

Food Allergy in Adults: Substantial Variation in Prevalence and Causative Foods Across Europe



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What is already known about this topic? Prevalence of self-reported food allergy ranges from 1% to 37% across Europe. Data on prevalence of clinically manifest food allergy are lacking, especially in adults, and incomparable study protocols hamper accurate evaluation of intracontinental differences.

What does this article add to our knowledge? On applying a standardized protocol across Europe, we found that the prevalence of food allergy defined as symptoms plus specific IgE-sensitization ranged from 0.3% in Greece to 5.6% in Switzerland in adults. Plant foods dominated as causative foods in most countries.

How does this study impact current management guidelines? Prevalence of food allergy defined as symptoms plus specific IgE-sensitization is less common than self-reported food allergy, with prevalence estimates now available for 24 commonly implicated foods in 6 countries.

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Abbreviations used

DBPCFC- double-blind placebo-controlled food challenge

FA- food allergy

LTP- lipid transfer protein

BACKGROUND: According to the community-based EuroPrevall surveys, prevalence of self-reported food allergy (FA) in adults across Europe ranges from 2% to 37% for any food and 1% to 19% for 24 selected foods.

OBJECTIVE: To determine the prevalence of probable FA (symptoms plus specific IgE-sensitization) and challenge-confirmed FA in European adults, along with symptoms and causative foods.

METHODS: In phase I of the EuroPrevall project, a screening questionnaire was sent to a random sample of the general adult population in 8 European centers. Phase II consisted of an extensive questionnaire on reactions to 24 preselected commonly implicated foods, and measurement of specific IgE levels. Multiple imputation was performed to estimate missing symptom and serology information for nonresponders. In the final phase, subjects with probable FA were invited for double-blind placebo-controlled food challenge.

RESULTS: Prevalence of probable FA in adults in Athens, Reykjavik, Utrecht, Lodz, Madrid, and Zurich was respectively 0.3%, 1.4%, 2.1%, 2.8%, 3.3%, and 5.6%. Oral allergy symptoms were reported most frequently (81.6%), followed by skin symptoms (38.2%) and rhinoconjunctivitis (29.5%). Hazelnut, peach, and apple were the most common causative foods in Lodz, Utrecht, and Zurich. Peach was also among the top 3 causative foods in Athens and Madrid. Shrimp and fish allergies were relatively common in Madrid and Reykjavik. Of the 55 food challenges performed, 72.8% were classified as positive.

CONCLUSIONS: FA shows substantial geographical variation in prevalence and causative foods across Europe. Although probable FA is less common than self-reported FA, prevalence still reaches almost 6% in parts of Europe. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1920-8)

Key words: Food allergy; Prevalence; Causative foods; Europe; Adults

INTRODUCTION

Assessing the prevalence of food allergy (FA) is a challenging task. Most studies only investigate the prevalence of self-reported FA.¹⁻⁴ Prevalence of self-reported FA is known to be higher than the prevalence of FA defined as symptoms plus specific IgE (sIgE)-sensitization or challenge-confirmed FA,^{4,5} on which data are much scarcer.^{4,6} For instance, the most recent systematic review focusing on the prevalence of FA found in European studies reports an adult lifetime prevalence of self-reported FA of 9.5% to 35.0%.⁴ In comparison, prevalence of symptoms in combination with sIgE-positivity (probable FA) was addressed in only 1 study in German adults and found to be 2.2%.^{4,7} Prevalence of challenge-confirmed FA was suggested to be as low as 0.9%.⁴

Prevalence estimates also appear to differ remarkably between European countries.⁴ It is unknown whether these differences are caused by incomparable study protocols (eg, different age groups, food types, sampling methods, and outcome definitions) or whether these variations really reflect geographical differences in the prevalence of FA. Data from Southern and Eastern Europe are scarce.^{4,6,8} To appropriately assess the differences in prevalence of FA across Europe, it is necessary to evaluate countries from all parts of Europe and to use the same study design and outcome definitions in all participating countries.

This was done in the European Union—funded EuroPrevall project, where a standardized protocol was applied in a large population to establish the prevalence of FAs across Europe.⁹ In a previous analysis focusing on the prevalence of IgE-sensitization in the adult EuroPrevall population, the prevalence of self-reported FA was briefly evaluated and found to range from less than 2% in Vilnius to 37% in Zurich for any food and from less than 1% in Vilnius and Sofia to 19% in Madrid for 24 commonly implicated foods.¹⁰ In this study, the objective was to thoroughly investigate the prevalence of probable FA (ie, a combination of self-reported FA and matching IgE-sensitization) and of confirmed FA (diagnosed by double-blind placebo-controlled food challenge [DBPCFC]) in adults across Europe, using the EuroPrevall data. Furthermore, symptoms and causative foods were evaluated.

METHODS

Study design

Data for this multicenter cross-sectional study were collected from 2005 to 2009 as part of the EuroPrevall project, with a case-control study nested within for each center. The methods have been reported in detail previously.^{9,11} In short, a representative sample of 20- to 54-year-old adults was randomly selected from the general population by 8 European centers, representing different socioeconomic and climatic regions across Europe: Zurich (Switzerland), Madrid (Spain), Athens (Greece), Sofia (Bulgaria), Lodz (Poland), Vilnius (Lithuania), Reykjavik (Iceland), and Utrecht (the Netherlands).

The study involved 3 phases. For phase I, information regarding adverse reactions to any food, symptoms, and incriminated foods was collected in a self-administered 1-page screening questionnaire (see Figure E1 in this article Online Repository at www.jaci-inpractice.org). For further evaluation including serum sIgE-measurement, 24 foods that were either known to commonly cause food allergic reactions or thought to be potentially important because of frequent consumption in 1 or more of the participating countries, were determined the so-called *priority foods*. The 24 selected foods were 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. Responders reporting symptoms to 1 of these priority foods (cases) were invited to participate in phase II, along with a random sample of responders who did not report symptoms to any of the priority foods (controls). Phase II consisted of an extensive questionnaire administered by a trained interviewer and serum sIgE-testing to the priority foods and common inhalant allergens. Additional information was obtained on reactions to all priority foods, allergic comorbidities, and other potential risk factors. Finally, participants with self-reported symptoms and matching sIgE to 1 of the 9 priority foods selected for challenge

testing (milk, egg, fish, shrimp, peanut, hazelnut, apple, peach, celery) were subjected to phase III, a full clinical evaluation including DBPCFC.

Ethical approval was obtained from the local ethical committees of all participating centers, and all participants gave informed consent.

Outcome definitions

Two working definitions of FA were used as outcome measures:

- I. Prevalence of probable FA; representing individuals with self-reported FA in combination with matching positive serology ($sIgE \geq 0.35$ kUA/L) to at least 1 of the 24 priority foods.
- II. Prevalence of confirmed FA; representing individuals with DBPCFC-confirmed FA to at least 1 of the 9 foods selected for challenge testing.

Questionnaires

The questionnaires used in the EuroPrevall study were based on preexisting well-standardized allergy questionnaires¹² and enriched with specific questions regarding reactions to the selected priority foods.⁹

sIgE-testing

Commercially available ImmunoCAP tests (Phadia, currently ThermoFisher Scientific, Uppsala, Sweden) were used to measure serum sIgE levels, following the manufacturer's instructions. All serology testing was performed at a single laboratory in the Amsterdam University Medical Center, the Netherlands.⁹ Specific IgE levels of greater than or equal to 0.35 kUA/L were considered positive.

DBPCFC methods

The DBPCFC methods were described in detail elsewhere.¹¹ DBPCFC was performed on 2 separate days with gradually increasing doses of either placebo or the concerned food with 20-minute intervals. The challenge continued until participants had completely ingested the challenge meal, or had objective symptoms or severe subjective symptoms (eg, severe itching of palms, soles, head or severe abdominal pain) lasting more than 45 minutes.¹¹

Statistical analysis

Prevalence of probable FA was calculated after missing history and serology data in phase II were handled with multiple imputation. Comparison of the cases participating in phase II ($N = 862$) to the cases not participating in phase II ($N = 803$; thus, 48% missing data) suggested that FA prevalence based on the participating cases alone would lead to an overestimation, because participating cases reported more recognizable signs of typical FA. Overall, participating cases reported significantly more frequent reactions than nonparticipating cases ($P < .001$). In most countries, there also appeared to be a tendency for participating cases to report more previous doctor-diagnosed FA, oral allergy symptoms, respiratory symptoms, and cardiovascular symptoms, and less gastrointestinal symptoms, than nonparticipating cases. On the basis of this, we considered data in the nonparticipating cases likely to be "missing at random." Multiple imputation was performed by chained equations.^{13,14} Included as predictors in all imputation models were center, age, sex, all screening variables related to type and frequency of symptoms, previous doctor-diagnosed FA, and a clinical variable indicating occurrence of symptoms to the food corresponding to the respective serology variable. A total of 40 imputations with each 20 iterations were performed.^{15,16}

This process resulted in complete data on the presence or absence of symptoms to, and positive or negative serology against, the 24 priority foods for both participating and nonparticipating cases in phase II. These values were subsequently used to calculate the prevalence of "probable FA" in each imputed data set. The calculated rates were weighted back to estimate the population prevalence in each center according to the sample selection illustrated in the flowcharts (see "Weighting procedure for population prevalence estimation of probable FA" section in this article's Online Repository at www.jaci-inpractice.org; see Figures E2-E7 in this article's Online Repository at www.jaci-inpractice.org). After double arcsine transformation, which is recommended for stabilizing variance when pooling proportions close to 0 or 1,¹⁷ the prevalence estimates were pooled and their 95% CIs were calculated using Rubin's rules.^{14,16,18}

For comparison, prevalence estimates of self-reported FA¹⁰ along with 95% CIs were reobtained in this study. Sofia and Vilnius were not included in the analysis beyond self-reported FA, because too few cases participated in phase II to justify separate evaluation: 7 cases and 4 cases, respectively. Subjects with evident discrepancies in the questionnaires were also excluded from further analysis (Figure 1).

Self-reported and probable FA were further characterized by determining the absolute number and percentage of subjects with various symptoms and frequencies of reactions. Causative foods were assessed for self-reported FA by calculating the percentage of subjects faulting each specific priority food, and for probable FA by calculating the population prevalence plus 95% CI for each specific priority food as described above in this section.

For confirmed FA, the absolute number and percentage of eligible subjects challenged with each of the selected foods and the frequency of positive challenge tests were determined.

Analyses were conducted with SPSS version 25 (IBM Corporation, Armonk, NY) and R version 3.4.1. (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Phase I—Self-Reported FA

The flowcharts of the study are depicted in Figure 1 and in Figures E2 to E9 in this article's Online Repository at www.jaci-inpractice.org. Response rates per center and prevalence estimates of self-reported FA were published previously by Burney et al,¹⁰ the latter of which are shown in Figure 2 for comparison with the prevalence of probable FA. In subjects with self-reported FA, the most commonly reported causative priority foods were milk (7.8%), apple (5.6%), tomato (4.3%), egg (4.2%), kiwi (3.8%), shrimp (3.5%), fish (3.1%), hazelnut (3.0%), walnut (2.2%), wheat (2.2%), and peanut (2.0%).

Subjects with a self-reported allergy to any food most often reported either gastrointestinal symptoms (44.5%) or skin symptoms (38.8%) (Table I). Oral allergy symptoms were reported by 34.8%. For subjects with a self-reported allergy to priority foods, oral allergy symptoms (46.9%), skin symptoms (42.5%), or gastrointestinal symptoms (41.1%) were the most commonly mentioned. Alternatively, 18.8% of subjects with self-reported allergy to any food and 20.5% of subjects with self-reported allergy to priority foods reported respiratory or cardiovascular symptoms.

Phase II—Probable FA

For prevalence of probable FA, a sample of 693 cases and 1355 controls was studied. Of the subjects in the control arm,

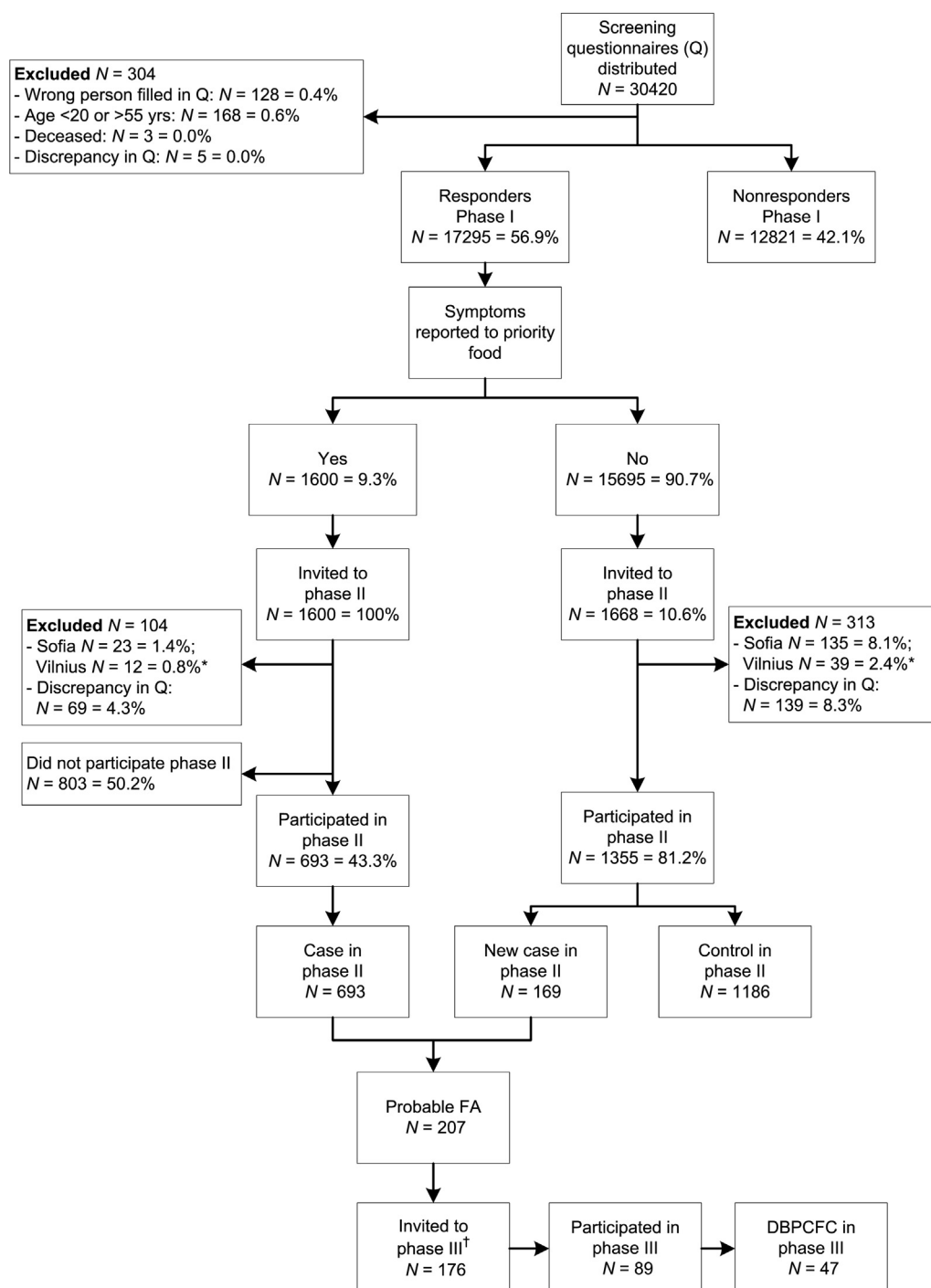


FIGURE 1. Flowchart: overall participation in phase I, II and III of the EuroPrevall population-based study in adults. Case = subject self-reporting symptoms to at least 1 priority food. Control = subject not reporting symptoms to any priority food. *Sofia and Vilnius were excluded from calculation of probable FA prevalence because of lack of cases participating in phase I. †Probable FA to milk, egg, fish, shrimp, peanut, hazelnut, apple, peach, or celery.

12.5% (169 of 1355) reported symptoms to priority foods in phase II in addition to symptoms to only nonpriority foods in phase I (Figure 1). This was most likely due to limitations in space for reporting foods in the phase I questionnaire, whereas in phase II subjects were asked whether they had ever experienced symptoms to each of the 24 priority foods separately. These 169

subjects were defined as “new cases” and analyzed along with the 693 original cases, leading to a total of 862 cases. Cases had a median age of 37.3 years and 65.7% were females; controls had a median age of 38.9 years and 50.9% were females.

Of the 862 cases participating in phase II, 207 were found to have probable FA (Figure 1). The weighted population prevalence

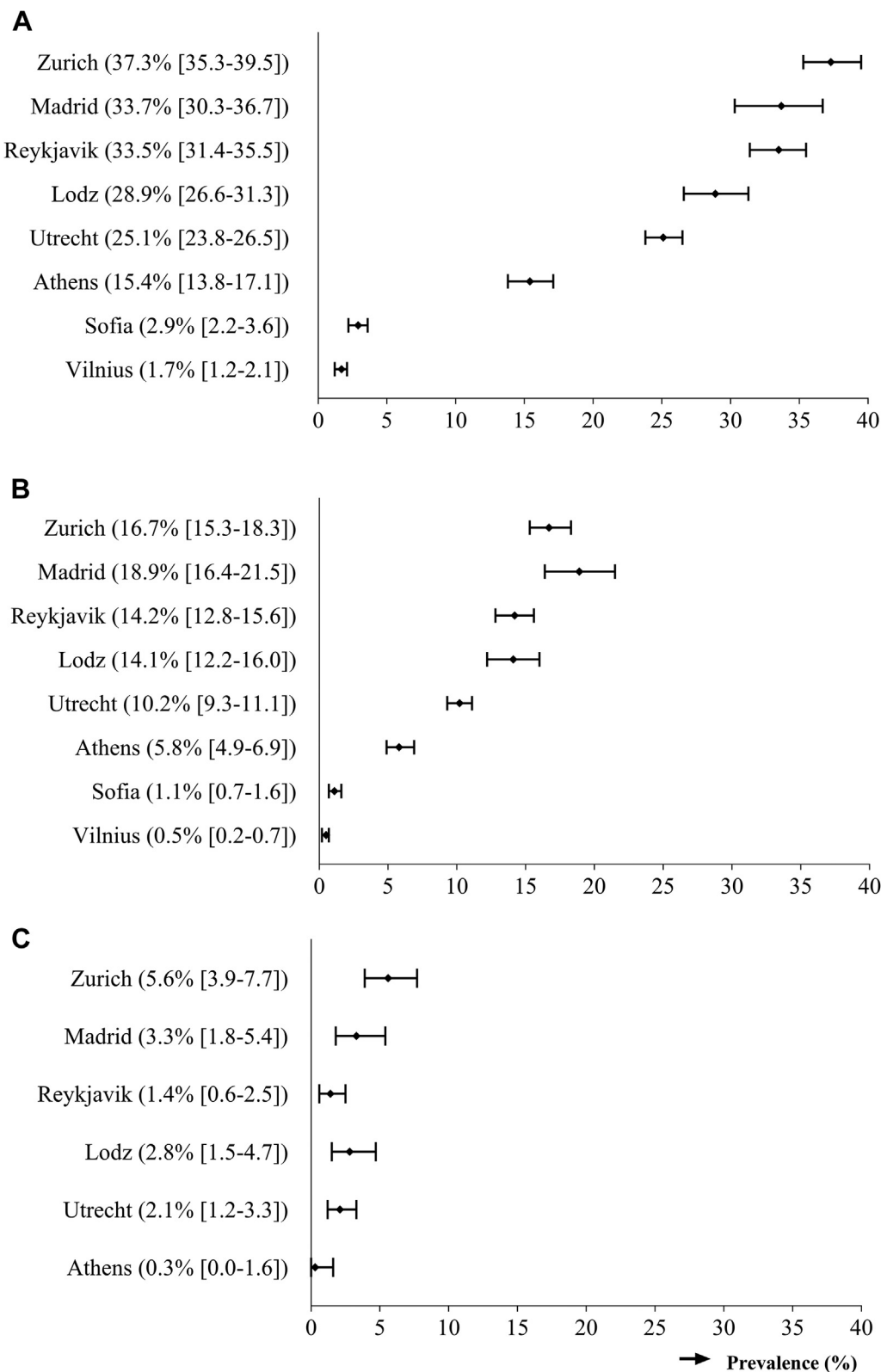


FIGURE 2. Prevalence of probable FA compared with prevalence of self-reported FA. (A) Self-reported allergy to ANY food, (B) self-reported allergy to at least 1 PRIORITY food, and (C) probable food allergy to at least 1 PRIORITY food.

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

Variable	Self-reported FA to any food (N = 3657)	Self-reported FA to priority food (N = 1600)	Probable FA to priority food (N = 207)
Age (y), median (IQR)	36.6 (29.0-44.9)	36.9 (29.2-44.8)	35.4 (28.8-42.6)
Female sex	2286 (62.8)	1057 (66.3)	114 (55.1)
Oral allergy symptoms	1203 (34.8)	725 (46.9)	169 (81.6)
Skin symptoms	1340 (38.8)	649 (42.5)	79 (38.2)
Rhinoconjunctivitis	686 (20.2)	367 (24.4)	61 (29.5)
Gastrointestinal symptoms	1550 (44.5)	630 (41.1)	52 (25.1)
Difficulty swallowing	350 (10.3)	192 (12.8)	49 (23.7)
Respiratory symptoms	407 (12.0)	212 (14.1)	44 (21.3)
Cardiovascular symptoms	333 (9.8)	145 (9.7)	15 (7.2)
Other symptoms	1466 (43.0)	647 (42.9)	61 (29.5)
Lifetime frequency of reactions			
1 ×	645 (18.1)	183 (11.7)	9 (4.4)
2-4 ×	963 (27.0)	361 (23.0)	34 (16.7)
>4 ×	1954 (54.8)	1025 (65.3)	161 (78.9)
Previous doctor-diagnosis of FA	676 (18.9)	418 (26.6)	79 (38.7)

IQR, interquartile range.

Oral 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 = diarrhea or vomiting; Respiratory symptoms = breathlessness; Cardiovascular symptoms = fainting or dizziness; Other = stiffness in joints or headaches or other symptoms.

Values are n (%) unless otherwise indicated.

TABLE II. Prevalence of probable food allergy per priority food and per center

Prevalence (95% CI) of probable FA to:	Zurich	Madrid	Reykjavik	Lodz	Utrecht	Athens
At least 1 priority food	5.64 (3.94-7.66)	3.28 (1.78-5.35)	1.36 (0.57-2.54)	2.84 (1.51-4.65)	2.12 (1.19-3.35)	0.31 (0.02-1.65)
Hazelnut	2.57 (1.47-4.02)	0.76 (0.16-1.96)	0.10 (0.00-0.60)	1.33 (0.49-2.66)	0.93 (0.36-1.81)	0.06 (0.19-0.99)
Peach	2.02 (1.08-3.30)	1.61 (0.63-3.18)	0.00 (0.00-0.28)	0.45(0.05-1.35)	0.60 (0.17-1.33)	0.10 (0.00-1.14)
Apple	1.90 (0.99-3.15)	0.57 (0.08-1.65)	0.05 (0.02-0.48)	0.75 (0.17-1.83)	0.91 (0.34-1.77)	0.00 (0.00-0.68)
Kiwi	1.34 (0.60-2.42)	0.64 (0.11-1.77)	0.31 (0.02-0.99)	0.30 (0.01-1.09)	0.57 (0.15-1.29)	0.00 (0.00-0.68)
Carrot	1.01 (0.39-1.97)	0.81 (0.18-2.03)	0.38 (0.05-1.12)	0.15 (0.00-0.80)	0.23 (0.01-0.76)	0.00 (0.00-0.68)
Walnut	0.58 (0.11-1.45)	0.71 (0.14-1.88)	0.05 (0.02-0.48)	0.15 (0.00-0.80)	0.10 (0.00-0.51)	0.29 (0.02-1.61)
Melon	0.46 (0.09-1.17)	0.95 (0.25-2.24)	0.10 (0.00-0.60)	0.00 (0.00-0.36)	0.05 (0.01-0.39)	0.00 (0.00-0.68)
Shrimp	0.37 (0.05-1.04)	0.82 (0.19-2.04)	0.36 (0.04-1.08)	0.35 (0.02-1.18)	0.36 (0.06-0.97)	0.00 (0.00-0.68)
Peanut	0.37 (0.02-1.17)	0.45 (0.05-1.45)	0.00 (0.00-0.28)	0.35 (0.02-1.18)	0.05 (0.01-0.39)	0.02 (0.00-0.82)
Celery	0.24 (0.01-0.81)	0.00 (0.00-0.44)	0.33 (0.03-1.03)	0.07 (0.02-0.63)	0.03 (0.03-0.32)	0.00 (0.00-0.68)
Milk	0.24 (0.00-1.02)	0.18 (0.00-0.97)	0.00 (0.00-0.28)	0.12 (0.01-0.74)	0.00 (0.00-0.21)	0.00 (0.00-0.68)
Wheat	0.19 (0.00-0.73)	0.37 (0.02-1.31)	0.10 (0.00-0.60)	0.00 (0.00-0.36)	0.05 (0.01-0.39)	0.00 (0.00-0.68)
Lentil	0.16 (0.07-0.93)	0.00 (0.00-0.44)	0.00 (0.00-0.28)	0.00 (0.00-0.36)	0.03 (0.03-0.32)	0.00 (0.00-0.68)
Tomato	0.10 (0.00-0.55)	0.15 (0.01-0.90)	0.15 (0.00-0.71)	0.30 (0.01-1.10)	0.08 (0.01-0.46)	0.00 (0.00-0.68)
Soy	0.08 (0.02-0.56)	0.00 (0.00-0.44)	0.00 (0.00-0.28)	0.00 (0.00-0.36)	0.03 (0.03-0.32)	0.00 (0.00-0.68)
Sunflower seed	0.05 (0.02-0.42)	0.00 (0.00-0.44)	0.00 (0.00-0.28)	0.00 (0.00-0.36)	0.00 (0.00-0.21)	0.07 (0.17-1.05)
Banana	0.05 (0.02-0.42)	0.04 (0.00-0.65)	0.49 (0.08-1.29)	0.00 (0.00-0.36)	0.05 (0.01-0.39)	0.00 (0.00-0.68)
Corn	0.05 (0.02-0.42)	0.00 (0.00-0.44)	0.05 (0.02-0.48)	0.00 (0.00-0.36)	0.00 (0.00-0.21)	0.00 (0.00-0.68)
Sesame seed	0.03 (0.00-0.37)	0.00 (0.00-0.44)	0.00 (0.00-0.28)	0.00 (0.00-0.36)	0.00 (0.00-0.21)	0.00 (0.00-0.68)
Fish	0.02 (0.00-0.35)	0.44 (0.04-1.44)	0.15 (0.00-0.71)	0.00 (0.00-0.36)	0.08 (0.01-0.46)	0.00 (0.00-0.68)
Egg	0.00 (0.00-0.25)	0.06 (0.00-0.70)	0.21 (0.00-0.81)	0.31 (0.01-1.11)	0.00 (0.00-0.21)	0.02 (0.00-0.84)
Mustard seed	0.00 (0.00-0.25)	0.00 (0.00-0.44)	0.00 (0.00-0.28)	0.03 (0.00-0.52)	0.00 (0.00-0.21)	0.00 (0.00-0.68)
Buckwheat	0.00 (0.00-0.25)	0.00 (0.00-0.44)	0.00 (0.00-0.28)	0.00 (0.00-0.36)	0.00 (0.00-0.21)	0.00 (0.00-0.68)
Poppy seed	0.00 (0.00-0.25)	0.00 (0.00-0.44)	0.00 (0.00-0.28)	0.00 (0.00-0.36)	0.00 (0.00-0.21)	0.00 (0.00-0.68)

Bold indicates 3 foods most commonly causing probable FA per center.

of probable FA is presented per center and per food in [Figure 2](#) and [Table II](#) for the 6 centers for which we could calculate the prevalence. The given prevalence estimates are the results from multiple

imputation, which included estimation of probable FA in subjects who did not participate in phase II. These prevalence estimates were a factor 1.5 to 5.5 lower than those based on analysis without

TABLE III. Challenge-confirmed FA

Food	No. of challenges*	Reactive	Tolerant	Placebo reactive
Hazelnut	28	23	3	2
Apple	12	8	1	3
Peach	9	5	2	2
Peanut	3	2	0	1
Celery	2	1	1	0
Shrimp	1	1	0	0
Total	55	40	7	8

*Twenty-nine subjects were challenged in Zurich, 12 in Utrecht, 4 in Madrid, 1 in Lodz, and 1 in Athens. No challenges were performed for milk, egg, or fish. Six subjects underwent challenge with 2 foods, and 1 subject underwent challenge with 3 foods.

imputation (for complete case analysis, see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org). This indicates that prevalence estimates without adjusting for nonresponse (ie, without imputation) could lead to overestimation of the prevalence.

The prevalence of probable FA to at least 1 priority food was much lower than the prevalence of self-reported FA and ranged from 0.3% (95% CI, 0.0-1.7) to 5.6% (95% CI, 3.9-7.7) ([Figure 2](#)). Of subjects with self-reported FA to a priority food, matching IgE-sensitization was found for 17.9%. Positive serology was mostly found if symptoms to apple, peach, carrot, or hazelnut were reported, in 46.8% to 60.0% of cases. Positive serology was found in 0.5% or less when subjects reported symptoms to poppy seed, sesame seed, mustard seed, or milk. The centers with the highest prevalence of probable FA were the same as those with the highest prevalence of self-reported FA: Zurich and Madrid. The lowest prevalence was found in Reykjavik and Athens. Hazelnut, apple, and peach were the foods most frequently causing probable FA in Zurich, Lodz, and Utrecht ([Table II](#)). Probable FA to peach was also found frequently in the Mediterranean centers, Madrid and Athens. Shrimp was most commonly reported in Madrid, but was also one of the most important causative foods in Reykjavik. Probable fish allergy was most frequently seen in Madrid and Reykjavik.

Compared with self-reported FA, oral allergy symptoms, difficulty swallowing, rhinoconjunctivitis, and respiratory symptoms were more common in subjects with probable FA ([Table I](#)). Oral allergy symptoms were the most frequently reported symptoms for subjects with a probable FA in all included centers (81.6%, [Table I](#)) and ranged from 60.0% of subjects in Athens to 93.3% in Utrecht. In contrast, gastrointestinal symptoms were less frequently reported in subjects with probable FA than in subjects with self-reported FA. Although time until onset of symptoms was not available for all foods, 95.8% of subjects classified as having probable FA to a priority food and naming that same food as causing their most severe reaction, reported reacting within 2 hours of ingestion.

Phase III—Confirmed FA

Of the 207 subjects with probable FA to a priority food in phase II, 176 patients reported symptoms to 1 of the 9 priority foods selected for challenge testing. A total of 89 subjects with probable FA to 1 of these priority foods (50.6%) proceeded to phase III of the study, where 55 challenges were finally performed in 47 individuals who agreed to the procedure (29 from Zurich, 12 from Utrecht, 4 from Madrid, 1 from Lodz, and 1

from Athens). These 47 challenge-tested subjects had a median age of 35.5 years and 55.3% were females.

There were no significant differences in age, sex, level of education, or reported symptoms between the 47 subjects who underwent DBPCFC in phase III and the 129 subjects who declined further evaluation at a Bonferroni-corrected *P* value of .004. Details of the challenge results are presented in [Table III](#). Most challenges were performed for hazelnut (*n* = 28), apple (*n* = 12), and peach (*n* = 9). No challenges were performed for fish, milk, or egg. The percentage of positive challenges to foods for which at least 5 challenges were performed ranged from 55.6% for peach to 82.1% for hazelnut. Overall, 72.7% (40 of 55) of the challenge tests were classified as reactive. Too few challenges were performed to estimate the prevalence of confirmed FA or report on symptoms.

DISCUSSION

The standardized methodology used all across Europe for the first time in the EuroPrevall project provided the opportunity to conclude reliably that the prevalence of FA shows considerable geographical variation and depends strongly on the chosen definition. Compared with previously presented prevalence estimates of self-reported FA,¹⁰ probable FA was less common, with the highest prevalence found to be 5.6% in Switzerland, followed by Spain, Poland, the Netherlands, Iceland, and finally Greece at 0.3%. Causative foods differed between countries, with plant foods dominating. Challenge testing was positive in around 73% of subjects with probable FA who underwent DBPCFC.

This is the first study extensively addressing probable FA in multiple European countries and showing its prevalence to range from 0.3% to 5.6%. Systematic review in Europe identified only 1 article between 2002 and 2012 reporting probable FA in 2.2% of German adults.⁴ Although FA diagnosed by DBPCFC is considered the “criterion standard,” many patients decline to undergo this burdensome diagnostic process, as can be recognized in the large number of subjects unwilling to proceed to phase III in our study ([Figure 1](#)). In daily practice, diagnosis of FA is often based on the combination of symptoms and IgE-sensitization,⁸ which underlines the clinical relevance of probable FA and the value of prevalence estimates for FA defined as such.

The prevalence of probable FA after multiple imputation (0.3%-5.6%) was lower than with complete case analysis (1.7%-8.4%). Previous studies on FA prevalence in Europe did not perform multiple imputation for nonresponders. Prevalence estimates without adjusting for nonresponse could lead to overestimation of the prevalence, because individuals with typical FA complaints may have been more likely to participate, which investigation of reported symptomatology during screening in our study did indeed suggest. Soller et al¹⁹ previously evaluated this phenomenon using a Canadian population-based FA survey. They performed multiple imputation on nonparticipants and found FA prevalence estimates that were lower than the prevalence estimates without imputation. As a result, they recommend multiple imputation to correct for nonresponse bias in FA prevalence estimates. Application of multiple imputation in this study allowed us to secure unbiased results regarding the prevalence of probable FA in Europe.

Results from DBPCFC in our study indicate that around 73% of subjects with probable FA are likely to have a true clinically confirmed FA to common causative foods, which would suggest

a population prevalence of 0.2% to 4.1% for confirmed FA. The similarity of this prevalence of challenge-confirmed FA compared with that reported in the systematic review by Nwaru et al,⁴ 0.1% to 3.2%, support the accuracy of this estimate. However, we advise caution on interpretation of this derived prevalence estimate for challenge-confirmed FA, because this result was based on a limited number of challenge tests.

Prevalence of the various FA estimates was highest in Switzerland and Spain and lowest in Eastern Europe and Greece. An important explanation for differences between countries regarding the prevalence of FA and causative foods is likely to be found in pollen sensitization patterns. Birch pollen is known to be the most common tree pollen in Northern, Central, and Eastern Europe.²⁰ It is notorious for causing pollen-related FA based on cross-reactivity of IgE against the major birch pollen allergen Bet v 1 with homologous food allergens present in tree nuts (such as hazelnut), Rosaceae fruits (such as apple and peach), and Apiaceae vegetables (such as carrot and celery).^{21,22} In our data, we found that subjects with probable FA were most often cosensitized to birch pollen in Switzerland (94.7%), the Netherlands (88.6%), and Poland (72.0%) and that hazelnut, apple, and peach were indeed the most common causative foods in these countries. Peach was also among the top 3 causative foods in the Mediterranean countries Spain and Greece. In these Mediterranean regions, the high level of sensitization to lipid transfer proteins (LTPs) is considered the most important cause of FA to LTP-related fruits like peach.²¹ In our data, sensitization to Pru p 3 in subjects with probable FA to peach was indeed most common in Greece (100.0%) and Spain (44.4%) compared with 0% in Switzerland and the Netherlands. Outside birch pollen territory, cross-reaction with profilins in grasses and ragweed may also play an important role in pollen-related FA. In our data, this could explain the high prevalence of probable FA to melon and wheat in Spain, where grass pollen is abundant.²³ In Switzerland, probable FA to celery and carrot was markedly more common than in other countries. This could partly be explained by cross-reactivity to mugwort, which is common in Switzerland in addition to birch, and perhaps partly by frequent exposure.

Exposure may also play a key role in the differences found between causative foods. Data on consumption retrieved from the European Food Safety Authority Comprehensive European Food Consumption Database²⁴ were available only for children and for 3 of the countries included in this study, but showed that walnut consumption in Greece was 8 times higher than in the Netherlands and 9 times lower than in Spain. Apple consumption in Greece (23 g/d) was lower than in both Spain and the Netherlands (30 g/d and 43 g/d, respectively). As it appears, the more a food is consumed, the more probable FA is detected. In our data, probable FA to walnut was more common in Spain than in Greece and the Netherlands; probable FA to apple was most frequent in the Netherlands followed by Spain and then Greece. Similar results were documented with regard to seafood consumption, which is known to be highest in Southern and Northern Europe.²⁵ Our study showed that probable FA to seafood was indeed most often seen in these regions: probable FA to shrimp was 1 of the 3 most common probable FAs in Spain and Iceland and probable FA to fish in these 2 countries was the highest in Europe.

Some limitations of this study must be considered. First, estimation of confirmed FA prevalence was compromised by the

large proportion of subjects with probable FA refusing challenge testing. Moreover, the prevalence of probable FA was focused on the 24 priority foods and the prevalence of confirmed FA on 6 selected foods, so that nonpriority foods were not taken into account in the prevalence estimate. Although this is the most extensive and most recent European population data available for FA, it is somewhat dated and prevalence may have changed since data collection. Finally, the method of sampling from the general population in Athens differed from that of other centers, because subjects were approached via random digit dialing to mobile phones rather than via a questionnaire sent to a representative sample drawn from local population registers.⁹ This led to a very high response rate in Athens (Figure E7) and may have introduced a form of selection bias in this center.

The main strength of this study is that it is, to our knowledge, the first and only study designed to investigate FA prevalence across Europe using the same study design, questionnaires, challenge materials, and protocols. This made it possible to compare the prevalence of FA across different centers in Europe. Furthermore, multiple imputation was applied to obtain an estimation of probable FA for a complete sample, thus providing the most accurate estimates possible for the prevalence of probable FA, a clinically relevant definition of FA on which data were previously lacking.

In conclusion, this study shows that FA prevalence shows wide variation across Europe; that the foods responsible for the reactions differ per region; and that prevalence and causative foods are likely related to pollen exposure and possibly consumption. Although probable FA was far less common than previously published self-reported FA, prevalence of probable FA was still detected in 0.3% to 5.6% of the Greek, Icelandic, Dutch, Polish, Spanish, and Swiss population in increasing order.

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ONLINE REPOSITORY

WEIGHTING PROCEDURE FOR POPULATION PREVALENCE ESTIMATION OF PROBABLE FA

As described in the Methods section, “probable food allergy” was defined as having symptoms to a specific priority food and sensitization to the same food. The outcome probable FA was detected among the cases in phase I (those with self-reported FA), hereafter termed “original cases.”

However, some probable FAs were also found in the controls, that is, those without self-reported FA to a priority food in phase I who participated in phase II as controls (Figure 1). Of these “newly detected” cases, those who had also reported symptoms (to nonpriority foods) during screening were included for prevalence estimation of probable FA. These cases are hereafter termed “new cases.”

Because of the different sampling fractions for the original cases and the new cases, weighting was necessary to calculate the prevalence of probable FA in the population. The total number of probable FAs to priority foods was calculated by adding the number of probable FAs found in the original cases divided by the sampling fraction in the case arm to the number of probable FAs in the new cases divided by the sampling fraction of controls. This total number of probable FAs was then divided by the total number of responders to phase I to obtain the population prevalence of probable FA. The equation was as is given below.

The prevalence of probable FA to each priority food as estimated in this way was calculated per country and pooled over all imputations. Because some prevalence estimates were very low, 95% CIs were calculated after applying a double arcsine transformation. Results were then transformed back to obtain an estimate of the prevalence with 95% CIs for all probable FA prevalence estimates.

$$\frac{\left[\frac{(\text{Number of probable FAs in original cases})}{\text{Sampling fraction cases}} + \frac{(\text{Number of probable FAs in new cases})}{\text{Sampling fraction controls}} \right]}{\text{Number of responders in phase I}}$$



FOOD ALLERGY QUESTIONNAIRE

1. Have you ever had an illness or trouble caused by eating a food or foods? No ☐ Yes ☐

If you have answered "NO" please go to question 6. If "YES":

2. How often have you had this illness or trouble after eating this food or foods? Tick 1 box only
- | | |
|-------------------|--------------------------|
| Only once | ☐ |
| 2-4 times | ☐ |
| More than 4 times | ☐ |

3. Did this illness or trouble include: (please tick any of the following that apply)

	Yes
3.1 Itching, tingling, or swelling in the mouth, lips, or throat?	☐
3.2 A rash, nettle sting like rash, or itchy skin?	☐
3.3 Diarrhea or vomiting (other than food poisoning)?	☐
3.4 A runny or stuffy nose?	☐
3.5 Red, sore, or running eyes?	☐
3.6 Difficulty swallowing?	☐
3.7 Breathlessness?	☐
3.8 Stiffness in your joints?	☐
3.9 Fainting or dizziness?	☐
3.10 Headaches?	☐

4. Have you had any other symptoms? No ☐ Yes ☐

4.1 If yes, please describe _____

5. What type of food(s) gave you this illness or symptoms? (list up to 3) office use only
- | | |
|----------------|--------------------------|
| 5.1 Food _____ | ☐ |
| 5.2 Food _____ | ☐ |
| 5.3 Food _____ | ☐ |

6. Have you ever been told by a doctor that you have a food allergy? No ☐ Yes ☐

7. Date of birth: Day Month Year

8. Today's date: Day Month Year

9. Are you: ☐ Male ☐ Female

Thank you very much for completing this questionnaire.

FIGURE E1. EuroPrevall phase I (screening) questionnaire.

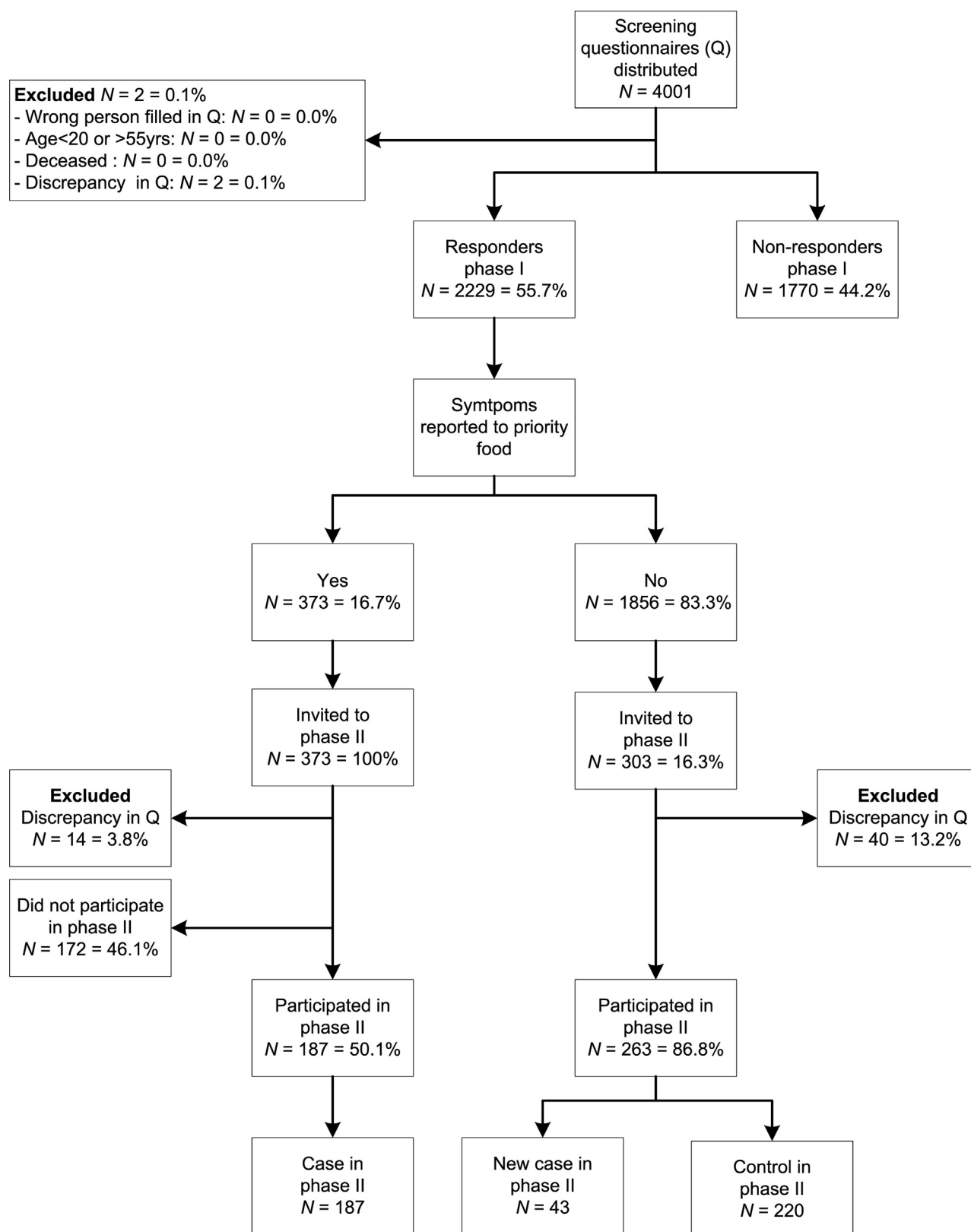


FIGURE E2. Flowchart Zurich. Case = subject self-reporting symptoms to at least 1 priority food. Control = subject not reporting symptoms to any priority food.

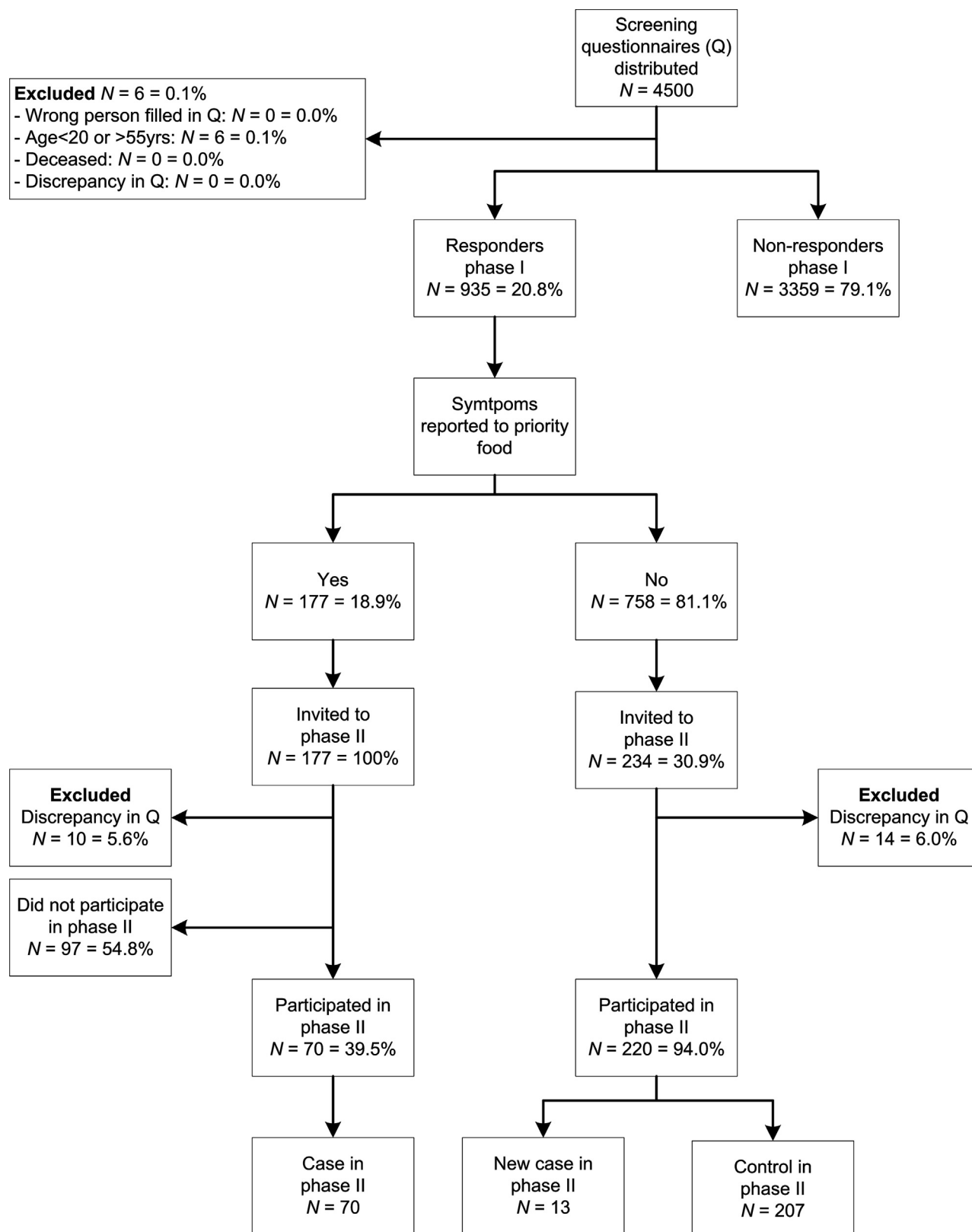


FIGURE E3. Flowchart Madrid. Case = subject self-reporting symptoms to at least 1 priority food. Control = subject not reporting symptoms to any priority food.

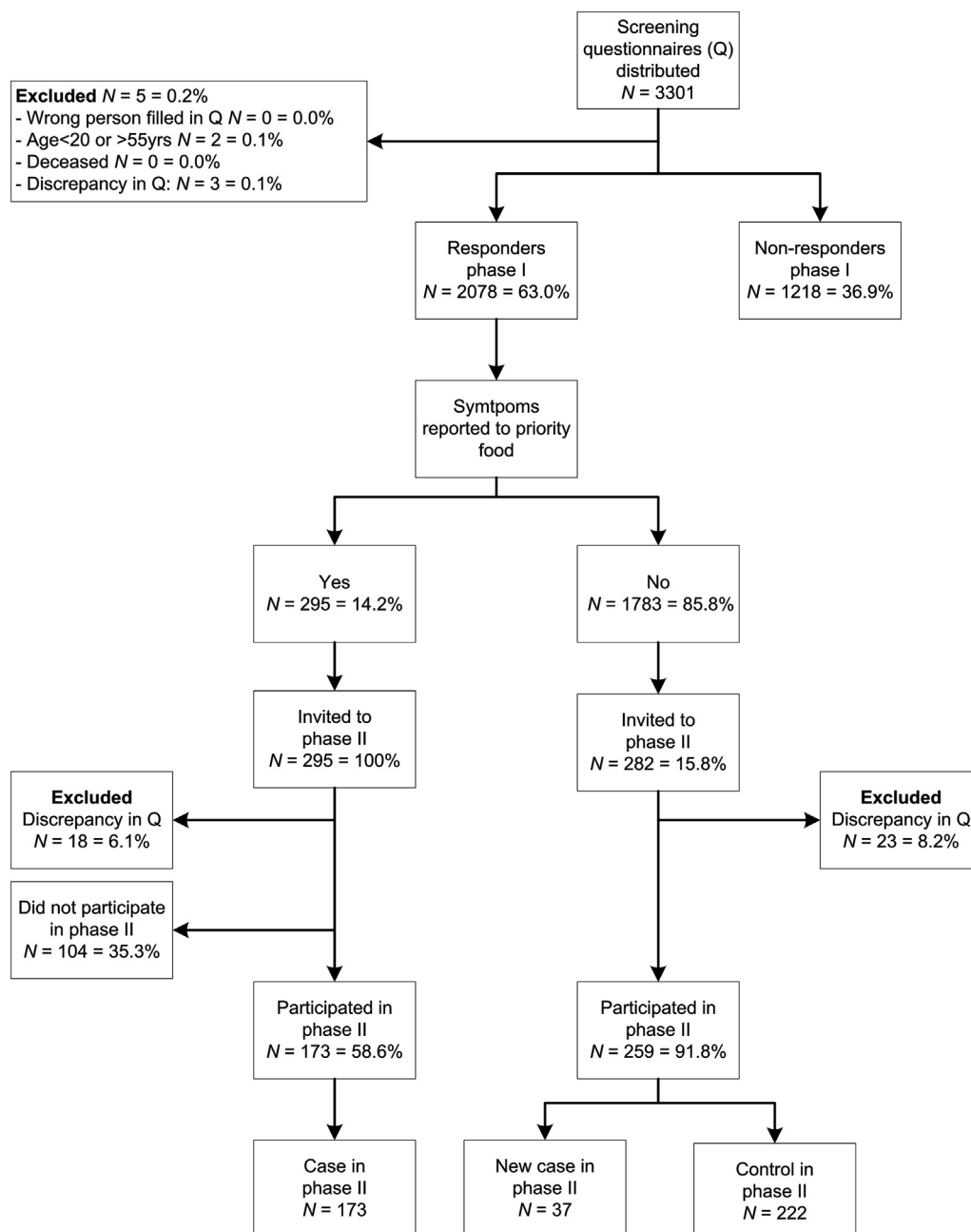


FIGURE E4. Flowchart Reykjavik. Case = subject self-reporting symptoms to at least 1 priority food. Control = subject not reporting symptoms to any priority food.

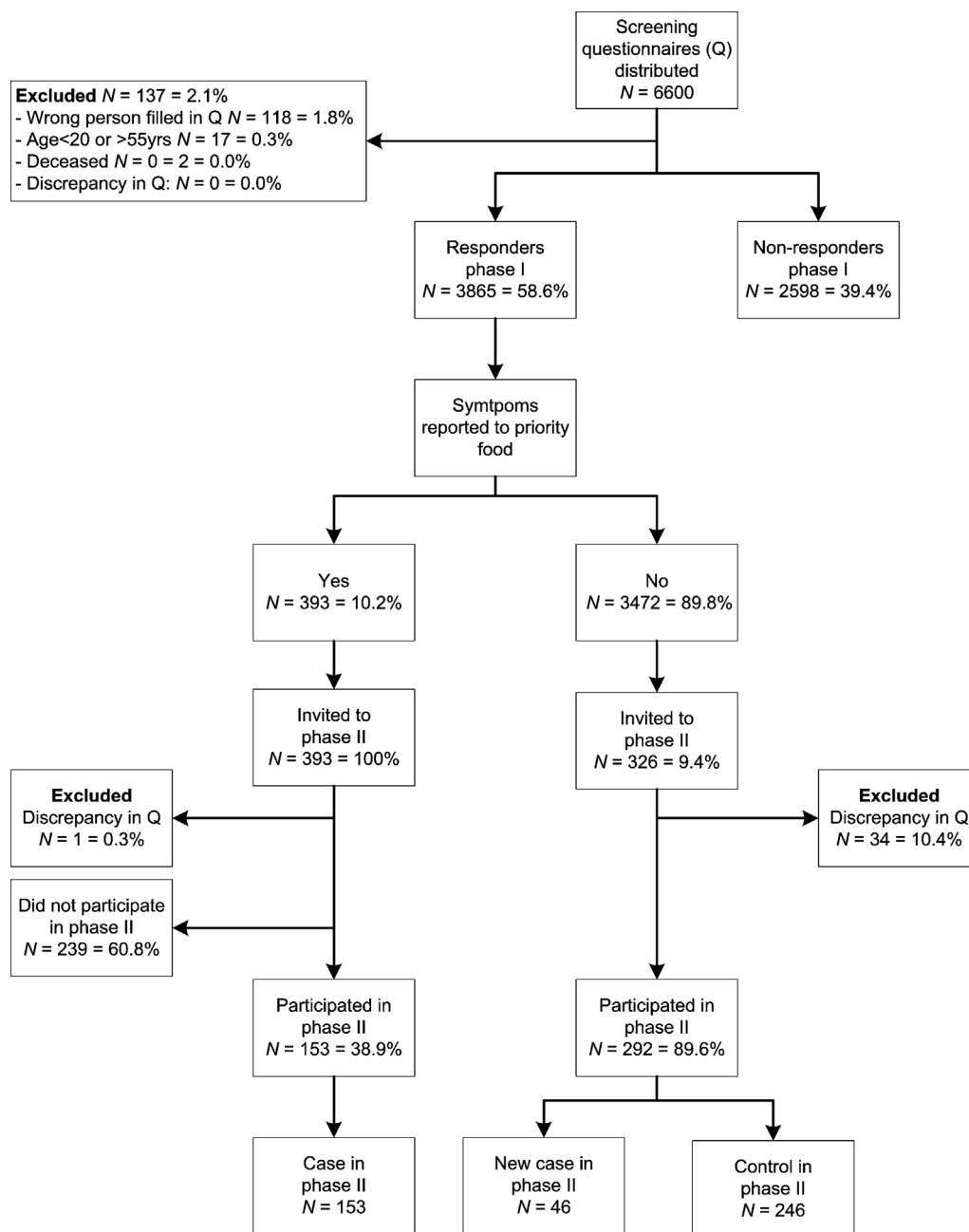


FIGURE E5. Flowchart Utrecht. Case = subject self-reporting symptoms to at least 1 priority food. Control = subject not reporting symptoms to any priority food.

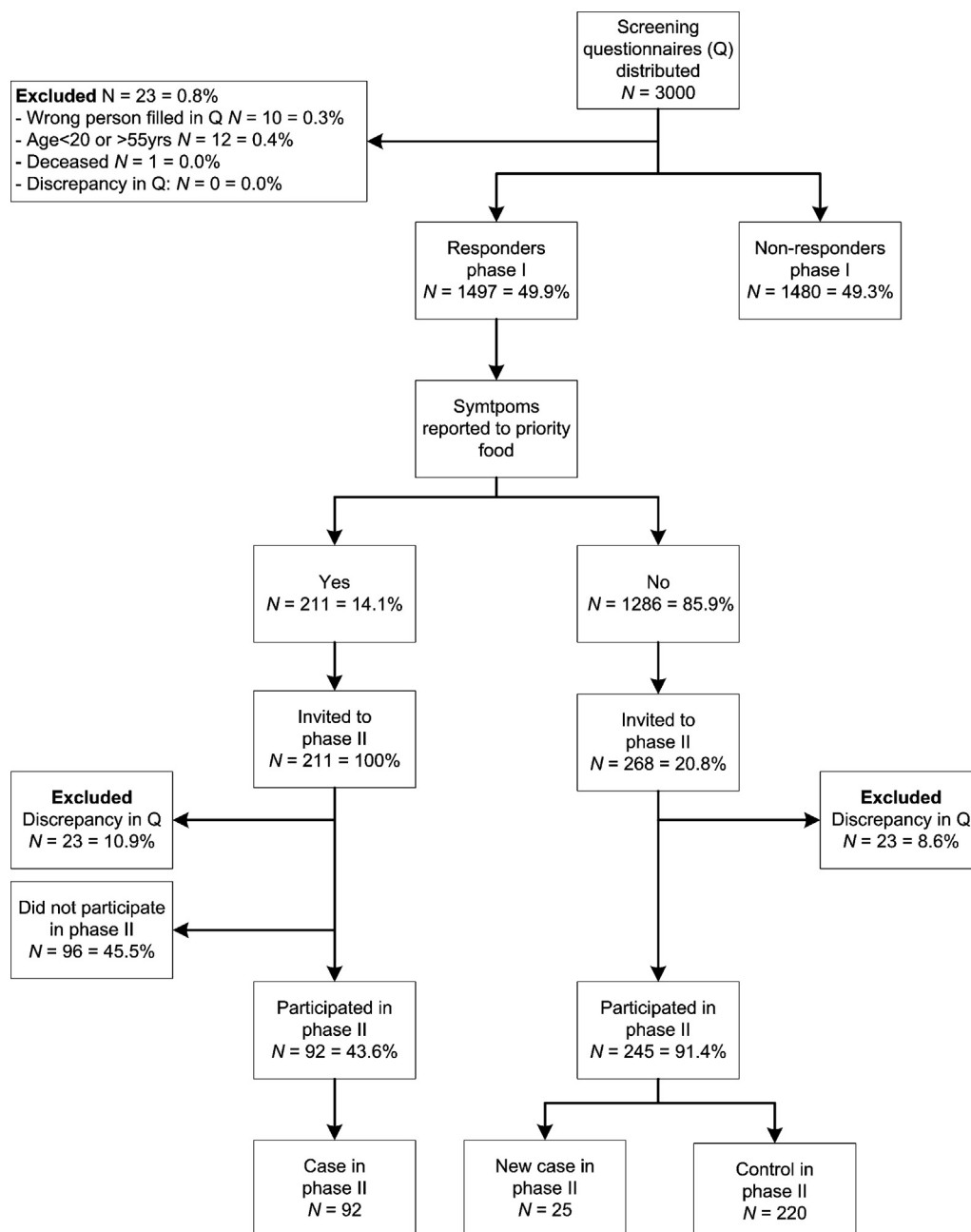


FIGURE E6. Flowchart Lodz. Case = subject self-reporting symptoms to at least 1 priority food. Control = subject not reporting symptoms to any priority food.

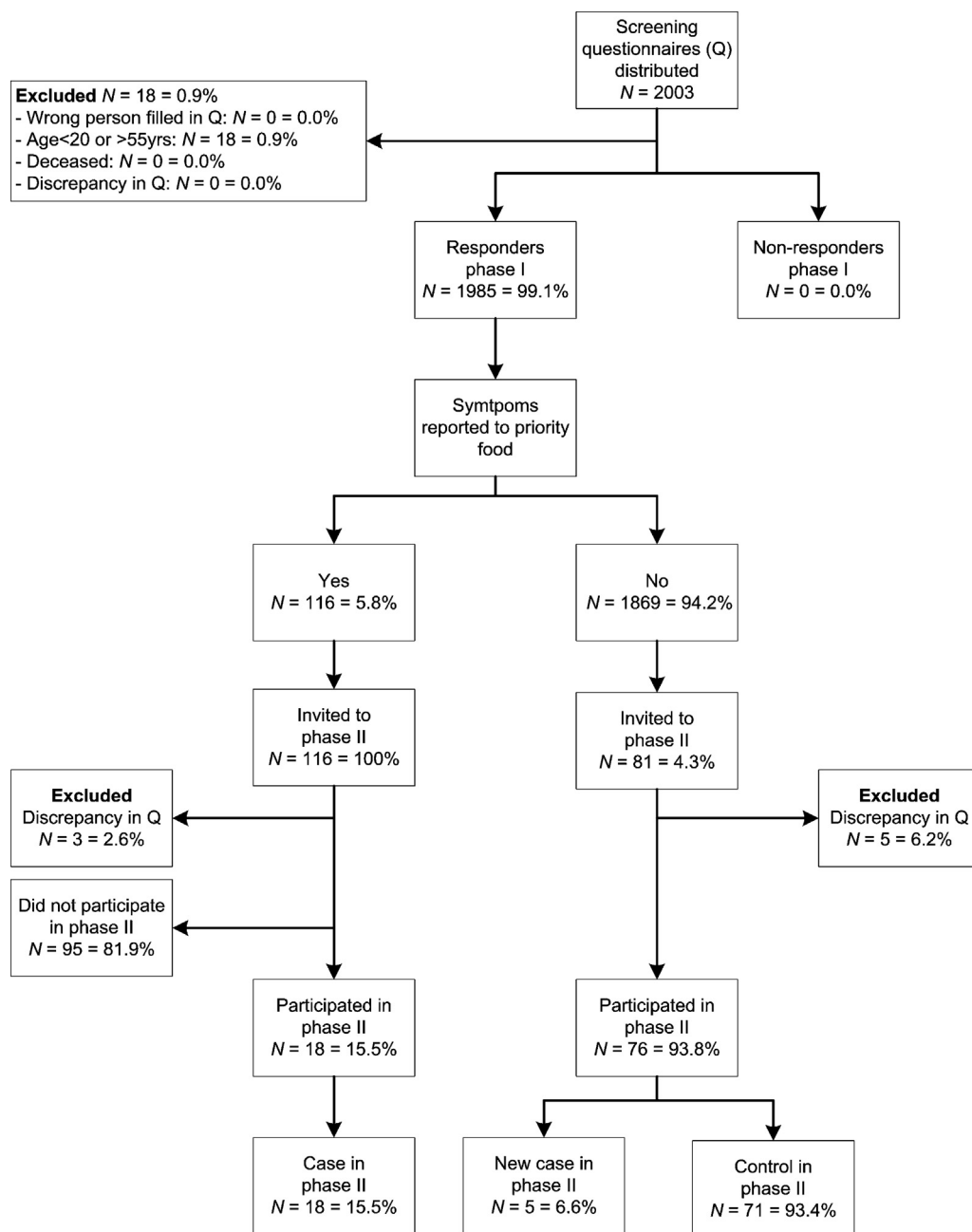


FIGURE E7. Flowchart Athens. Case = subject self-reporting symptoms to at least 1 priority food. Control = subject not reporting symptoms to any priority food.

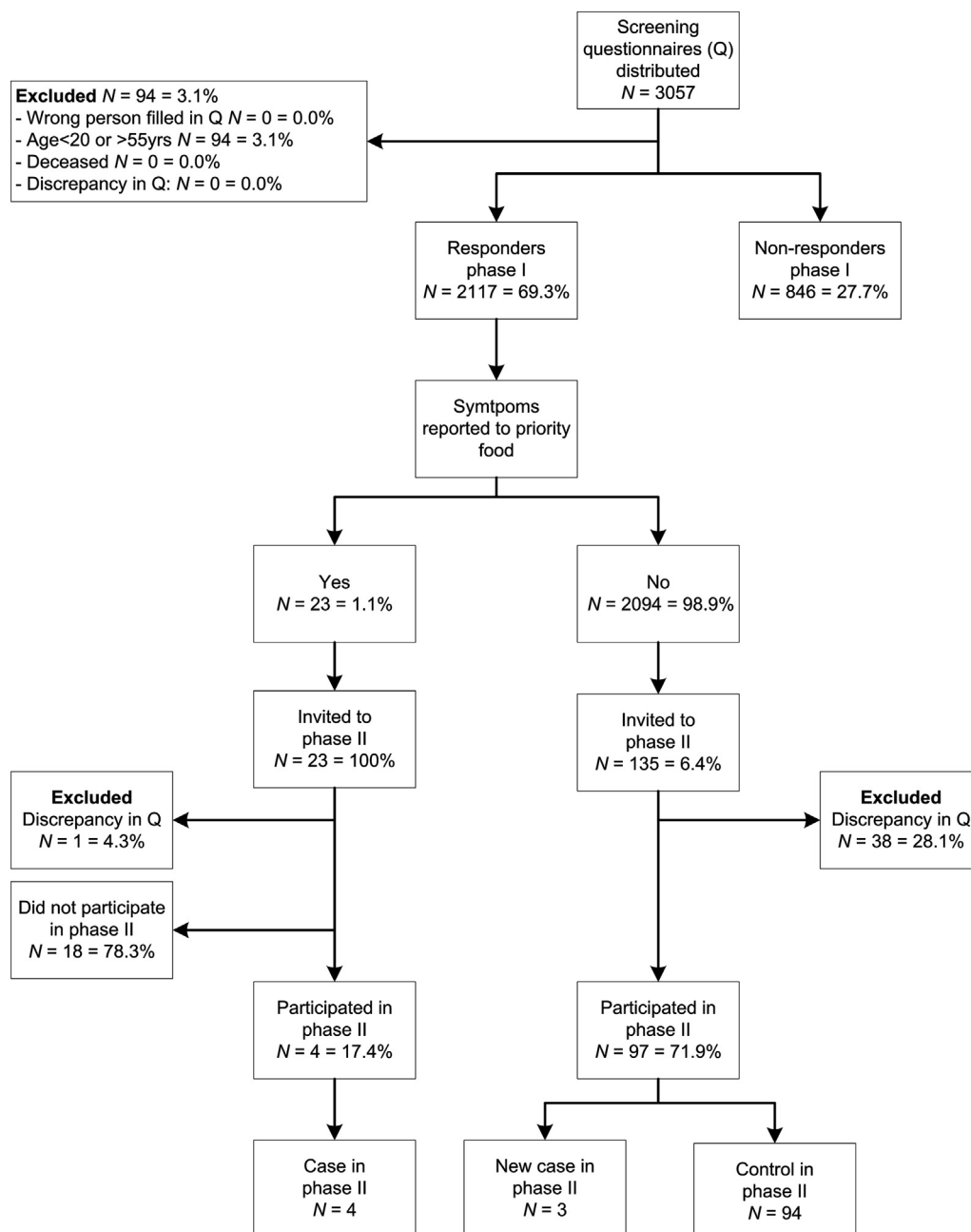


FIGURE E8. Flowchart Sofia. Case = subject self-reporting symptoms to at least 1 priority food. Control = subject not reporting symptoms to any priority food.

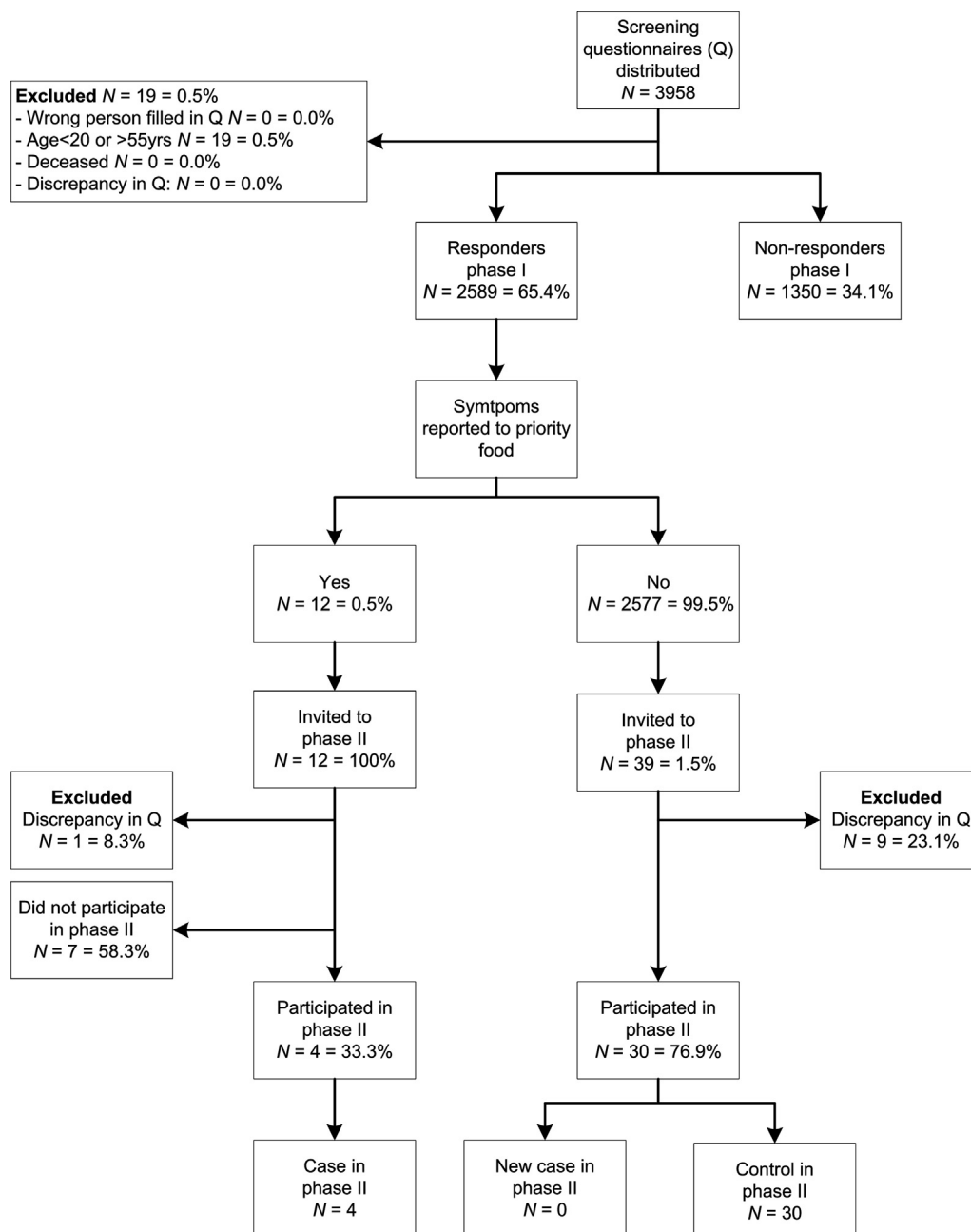


FIGURE E9. Flowchart Vilnius. Case = subject self-reporting symptoms to at least 1 priority food. Control = subject not reporting symptoms to any priority food.

TABLE E1. Comparison of prevalence of probable food allergy based on imputed data vs complete case analysis

Prevalence (95% CI) of probable FA to:												
	Zurich I	Zurich CC	Madrid I	Madrid CC	Reykjavik I	Reykjavik CC	Lodz I	Lodz CC	Utrecht I	Utrecht CC	Athens I	Athens CC
At least 1 priority food	5.64 (3.94-7.66)	8.39 (5.98-11.21)	3.28 (1.78-5.35)	5.62 (3.29-8.64)	1.36 (0.57-2.54)	1.97 (0.89-3.52)	2.84 (1.51-4.65)	4.70 (2.72-7.26)	2.12 (1.19-3.35)	4.48 (2.76-6.62)	0.31 (0.02-1.65)	1.72 (0.01-6.48)
Hazelnut	2.57 (1.47-4.02)	4.51 (2.77-6.70)	0.76 (0.16-1.96)	1.20 (0.29-2.86)	0.10 (0.00-0.60)	0.16 (0.00-0.82)	1.33 (0.49-2.66)	2.41 (1.06-4.37)	0.93 (0.36-1.81)	2.39 (1.18-4.04)	0.06 (0.19-0.99)	0.34 (0.41-3.41)
Peach	2.02 (1.08-3.30)	3.32 (1.85-5.24)	1.61 (0.63-3.18)	2.67 (1.16-4.92)	0.00 (0.00-0.28)	0.00 (0.00-0.34)	0.45 (0.05-1.35)	0.95 (0.21-2.32)	0.60 (0.17-1.33)	1.53 (0.60-2.90)	0.10 (0.00-1.14)	0.69 (0.16-4.32)
Apple	1.90 (0.99-3.15)	3.37 (1.89-5.31)	0.57 (0.08-1.65)	0.65 (0.07-2.00)	0.05 (0.02-0.48)	0.08 (0.02-0.63)	0.75 (0.17-1.83)	1.58 (0.54-3.24)	0.91 (0.34-1.77)	2.33 (1.14-3.95)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Kiwi	1.34 (0.60-2.42)	1.65 (0.68-3.10)	0.64 (0.11-1.77)	0.92 (0.17-2.44)	0.31 (0.02-0.99)	0.49 (0.06-1.41)	0.30 (0.01-1.09)	0.63 (0.08-1.82)	0.57 (0.15-1.29)	0.98 (0.28-2.12)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Carrot	1.01 (0.39-1.97)	1.66 (0.68-3.11)	0.81 (0.18-2.03)	0.75 (0.10-2.17)	0.38 (0.05-1.12)	0.41 (0.04-1.28)	0.15 (0.00-0.80)	0.32 (0.00-1.27)	0.23 (0.01-0.76)	0.60 (0.10-1.55)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Walnut	0.58 (0.11-1.45)	0.67 (0.13-1.69)	0.71 (0.14-1.88)	1.65 (0.53-3.52)	0.05 (0.02-0.48)	0.08 (0.02-0.63)	0.15 (0.00-0.80)	0.32 (0.00-1.27)	0.10 (0.00-0.51)	0.27 (0.00-0.99)	0.29 (0.02-1.61)	1.72 (0.01-6.48)
Melon	0.46 (0.09-1.17)	0.61 (0.11-1.60)	0.95 (0.25-2.24)	1.75 (0.58-3.66)	0.10 (0.00-0.60)	0.16 (0.00-0.82)	0.00 (0.00-0.36)	0.00 (0.00-0.44)	0.05 (0.01-0.39)	0.13 (0.01-0.72)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Shrimp	0.37 (0.05-1.04)	0.42 (0.04-1.29)	0.82 (0.19-2.04)	1.47 (0.43-3.27)	0.36 (0.04-1.08)	0.57 (0.09-1.54)	0.35 (0.02-1.18)	0.35 (0.01-1.33)	0.36 (0.06-0.97)	0.44 (0.04-1.30)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Peanut	0.37 (0.02-1.17)	0.38 (0.03-1.22)	0.45 (0.05-1.45)	1.10 (0.24-2.71)	0.00 (0.00-0.28)	0.00 (0.00-0.34)	0.35 (0.02-1.18)	0.35 (0.01-1.33)	0.05 (0.01-0.39)	0.13 (0.01-0.72)	0.02 (0.00-0.82)	0.00 (0.00-1.84)
Celery	0.24 (0.01-0.81)	0.48 (0.05-1.38)	0.00 (0.00-0.44)	0.00 (0.00-0.55)	0.33 (0.03-1.03)	0.33 (0.02-1.13)	0.07 (0.02-0.63)	0.16 (0.01-0.94)	0.03 (0.03-0.32)	0.07 (0.03-0.56)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Milk	0.24 (0.00-1.02)	0.00 (0.00-0.33)	0.18 (0.00-0.97)	0.27 (0.00-1.32)	0.00 (0.00-0.28)	0.00 (0.00-0.28)	0.12 (0.01-0.74)	0.16 (0.01-0.94)	0.00 (0.00-0.21)	0.00 (0.00-0.30)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Wheat	0.19 (0.00-0.73)	0.38 (0.03-1.22)	0.37 (0.02-1.31)	0.38 (0.01-1.51)	0.10 (0.00-0.60)	0.16 (0.00-0.82)	0.00 (0.00-0.36)	0.00 (0.00-0.44)	0.05 (0.01-0.39)	0.13 (0.01-0.72)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Lentil	0.16 (0.07-0.93)	0.00 (0.00-0.33)	0.00 (0.00-0.44)	0.00 (0.00-0.55)	0.00 (0.00-0.28)	0.00 (0.00-0.34)	0.00 (0.00-0.36)	0.00 (0.00-0.44)	0.03 (0.03-0.32)	0.07 (0.03-0.56)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Tomato	0.10 (0.00-0.55)	0.19 (0.00-0.87)	0.15 (0.01-0.90)	0.27 (0.00-1.32)	0.15 (0.00-0.71)	0.25 (0.00-0.98)	0.30 (0.01-1.10)	0.63 (0.08-1.82)	0.08 (0.01-0.46)	0.20 (0.00-0.86)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Soy	0.08 (0.02-0.56)	0.10 (0.02-0.66)	0.00 (0.00-0.44)	0.00 (0.00-0.55)	0.00 (0.00-0.28)	0.00 (0.00-0.34)	0.00 (0.00-0.36)	0.00 (0.00-0.44)	0.03 (0.03-0.32)	0.07 (0.03-0.56)	0.00 (0.00-0.68)	0.00 (0.00-0.68)
Banana	0.05 (0.02-0.42)	0.10 (0.02-0.66)	0.04 (0.00-0.65)	0.00 (0.00-0.55)	0.49 (0.08-1.29)	0.58 (0.09-1.55)	0.00 (0.00-0.36)	0.00 (0.00-0.44)	0.05 (0.01-0.39)	0.13 (0.01-0.72)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Corn	0.05 (0.02-0.42)	0.10 (0.02-0.66)	0.00 (0.00-0.44)	0.00 (0.00-0.55)	0.05 (0.02-0.48)	0.08 (0.02-0.63)	0.00 (0.00-0.36)	0.00 (0.00-0.44)	0.00 (0.00-0.21)	0.00 (0.00-0.30)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Sunflower seed	0.05 (0.02-0.42)	0.10 (0.02-0.66)	0.00 (0.00-0.44)	0.00 (0.00-0.55)	0.00 (0.00-0.28)	0.00 (0.00-0.34)	0.00 (0.00-0.36)	0.00 (0.00-0.44)	0.00 (0.00-0.21)	0.00 (0.00-0.30)	0.07 (0.17-1.05)	0.34 (0.41-3.41)
Sesame seed	0.03 (0.00-0.37)	0.00 (0.00-0.33)	0.00 (0.00-0.44)	0.00 (0.00-0.55)	0.00 (0.00-0.28)	0.00 (0.00-0.34)	0.00 (0.00-0.36)	0.00 (0.00-0.44)	0.00 (0.00-0.21)	0.00 (0.00-0.30)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Fish	0.02 (0.00-0.35)	0.00 (0.00-0.33)	0.44 (0.04-1.44)	0.38 (0.01-1.51)	0.15 (0.00-0.71)	0.25 (0.00-0.98)	0.00 (0.00-0.36)	0.00 (0.00-0.44)	0.08 (0.01-0.46)	0.20 (0.00-0.86)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Buckwheat	0.00 (0.00-0.25)	0.10 (0.02-0.66)	0.00 (0.00-0.44)	0.00 (0.00-0.55)	0.00 (0.00-0.28)	0.00 (0.00-0.34)	0.00 (0.00-0.36)	0.00 (0.00-0.44)	0.00 (0.00-0.21)	0.00 (0.00-0.30)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Egg	0.00 (0.00-0.25)	0.00 (0.00-0.33)	0.06 (0.00-0.70)	0.00 (0.00-0.55)	0.21 (0.00-0.81)	0.33 (0.01-1.13)	0.31 (0.01-1.11)	0.63 (0.08-1.82)	0.00 (0.00-0.21)	0.00 (0.00-0.30)	0.02 (0.00-0.84)	0.00 (0.00-1.84)
Mustard seed	0.00 (0.00-0.25)	0.00 (0.00-0.33)	0.00 (0.00-0.44)	0.00 (0.00-0.55)	0.00 (0.00-0.28)	0.00 (0.00-0.34)	0.03 (0.00-0.52)	0.00 (0.00-0.44)	0.00 (0.00-0.21)	0.00 (0.00-0.30)	0.00 (0.00-0.68)	0.00 (0.00-1.84)
Poppy seed	0.00 (0.00-0.25)	0.00 (0.00-0.33)	0.00 (0.00-0.44)	0.00 (0.00-0.55)	0.00 (0.00-0.28)	0.00 (0.00-0.34)	0.00 (0.00-0.36)	0.00 (0.00-0.44)	0.00 (0.00-0.21)	0.00 (0.00-0.30)	0.00 (0.00-0.68)	0.34 (0.41-3.41)

I: Prevalence based on imputed data. CC: Prevalence based on complete case analysis (= data without imputations).

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