poland, and Iceland). The prevalence of probable FA, however, was lower in children than in adults in Switzerland, the Netherlands, and Spain (>1.5% lower), and similar between children and adults in Poland, Iceland, and Greece (<1% difference).[5]

Although the high prevalence estimates of FS compared with probable FA in children may be influenced by high nonresponse rates, a more likely explanation is an increase in the prevalence of FS over time,[19-21] without a parallel increase in symptoms. This theory is supported by recent analyses of longitudinal data from the Isle of Wight Birth Cohort study, where the temporal rise in the prevalence of FS was found to be much more prominent than the rise in the prevalence of FA in children followed from infancy to age 18 years.[22]

Why the prevalence of probable FA is lower in children than in adults in some countries, and not in others, is likely related to the geographical differences in pollen exposure, which plays a role in the prevalence of cross-reactive FS and associated FA (Figures 4 and E3). Both birch pollen— and profilin-related FA occur regularly in adults,[12,13,23,24] and the gap between the percentages of children and of adults demonstrating cross-reactivity with these allergens in Zurich (birch), Utrecht (birch), and Madrid (profilin) may partly explain why probable FA is more common in adults than in children in these countries in particular.

Strengths and limitations

As discussed, a limitation of the present study was the large number of subjects refusing participation in phase III, which prevented acquisition of prevalence estimates for challenge-confirmed FA. It is also important to be aware that the true prevalence estimates of probable FA are likely lower than found in this study. In adults, multiple imputation of missing data from nonresponders in phase II revealed that complete case analysis overestimates the prevalence of probable FA, because subjects with FA were more likely to participate in the study.[5] A similar selection bias in our pediatric population cannot be ruled out. Multiple imputation was deemed infeasible because of the high proportion of missing data, and a complete case analysis was preferred. Findings in adults suggest that prevalence estimates of probable FA to any priority food, when all nonresponders are included, are 1.5 to 5.5 times lower. For comparison of prevalence estimates in children and adults, unimputed data were used in both cohorts. One should further note that the prevalence of FS and of probable FA focused on 24 foods commonly implicated in FA or frequently consumed in participating countries, and nonpriority foods were not taken into account.

All in all, however, the data analyzed for this study are decidedly unique. They are the only pan-European data on FA ever collected according to the same predetermined protocol in a large sample of school-age children from the general population, making valid geographical comparisons possible for the first time. Furthermore, we were able to explore the prevalence of primary FS and cross-reactivity in the general population, and provide previously lacking prevalence estimates of probable FA, a valuable prevalence estimate for daily practice. Finally, because the same study design was applied in adults, the prevalence estimates for children can be compared with those previously published for adults.[5]

CONCLUSIONS

A remarkable percentage of 7- to 10-year-old children across Europe appear to be food sensitized, and to a somewhat lesser extent food allergic. Primary and cross-reactive FS, both of which appear clinically relevant in this pediatric age group, occur to varying degrees throughout Europe. Although cow's milk and hen's egg were found to be common causes of probable FA in most countries, the occurrence of reactions to various plant-source foods and seafood depends on geographical location, and is clearly related to pollen and, likely, food exposure.

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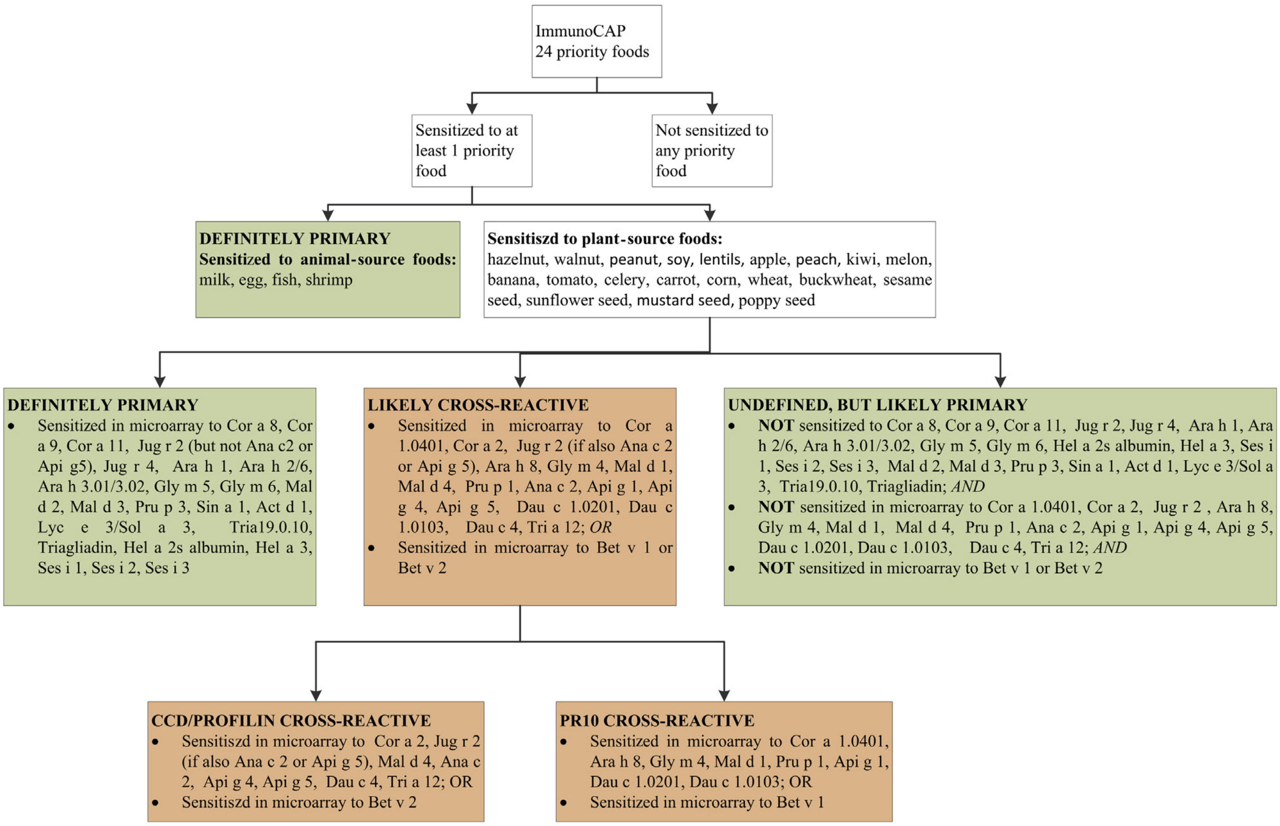


FIGURE E1. Classification of FS into primary sensitization and cross-reactive sensitization. Subjects were classified into 1 *or more* of the boxes depending on their sensitization patterns (ie, subjects could have both primary and cross-reactive sensitization). This is a simplified classification, designed for exploratory purposes, and subjects with cross-reactive sensitization through food rather than pollen, or with cross-reactive sensitization to tropomyosins (eg, shrimp through house-dust mite), have been classified as primary sensitization. However, aforementioned cross-reactivity patterns are much less common than pollen-related cross-reactivity, and are expected to have only limited influence on the prevalence estimates of primary FS. Green: Primary sensitization (= definite, or undefined but likely primary sensitization). Orange: cross-reactive sensitization.

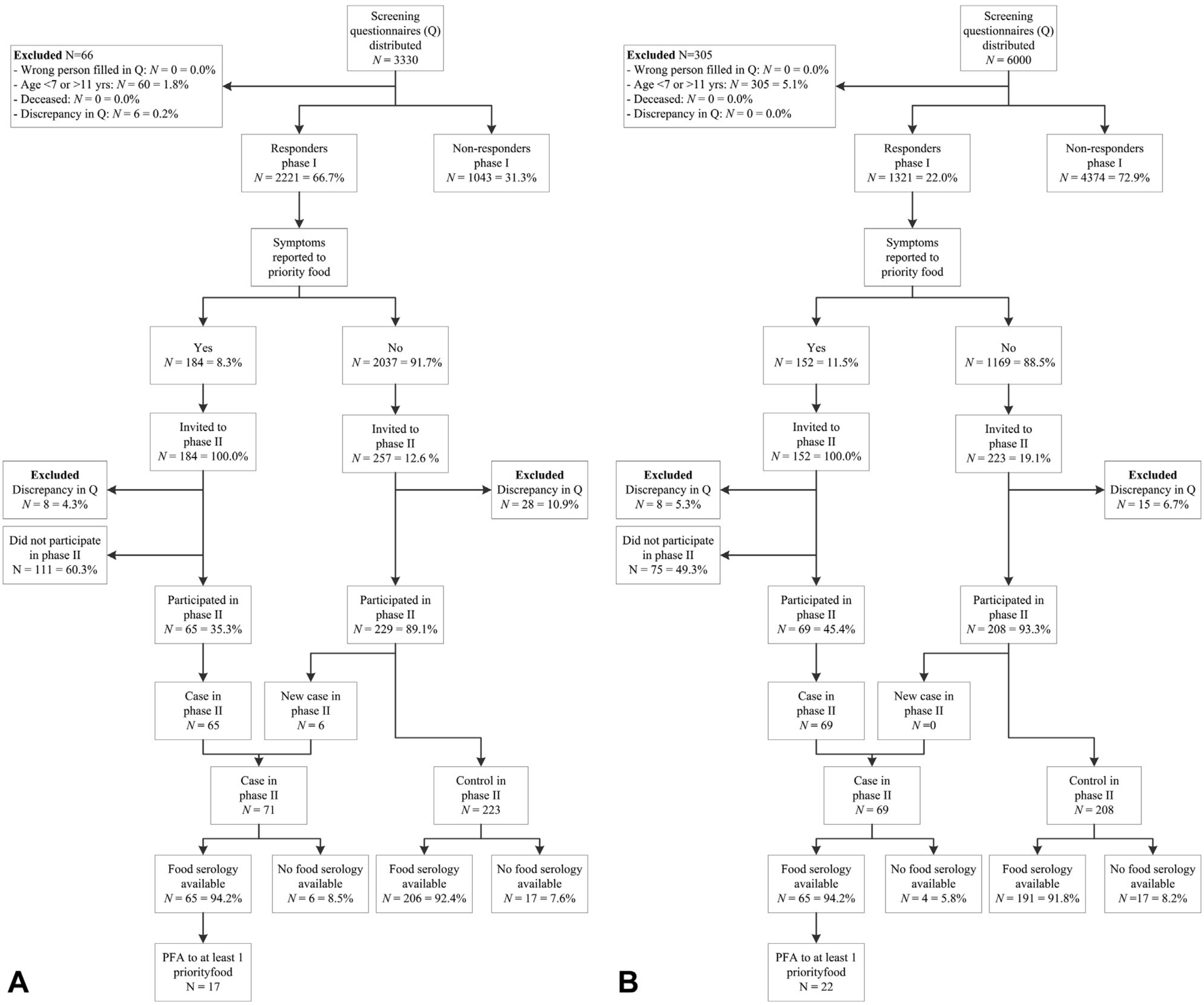


FIGURE E2. Flowcharts for **(A)** Zurich, (**B**) Madrid, (**C**) Athens, (**D**) Utrecht, (**E**) Lodz, (**F**) Vilnius, (**G**) Reykjavik, and (**H**) Sofia. Case: subject self-reporting symptoms to at least 1 priority food; Control: subject not reporting symptoms to any priority food; New case: subjects who reported symptoms to priority foods in phase II, but symptoms only to nonpriority foods in phase I, most likely due to the maximum of 3 foods that could be reported in phase I (see "Food Allergy Screening Questionnaire for Children" in this article's Online Repository at www.jaci-inpractice.org.). *PFA*, Probable food allergy.

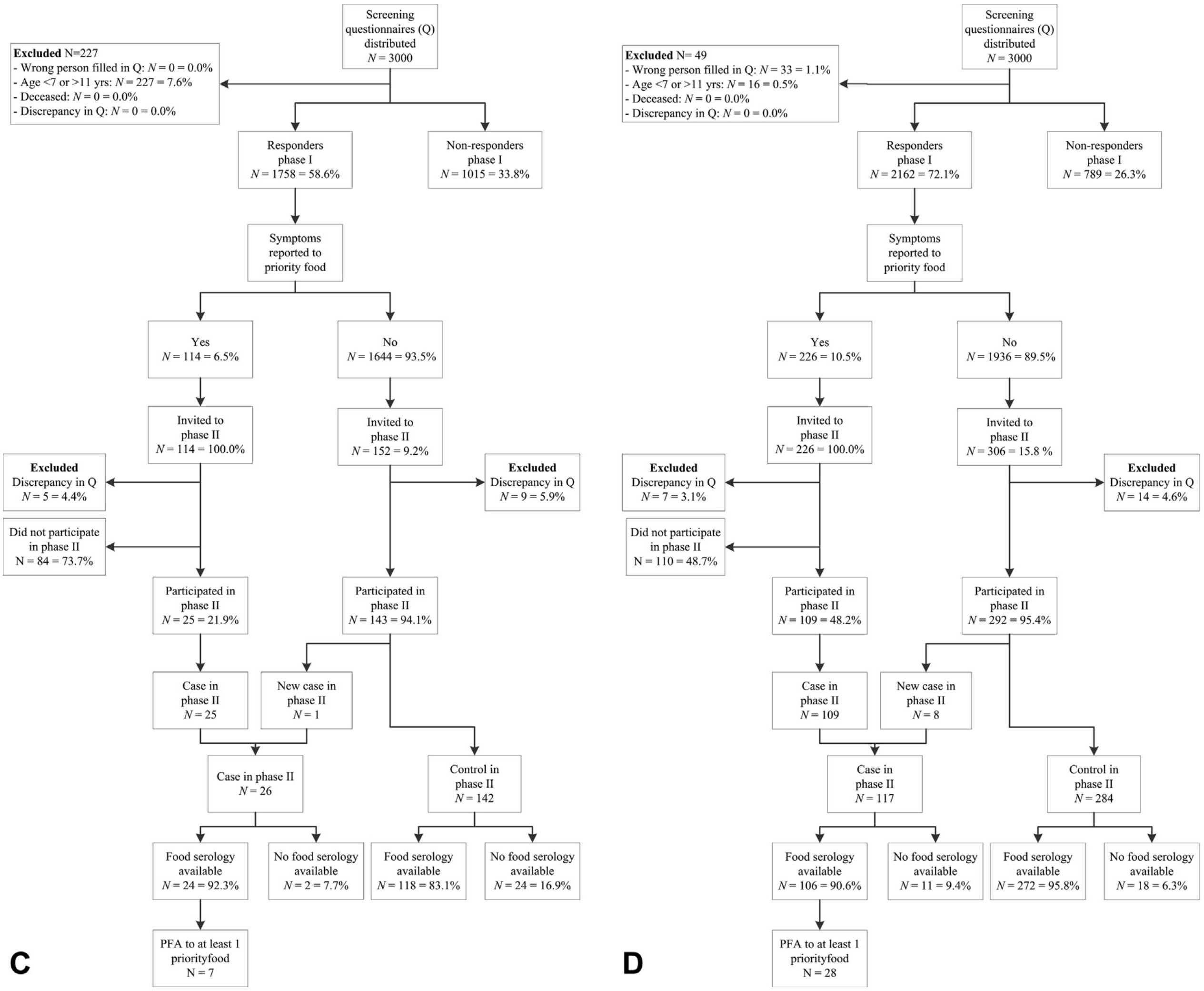
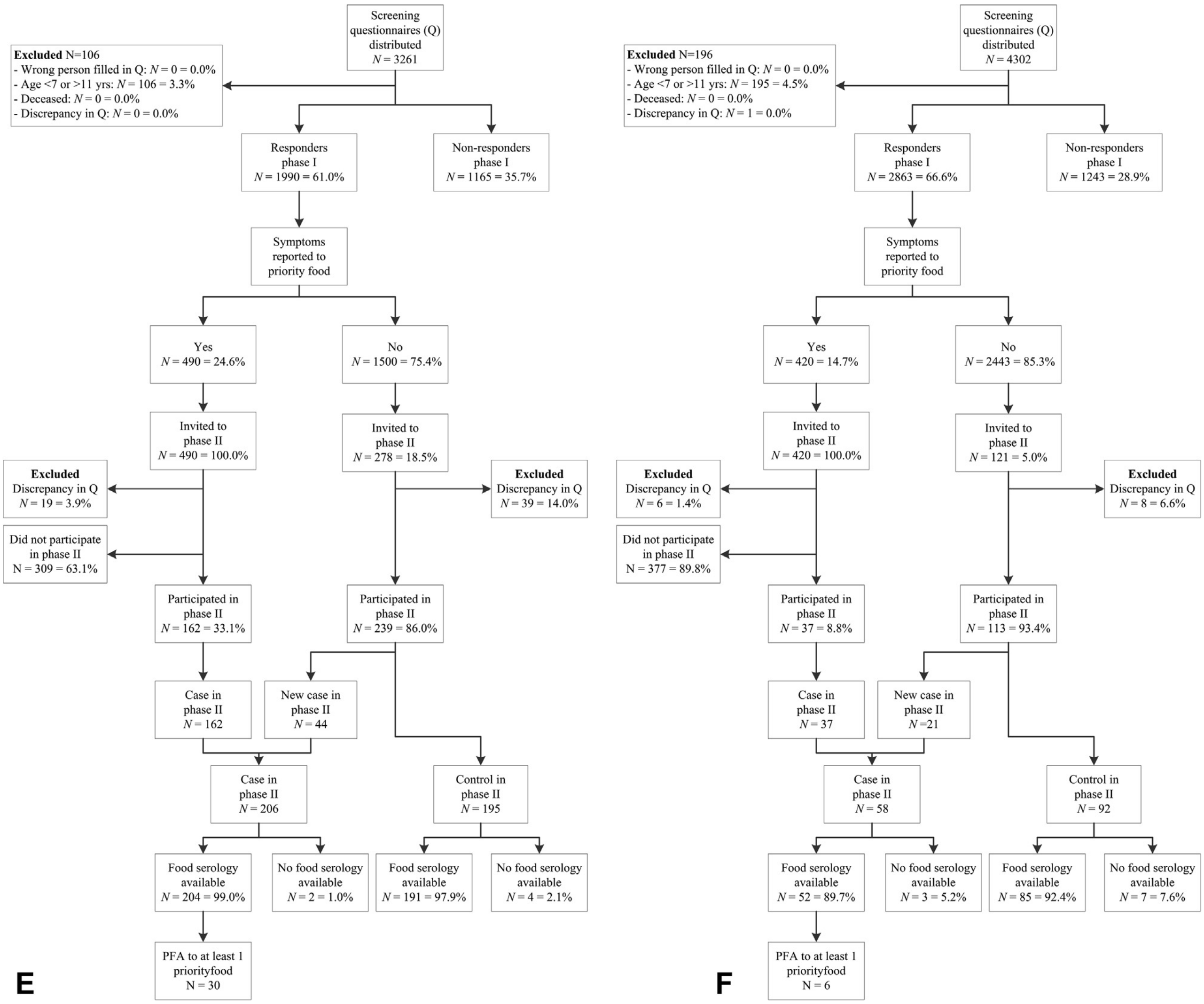


FIGURE E2. (*CONTINUED*).



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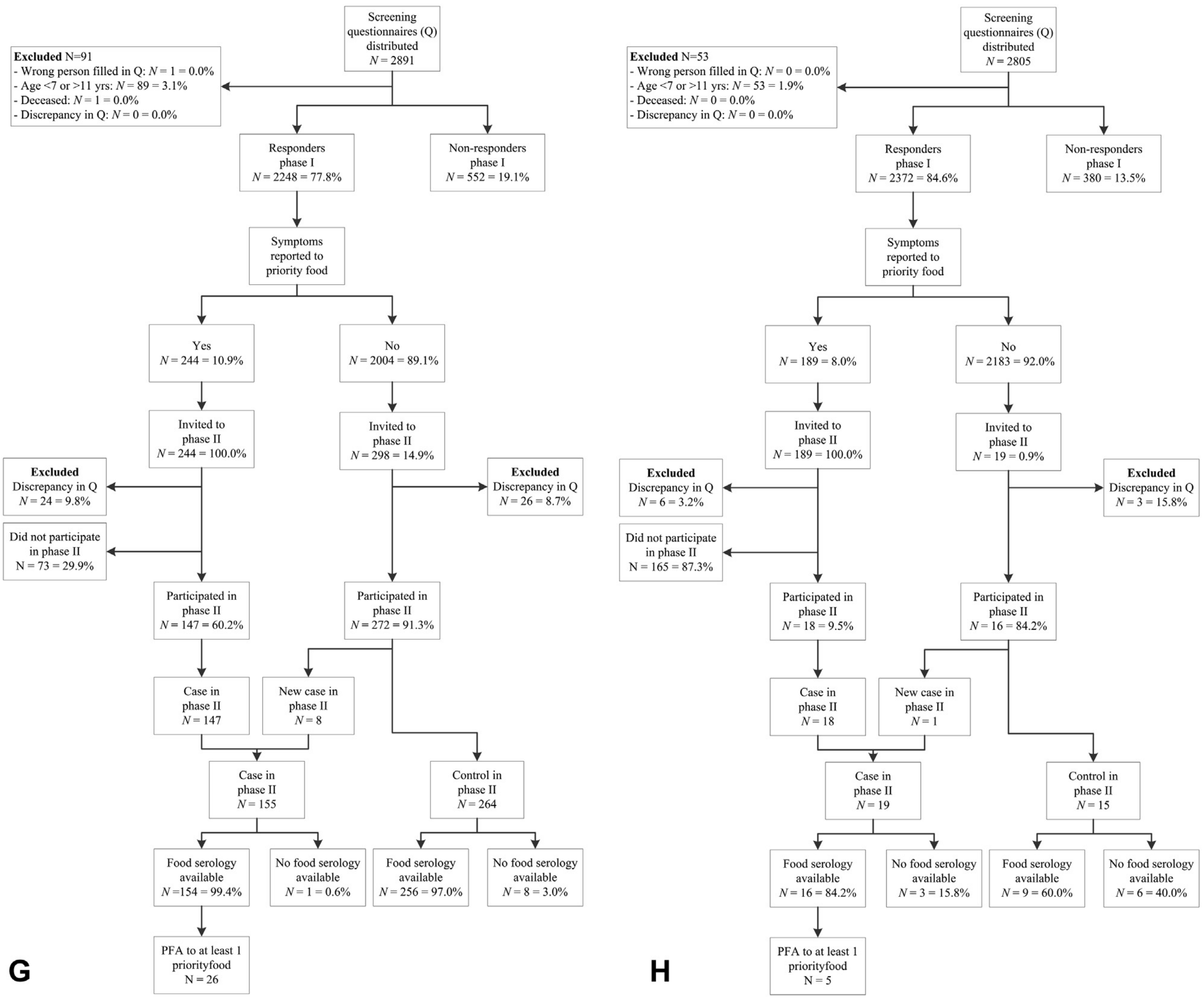

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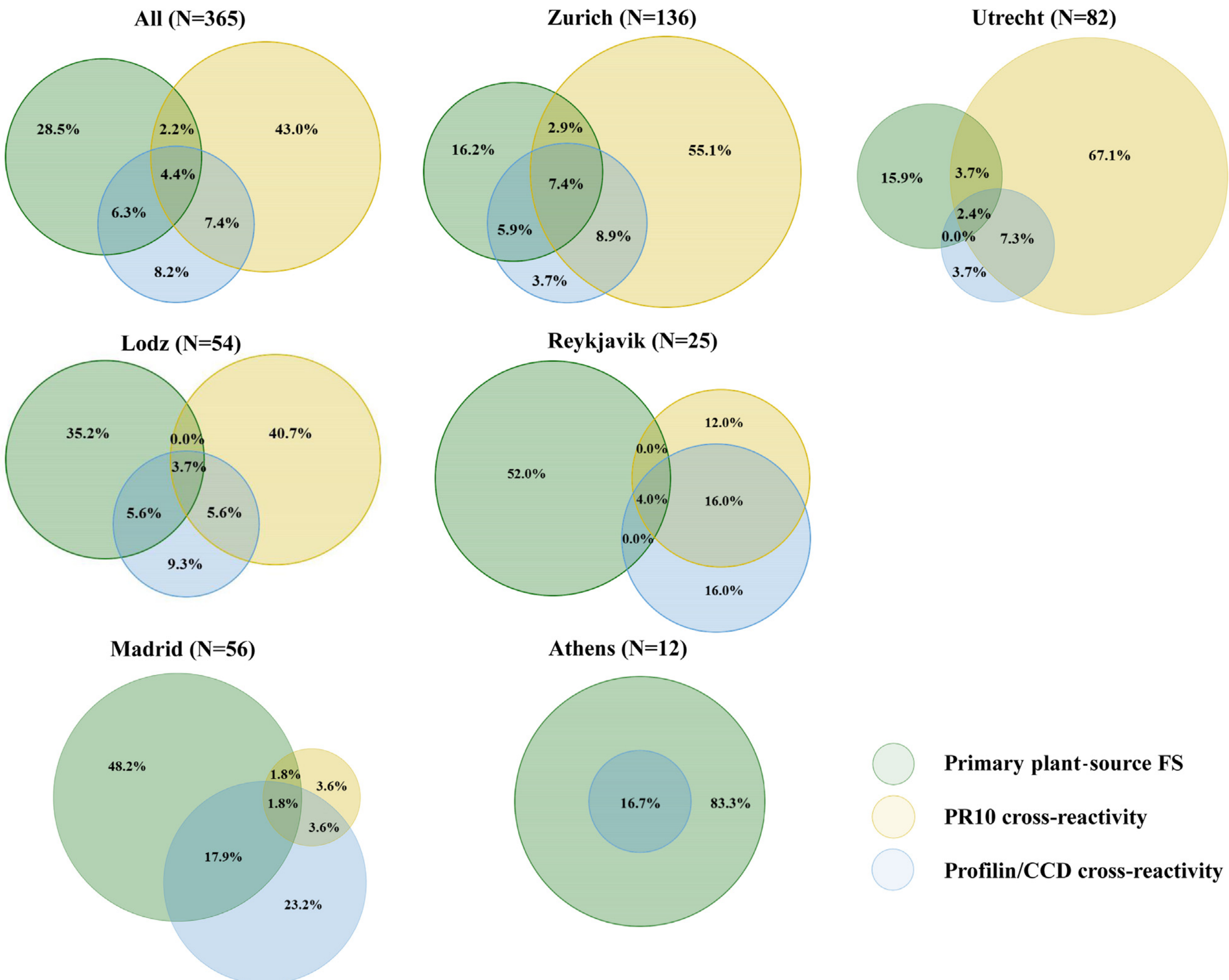

FIGURE E3. Plant FS: primary sensitization and cross-reactivity in adults. For classification of primary sensitization, PR-10, CCD, and profilin cross-reactivity, view Figure E1.

TABLE E1. Prevalence of FS per priority food and per center

Prevalence (95% CI) of FS to:	Zurich	Madrid	Athens	Utrecht	Vilnius	Lodz	Reykjavik
Banana	**15.46 (13.96-16.96)**	**15.01 (13.09-16.94)**	**9.48 (8.11-10.85)**	**8.93 (7.73-10.14)**	**7.21 (6.27-8.16)**	6.05 (5.00-7.10)	3.04 (2.33-3.75)
Wheat	**14.44 (12.98-15.90)**	10.83 (9.15-12.50)	6.56 (5.40-7.71)	**8.93 (7.73-10.14)**	3.79 (3.09-4.49)	**6.06 (5.01-7.10)**	**3.11 (2.39-3.82)**
Hazelnut	**14.35 (12.89-15.81)**	8.63 (7.12-10.15)	3.63 (2.76-4.51)	**9.52 (8.28-10.76)**	**6.82 (5.90-7.74)**	**7.56 (6.40-8.73)**	1.87 (1.31-2.43)
Tomato	13.27 (11.86-14.68)	9.00 (7.46-10.54)	4.85 (3.85-5.86)	6.09 (5.08-7.10)	3.79 (3.09-4.49)	5.09 (4.13-6.06)	2.55 (1.90-3.23)
Peach	13.21 (11.80-14.62)	**12.06 (10.30-13.81)**	**6.81 (5.63-7.98)**	8.30 (7.14-9.47)	5.68 (4.83-6.53)	**6.46 (5.38-7.54)**	2.49 (1.84-3.13)
Celery	13.09 (11.69-14.49)	8.09 (6.62-9.56)	3.88 (2.98-4.79)	6.89 (5.83-7.96)	4.93 (4.13-5.71)	5.78 (4.76-6.81)	2.42 (1.79-3.06)
Carrot	12.46 (11.09-13.83)	8.36 (6.87-9.85)	4.85 (3.85-5.86)	7.20 (7.11-8.29)	4.54 (3.78-5.31)	5.09 (4.13-6.06)	2.11 (1.52-2.71)
Sesame seed	12.10 (10.74-13.45)	**11.90 (10.15-13.64)**	5.82 (4.73-6.92)	6.50 (5.46-7.54)	3.03 (2.40-3.66)	5.50 (4.50-6.51)	2.86 (2.17-3.55)
Apple	11.95 (10.60-13.30)	10.13 (8.50-11.76)	4.85 (3.85-5.86)	7.90 (6.77-9.04)	4.93 (4.14-5.72)	5.50 (4.50-6.50)	2.05 (1.46-2.64)
Peanut	10.06 (8.81-11.31)	7.82 (6.37-9.27)	4.12 (3.19-5.05)	6.18 (5.17-7.20)	2.65 (2.06-3.24)	4.82 (3.87-5.76)	2.31 (1.69-2.93)
Walnut	9.52 (8.30-10.74)	7.45 (6.04-8.87)	5.33 (4.28-6.38)	3.55 (2.77-4.33)	2.28 (1.73-2.82)	3.58 (2.76-4.40)	1.37 (0.89-1.85)
Kiwi	9.49 (8.27-10.71)	9.22 (7.66-10.78)	5.10 (4.08-6.13)	**9.53 (8.29-10.77)**	4.54 (3.78-5.31)	5.37 (4.38-6.36)	1.74 (1.20-2.28)
Melon	9.19 (7.99-10.39)	6.70 (5.35-8.05)	3.40 (2.56-4.25)	4.26 (3.41-5.12)	2.28 (1.73-2.82)	3.99 (3.13-4.86)	0.81 (0.44-1.18)
Buckwheat	8.89 (7.70-10.07)	7.55 (6.13-8.98)	5.58 (4.51-6.66)	4.77 (3.87-5.67)	2.65 (2.06-3.24)	3.99 (3.13-4.85)	1.37 (0.89-1.85)
Sunflower seed	8.89 (7.70-10.07)	6.16 (4.87-7.46)	4.85 (3.85-5.86)	4.67 (3.78-5.56)	3.41 (2.75-4.08)	4.54 (3.63-5.46)	1.37 (0.89-1.85)
Poppy seed	8.50 (7.34-9.66)	6.32 (5.01-7.64)	3.15 (234-3.97)	4.88 (3.97-5.78)	2.28 (1.73-2.82)	3.99 (3.13-4.85)	0.75 (0.39-1.10)
Corn	8.35 (7.20-9.50)	9.43 (7.85-11.01)	5.82 (4.73-6.92)	6.09 (5.08-7.10)	3.04 (2.41-3.67)	3.86 (3.01-4.70)	1.80 (1.25-2.35)
Cow's milk	8.29 (7.14-9.43)	8.15 (6.68-9.63)	**15.08 (13.41-16.75)**	8.22 (7.06-9.37)	**8.74 (7.70-9.11)**	5.09 (4.13-6.06)	**3.74 (2.95-4.52)**
Lentils	7.99 (6.86-9.11)	7.45 (6.04-8.87)	3.63 (2.76-4.51)	5.38 (4.43-6.33)	2.65 (2.06-3.24)	3.99 (3.13-4.85)	2.11 (1.52-2.71)
Soy bean	7.72 (6.61-8.83)	5.89 (4.62-7.16)	4.12 (3.19-5.05)	4.15 (3.31-4.99)	2.65 (2.06-3.24)	4.27 (3.38-5.15)	1.19 (0.74-1.63)
Hen's egg	6.06 (5.07-7.06)	7.34 (5.94-8.75)	6.57 (5.41-7.72)	4.77 (3.87-5.67)	3.41 (2.75-4.08)	4.68 (3.75-5.60)	**3.12 (2.40-3.84)**
Mustard seed	4.92 (4.02-5.82)	3.33 (2.36-4.29)	2.18 (1.50-2.86)	1.72 (1.17-2.27)	3.04 (2.41-3.67)	2.48 (1.80-3.16)	0.37 (0.12-0.63)
Shrimp	3.75 (2.96-4.54)	2.68 (1.81-3.55)	0.97 (0.51-1.43)	3.35 (2.59-4.11)	0.38 (0.15-0.60)	2.34 (1.67-3.00)	0.88 (0.49-1.26)
Fish	0.51 (0.21-0.81)	0.91 (0.40-1.42)	0.24 (0.01-0.47)	0.50 (0.21-0.80)	0.76 (0.44-1.08)	0.00 (0.00-0.33)	0.44 (0.17-0.71)
Overall FS	28.73 (26.85 -30.61)	25.78 (23.42-28.14)	23.34 (21.36-25.32)	22.72 (20.96-24.49)	17.84 (16.44-19.24)	16.65 (15.01-18.28)	10.98 (9.69-12.27)
Primary FS	20.26 (18.59-21.94)	21.71 (19.48-23.93)	21.15 (19.24-23.06)	17.17 (15.58-18.76)	15.19 (13.87-16.50)	12.66 (11.20-14.12)	8.62 (7.46-9.78)

Bold: Three foods most commonly causing FS per center (more than 3 marked if identical prevalence estimates). Centers are sorted from high to low prevalence of overall FS; foods are sorted from high to low prevalence of FS in Zurich. For prevalence estimates that were close to 0, the double arcsine transformation method was used to prevent obtaining confidence limits with negative values. Subjects with discrepancies in the clinical questionnaires were included in the study population for calculation of prevalence of FS (Figure 1).

TABLE E2. Percentage of subjects with self-reported FA who had matching FS per priority food

Priority food	No. of subjects with FS*	No. of subjects with self-reported FA*	N (%) of subjects with self-reported FA who had matching FS (probable FA)*
Lentils	105	11	5 (45.5)
Apple	152	51	22 (43.1)
Hazelnut	179	69	26 (37.7)
Sunflower seed	104	8	3 (37.5)
Peach	180	48	16 (33.3)
Carrot	143	33	10 (30.3)
Peanut	129	91	26 (28.6)
Celery	147	30	8 (26.7)
Sesame seed	149	8	2 (25.0)
Banana	188	52	12 (23.1)
Soy bean	101	27	6 (22.2)
Shrimp	53	43	9 (20.9)
Walnut	101	74	14 (18.9)
Kiwi	147	104	19 (18.3)
Hen's egg	116	165	26 (15.8)
Buckwheat	109	15	2 (13.3)
Fish	14	74	8 (10.8)
Wheat	165	52	5 (9.6)
Tomato	141	121	10 (8.3)
Cow's milk	149	437	35 (8.0)
Melon	90	15	1 (6.7)
Corn	119	15	1 (6.7)
Mustard seed	50	0	0 (0.0)
Poppy seed	95	0	0 (0.0)
Overall	2926	1543	266 (17.2)†

*Source population: cases and controls participating in phase II with available food serology (N = 1989).
†These 266 probable FAs were found in 136 subjects.

TABLE E3. Prevalence of probable FA per priority food and per center

Prevalence (95% CI) of probable FA to:	Lodz	Madrid	Vilnius	Utrecht	Zurich	Athens	Reykjavik
Cow's milk	**1.70 (0.68-3.24)**	**0.89 (0.12-2.46)**	**0.89 (0.01-3.17)**	**1.16 (0.34-2.52)**	0.00 (0.00-0.49)	**0.56 (0.00-2.51)**	**0.37 (0.02-1.23)**
Celery	**1.24 (0.40-2.60)**	0.00 (0.00-0.56)	0.00 (0.00-0.86)	0.00 (0.00-0.37)	0.14 (0.04-0.98)	0.00 (0.00-0.88)	0.00 (0.00-0.35)
Apple	**1.09 (0.32-2.38)**	0.18 (0.02-1.15)	**0.89 (0.01-3.17)**	**0.84 (0.18-2.05)**	**0.54 (0.02-1.80)**	0.00 (0.00-0.88)	0.07 (0.03-0.63)
Banana	0.95 (0.25-2.18)	0.18 (0.02-1.15)	0.00 (0.00-0.86)	0.32 (0.01-1.18)	0.14 (0.04-0.98)	**0.56 (0.00-2.51)**	0.07 (0.03-0.63)
Peanut	0.78 (0.16-1.92)	**0.89 (0.12-2.46)**	0.00 (0.00-0.86)	0.63 (0.09-1.72)	0.41 (0.00-1.56)	0.28 (0.07-1.89)	**0.52 (0.06-1.48)**
Hazelnut	0.78 (0.16-1.92)	0.53 (0.02-1.85)	**2.15 (0.41-5.26)**	**0.74 (0.14-1.89)**	**0.81 (0.10-2.27)**	0.28 (0.07-1.89)	0.07 (0.03-0.63)
Hen's egg	0.76 (0.16-1.90)	**0.89 (0.12-2.46)**	0.44 (0.02-2.28)	0.21 (0.00-0.97)	0.00 (0.00-0.49)	**0.85 (0.01-3.06)**	**0.74 (0.15-1.84)**
Tomato	0.63 (0.10-1.68)	0.35 (0.00-1.52)	0.00 (0.00-0.86)	0.11 (0.02-0.74)	0.27 (0.00-1.29)	0.28 (0.07-1.89)	0.07 (0.03-0.63)
Peach	0.48 (0.05-1.43)	**1.06 (0.19-2.74)**	0.44 (0.02-2.28)	0.53 (0.06-1.55)	0.14 (0.04-0.98)	0.28 (0.07-1.89)	0.00 (0.00-0.35)
Walnut	0.48 (0.05-1.43)	0.53 (0.02-1.85)	0.00 (0.00-0.86)	0.53 (0.06-1.55)	0.27 (0.00-1.29)	**0.56 (0.00-2.51)**	0.00 (0.00-0.35)
Kiwi	0.31 (0.01-1.14)	**1.06 (0.19-2.74)**	0.44 (0.02-2.28)	0.63 (0.09-1.72)	0.27 (0.00-1.29)	0.00 (0.00-0.88)	0.15 (0.01-0.80)
Soy bean	0.31 (0.01-1.14)	0.18 (0.02-1.15)	0.00 (0.00-0.86)	0.21 (0.00-0.97)	0.00 (0.00-0.49)	0.00 (0.00-0.88)	0.07 (0.03-0.63)
Carrot	0.15 (0.01-0.83)	0.00 (0.00-0.56)	**0.89 (0.01-3.17)**	0.11 (0.02-0.74)	**0.81 (0.10-2.27)**	0.00 (0.00-0.88)	0.00 (0.00-0.35)
Shrimp	0.00 (0.00-0.37)	0.71 (0.06-2.16)	0.00 (0.00-0.86)	0.00 (0.00-0.37)	0.14 (0.04-0.98)	0.00 (0.00-0.88)	0.30 (0.01-1.10)
Fish	0.00 (0.00-0.37)	0.53 (0.02-1.85)	0.00 (0.00-0.86)	0.11 (0.02-0.74)	0.14 (0.04-0.98)	0.28 (0.07-1.89)	0.15 (0.01-0.80)
Lentil	0.00 (0.00-0.37)	0.53 (0.02-1.85)	0.00 (0.00-0.86)	0.00 (0.00-0.37)	0.00 (0.00-0.49)	**0.56 (0.00-2.51)**	0.00 (0.00-0.35)
Sunflower seed	0.00 (0.00-0.37)	0.53 (0.02-1.85)	0.00 (0.00-0.86)	0.00 (0.00-0.37)	0.00 (0.00-0.49)	0.00 (0.00-0.88)	0.00 (0.00-0.35)
Melon	0.00 (0.00-0.37)	0.18 (0.02-1.15)	0.00 (0.00-0.86)	0.00 (0.00-0.37)	0.00 (0.00-0.49)	0.00 (0.00-0.88)	0.00 (0.00-0.35)
Corn	0.00 (0.00-0.37)	0.18 (0.02-1.15)	0.00 (0.00-0.86)	0.00 (0.00-0.37)	0.00 (0.00-0.49)	0.00 (0.00-0.88)	0.00 (0.00-0.35)
Wheat	0.00 (0.00-0.37)	0.00 (0.00-0.56)	0.00 (0.00-0.86)	0.21 (0.00-0.97)	0.14 (0.04-0.98)	0.00 (0.00-0.88)	0.15 (0.01-0.80)
Buckwheat	0.00 (0.00-0.37)	0.00 (0.00-0.56)	0.00 (0.00-0.86)	0.00 (0.00-0.37)	0.14 (0.04-0.98)	0.00 (0.00-0.88)	0.07 (0.03-0.63)
Sesame seed	0.00 (0.00-0.37)	0.00 (0.00-0.56)	0.00 (0.00-0.86)	0.00 (0.00-0.37)	0.00 (0.00-0.49)	0.00 (0.00-0.88)	0.15 (0.01-0.80)
Mustard seed	0.00 (0.00-0.37)	0.00 (0.00-0.56)	0.00 (0.00-0.86)	0.00 (0.00-0.37)	0.00 (0.00-0.49)	0.00 (0.00-0.88)	0.00 (0.00-0.35)
Poppy seed	0.00 (0.00-0.37)	0.00 (0.00-0.56)	0.00 (0.00-0.86)	0.00 (0.00-0.37)	0.00 (0.00-0.49)	0.00 (0.00-0.88)	0.00 (0.00-0.35)
Overall	5.60 (3.57-8.11)	3.89 (1.90-6.65)	3.04 (0.85-6.58)	2.96 (1.51-4.93)	2.31 (0.88-4.46)	1.97 (0.36-4.94)	1.93 (0.84-3.52)

Bold: Three foods most commonly causing probable FA per center (more than 3 marked if identical prevalence estimates). Centers are sorted from high to low prevalence of overall probable FA; foods are sorted from high to low prevalence of probable FA in Lodz. For prevalence estimates that were close to 0, the double arcsine transformation method was used to prevent obtaining confidence limits with negative values. Subjects with discrepancies in the clinical questionnaires were excluded from the study population for calculation of prevalence of probable FA (because of uncertainties regarding symptomatology) (Figure 1).