# Title

Frequency of food allergy in school-aged children in eight European countries – the EuroPrevall-iFAAM birth cohort

**Short title**

Frequency of food allergy in European school children

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**Contributions**

ENCM was overall coordinator of the collaborative research initiatives EuroPrevall and iFAAM and supervised food challenge meals; KB was initiator, principal investigator and iFAAM theme leader of the birth cohort study; TK was co-PI and iFAAM work package leader of the birth cohort; LG coordinated the iFAAM school-age follow-up of the birth cohort, carried out statistical analyses, and prepared the

manuscript; RvR was responsible for laboratory analyses for the whole project (data not used in this manuscript) and participated in the planning of the study design; SV conducted the laboratory analyses; MFR was responsible for laboratory analyses including skin prick tests and participated in the planning of the study design; PC was responsible for all central IT aspects, and participated in the planning of the school-age follow-up; AR was responsible for the central data management, participated in the cohort management and planning of the study; all authors participated in the planning and local implementation of the follow-up assessment including the clinical visits; all authors reviewed and commented the draft of the manuscript and approved the final version.

# Abstract

*Background.* The prevalence of food allergy (FA) among European school children is poorly defined. Estimates have commonly been based on parent-reported symptoms. We aimed to estimate the frequency of FA and sensitization against food allergens in primary school children in eight European countries.

*Methods.* A follow-up assessment at age 6-10 years of a multi-centre European birth cohort, based was undertaken using an online parental questionnaire, clinical visits including structured interviews and skin prick tests (SPT). Children with suspected FA were scheduled for double-blind, placebo-controlled oral food challenges (DBPCFC).

*Results.* 6,105 children participated in in this school-age follow-up (57.8% of 10,563 recruited at birth). For 982 of 6,069 children (16.2%), parents reported adverse reactions after food consumption in the online questionnaire. Of 2,288 children with parental face-to-face interviews and/or skin prick testing, 238 (10.4%) were eligible for a DBPCFC. 63 foods were challenge-tested in 46 children. 20 food challenges were positive in 17 children, including seven to hazelnut and three to peanut. Another seventy-one children were estimated to suffer FA among those who were eligible but refused DBPCFC. This yielded prevalence estimates for FA in school-age between 1.4% (88 related to all 6,105 participants of this follow-up) and 3.8% (88 related to 2,289 with completed eligibility assessment).

*Interpretation.* In primary school children in eight European countries, the prevalence of FA was lower than expected even though parents of this cohort have become especially aware of allergic reactions to food. There was moderate variation between centres hampering valid regional comparisons.

# Introduction

Validly measuring the frequency of food allergy (FA) in the general population has been challenging, mainly due to the disease being very heterogeneous in terms of eliciting food allergens and clinical signs and symptoms. Furthermore, it is difficult to differentiate FA from other food hypersensitivities, such as food intolerances, in the general population. The different study settings and designs, case definitions, individual interpretations of the medical history including observed appearances of FA and varying consumption habits have hampered sound comparisons of FA prevalence between research projects, geographic regions and time trends.[1-3] For example, studies aiming to estimate the prevalence of FA have applied different assessment techniques from questionnaires to double-blind placebo-controlled food challenges and have arrived at profoundly different estimates.[4-9] A cross-sectional study in Germany targeting children from birth to 17 years reported a prevalence of FA of 61.6% based on self- and parent-reported information. Subsequently, suspected cases of FA were examined clinically with food challenge tests, giving an estimated prevalence of confirmed FA of 2.2%.[7] In a Danish sample including children and adults aged 4 to 22 years, the prevalence of FA was estimated at 1.0% and 0.3% based on open (i.e. non-blinded) and double-blind, placebo-controlled food challenges (DBPCFC), respectively.[5] The prevalence of self-reported FA assessed in primary school-age children was estimated at almost 6% in Turkey, and 6% to 12% in the United Kingdom. However, using DBPCFC led to prevalence estimates of 0.7% to 1.4% in these studies.[4,8,10,11]

The methodological challenges of assessing reactions to foods have prompted the development of standards for the diagnosis of FA, mainly in clinical settings.[12] The birth cohort study from EuroPrevall (The prevalence, cost and basis of food allergy in eight European countries) agreed on a harmonized approach in all centres to confirm suspected FA using the diagnostic clinical gold-standard, i.e. DBPCFC, stringently in a large scale population-based study.[13,14] Based on PRACTALL recommendations, the documentation and interpretation of oral food challenges has been developed further for the school-age follow-up of the birth cohort.[12,15]

In this manuscript we report the range of frequencies of challenge-confirmed FA and sensitization against food allergens in primary school children from eight countries covering different European regions.

# Methods

*Study design and setting.* Starting in 2005, the EuroPrevall birth cohort set out to recruit newborns from nine European countries, to prospectively trace the onset of food allergy (FA) from birth to 2.5 years.[14,16,17] Within the EU-funded iFAAM project (Integrated approaches to food allergen and allergy management), eight of the nine study centres (Iceland, United Kingdom, The Netherlands, Germany, Poland, Lithuania, Spain, and Greece) took part in a single follow-up assessment at early school age (6 to 10 years, between 2014 and 2017). This follow-up aimed to reach all children initially recruited at birth (10,563), and document any previous parent-reported reactions to food as well as the current FA status. Ethical approval was obtained separately for all participating country, as listed above.

*Participants and sample definitions (denominators).* Recruitment details have previously been described.[14] All recruited children of the EuroPrevall birth cohort (excluding the study centre in Italy) were re-invited for the current follow-up by invitation letters, electronic mail, and/or telephone calls, for up to seven approaches, as required.

Parents were asked to complete an online questionnaire at home, at the same time providing consent to participate in the follow-up. A very limited number of questionnaires were completed in the study centre or via telephone interviews, e.g. in cases where parents were unable or unwilling to access/complete the questionnaire by themselves. The questionnaire included items about previous reactions to food. Questionnaire data was reported for those with completed FA screening questions and the consumption history for a selection of commonly allergenic foods.

All children, irrespective of their FA history, were invited for a clinical visit to the local study centre, including a face-to-face interview on previous and current food reactions, consumption habits, and skin prick test (SPT) to a pre-defined panel of foods and aeroallergens, as well as foods reported to have previously caused reactions. The eligibility for one or more oral food challenges was defined using an algorithm based on interview data and SPT results (Figure 2). All forms and the diagnostic triage have been previously described.[15] Study outcomes based on interview data are reported for those who completed the clinical interview and have documented challenge eligibility.

*Data sources and variables (case definitions, numerators).* All outcome data reported in this manuscript were collected within the school-age follow-up of the birth cohort. Reports on previous or current reactions to food were derived from a single screening question (Q1, Figure 2), further differentiated by physician's diagnosed FA, challenge-proven FA, symptoms by organ system, exposure-symptom interval,

age at first occurrence (all Q3), tolerance development (Q4) and recent consumption (Q2, previous 3 months). Both the online-questionnaire and the clinical face-to-face interview covered all these aspects.[15]

The current FA status (period/current prevalence of the potential to react if exposed) was defined for a selected list of foods (termed core foods): cow's milk, hen's egg, wheat, soy, peanut, hazelnut, white and oily fish and crustacean shell-fish. The consumption history for non-core foods was not assessed for children who never reported problems to a specific food.

A multi-level outcome assessment for the likelihood of current FA was derived from the questionnaire/interview data using a decision algorithm.[15] This was further differentiated by details of recent symptoms, and avoidance behaviour. Food challenge eligibility was derived from the likelihood of current FA, complemented by SPT results i.e. individuals not currently consuming a suspected food with either previous symptoms following consumption of that food and/or a positive SPT (valid controls and largest wheal diameter ≥3mm, Figure 2) to that food.

*Assessment by DBPCFC tests.* These were conducted based on previously published methodology,[12] and documented and interpreted as previously described.[15] In brief, an escalating seven-dose protocol was followed to challenge children suspected to have FA. Children, families and medical staff were fully blinded to the order of the food/placebo given. Placebo days may have served as controls for more than one food, with each food/placebo tested on a separate day.

*Assessment of differential non-response.* With the expectedly high attrition, we used several sources of information to assess differential non-response at school age, aiming to cover important characteristics in question to impact and/or predict allergy development. From the baseline assessment of the birth cohort we included the following: the child's sex, delivery mode, season of birth, use of antibiotics in the first week of life, older siblings, mother's current and smoking during pregnancy, cat and dog in household, parental allergies, child's eczema (parental report of eczema symptoms) and child's FA (previously proven by DBPCFC within the study). From the school-age follow-up we included common atopy-associated diseases (asthma, allergic rhinitis and eczema), FA outcomes as described above, food-specific consumption habits and SPT results.

*Statistics and Software.* Study data was entered via a web interface, either by parents (questionnaire) or by study personnel (all other forms). The server architecture was specifically designed for data capturing in this project and to track completeness and congruency of the follow-up assessment. Cleaning and statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The initial sample size was set to assess the incidence of FA up to age 2 years, as described before.[14] Outcome measures are

reported by study centre, eliciting food and assessment method (questionnaire vs. interview). Raw frequencies were calculated as fractions of case definitions over corresponding samples, as described in the above subsections. Missing single items, besides those used to define sample membership, did not lead to the exclusion of the form or participant.

The potential for differential loss to follow-up was assessed comparing baseline characteristics and available outcome measures between groups of participants attending different numbers of follow-up assessments: (1) lost to follow-up, (2) questionnaire only, (3) eligible but not challenged, (4) eligible and challenged, and (5) not eligible, using group-to-group comparisons with a Chi-squared statistic. Comparing the characteristics in three different group-to-group assessments, comparisons with a p-value below 0.001 are highlighted. However, dichotomous test results were not used to guide the extrapolation strategy. As a manual weighting approach, the outcome frequencies in groups which were assessed were used as substitutes for groups where data for this outcome was not available. As an example, groups (3) and (4) were assumed to be quite similar, so the relative frequency of challenge-proven FA in those who completed the challenges (group (4)) was used to estimate the absolute number of potentially food allergic children in those who were not challenged. With the expectedly large differences between point estimates introduced by different but all justifiable sets of assumptions, we report ranges of frequency estimates. Confidence intervals for proportion estimates were calculated assuming that errors follow the beta distribution, and using sample sizes of actually assessed children for the respective outcome.

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# Results

*Participants.* Parents completed the online-questionnaire for 6,069 out of the 10,563 children recruited at birth (57.5%) at age 6-10 years. Of these 38.3% (n=2,322) of those came to the study centres for the face-to-face interview and physical examination including skin prick testing (SPT), which was carried out in 2,188 participants (Figure 1). Questionnaire response differed by centre, ranging from 39.8% of those recruited in Southampton, UK to 70.5% in Reykjavik, Iceland (Table 1). The mean age at follow-up was 8.3 years (standard deviation 0.9). This report therefore covers a total observation period of 50,733 person-years. The online-questionnaire and the face-to-face interview allowed estimation of the frequency symptoms after food consumption until school age based on parental reports.

*Lifetime prevalence of symptoms after food consumption and physician's diagnosis of food allergy reported by the parents*. Of the 6,069 children who completed the online questionnaire, 982 (16.2% [15.3-17.1]) had previous adverse reactions after food consumption. Physician's diagnosis of FA was less frequent when compared to symptoms alone for all countries, both based on parent report. Cow's milk, hen's egg, peanut, hazelnut, and wheat were the five most commonly implicated food items as causing symptoms (Table 1. e-Table 2). Numbers were similar for the 2,322 children who came to the study centre for the face-to-face interview (e-Table 1). The majority (85.0 %) of the reported reactions occurred <2 hours after food consumption. Skin symptoms such as rash or pruritus (itching) and gastrointestinal reactions such as diarrhoea were the most frequently reported symptoms in all countries (e-Table 3, e-Table 4).

*Food consumption and avoidance at school age.* Based on 6,069 online-questionnaires almost all children consumed foods containing cow's milk, hen's egg and wheat. Among the "core foods", soy and crustacean shell-fish were consumed less often by school-aged children. The reason for not consuming a particular food was usually because that food was not part of the regular diet of the family, as assessed in the face-to-face interview. The foods most often avoided to prevent the development of FA were peanut and hazelnut (e-Table 5).

*Food allergy at school age – patient history.* 2,289 children completed the eligibility assessment, based on reaction history (face-to-face interview) and complemented with allergic sensitization status based on skin prick tests (Figure 1). The decision tree to define current FA status was applied to all core foods separately, e.g. for peanut, for 57 of 2,322 children's parents reported allergic symptoms after peanut consumption (Figure 2, Question 1 "yes"). If children either did not become tolerant as described in the patient history (Question 4 "no/don't know", n=40) or became tolerant but did not consume the food

without symptoms recently (previous 3 months, Question 2 “no”, n=4), they were assessed further as likely food allergic. The majority (2,265) of children had never had symptoms upon peanut consumption (Figure 2, Question 1 “no”), and if peanuts were consumed in the previous 3 months without symptoms (Question 2 “yes”, n=1,863), the child was not eligible for a challenge (Type A), i.e. not peanut allergic on the basis of history alone. In children who did not consume peanuts in the last 3 months (n=402) FA had to be considered possible as reactions upon exposure could not be ruled out (Figure 2, Table 2).

*Food allergy at school age - Skin Prick Test (SPT)*. A total of 223 of 2,188 children (10.2% [9.0-11.5]) had a positive (≥3 mm) SPT to one or more “core foods”. Sensitization to peanut (5.6%) and hazelnut (5.2%) was most frequent (Figure 3).

*Food allergy at school age - DBPCFC*. Of 2,289 children for which eligibility was documented, 238 (10.4% [9.2-11.7]) were eligible for DBPCFC, either because they were likely to react based on the face-to-face interview (e.g. 42 children for cow’s milk and 34 for hen’s egg) or because they had not consumed the suspected food within the last 3 months and were sensitized to it (four children for cow’s milk and six for hen’s egg). The latter was common for hazelnut and peanut with 42 and 36 children, respectively (Table 2). In total, we performed 63 DBPCFC in 46 children, most often to assess hazelnut and peanut (16 and 15 challenges, respectively). The parents of 192 participants refused the DBPCFC (Figure 1).

Twenty DBPCFC days where the incriminated food was given to 17 children were rated positive (two with less pronounced symptoms on the placebo test day, and three without a placebo test day as the parents refused the placebo day after a clear positive reaction on the previous day where the incriminated food was given). Seven placebo tests were rated as positive out of all placebo challenges conducted in this study.

The 17 of 2,097 (0.8% [0.5-1.3]) completely assessed children with a positive DBPCFC included seven children who reacted to hazelnut (0.3% [0.1-0.7]) and three to peanut (0.1% [0.0-0.4]). Only one child reacted to hen’s egg (seven were challenged) and none to cow’s milk (six were challenged, Table 2). Parents of all seven hazelnut-allergic children reported nasal symptoms in their children in the previous 12 months and two children had a physician’s diagnosed allergic rhinitis. Among non-core foods, cashew (2), pine nut (2) and walnut (1) had positive DBPCFC tests (e-Table 6).

*Differential attrition.* Frequency of FA within the whole cohort sample was extrapolated as not all participants completed all the necessary diagnostic steps to confirm or rule out current (prevalent) FA in school-age. Children who did not take part in the school-age follow-up (group 1) came more often from less educated families but were quite similar in terms of allergic family predisposition, eczema in infancy

and early childhood and other factors to those whose parents responded to the questionnaire but refused the clinical assessment of their child (group 2). Therefore, frequencies of FA in group 2 were used as substitutes for those not participating in the school-age follow-up (data and group labels in Table 3).

Children who came for a clinical visit, but were not eligible for a food challenge (group 5) had more parent-reported allergic rhinitis, eczema and more often an allergic family history than those only responding to the questionnaire (group 2). They were similar with regard to other potential indicators of FA such as sex and caesarean section (Table 3). Therefore, using FA frequencies from group 5 as substitutes for those not showing up for the clinical visit may yield only slightly upwards biased estimates.

Those children eligible, but whose parents refused the oral challenge testing (group 3), were quite similar to those eligible and successfully challenged (group 4). The detailed comparison of these two groups in terms of food-specific sensitization, current symptoms (12m), previous FA diagnosis, and specific food avoidance behaviour showed also very similar distributions. Specifically, the proportion of SPT positivity was similar in groups 3 and 4, with a considerable difference only in hen's egg sensitization (Table 4 and eFigure 1). Thus, FA frequency in group 4 was used to estimate the number of potential food allergic children in group 3 (Table 3).

*Adjusted frequency of food allergy.* A total of 238 children were eligible for an oral food challenge, of which 46 underwent a DBPCFC (group 4). In 192 children parents refused this diagnostic step (group 3). In addition to the 17 positively challenged children, 71 children were estimated to have FA in the group eligible but refusing the challenge procedure under the assumption of identical FA prevalence in those challenged and those eligible but not challenged (Tables 3 and 4), summing up to an estimated number of 88 cases (rounding for the all-country estimator). These 88 cases would lead to an extrapolated prevalence estimate of 3.8% in the group of all 2,289 children who completed the eligibility assessment. Under the assumption that all who participated in this follow-up but were not eligible for a food challenge had no FA, these estimated 88 cases would extrapolate to a school-age lower limit prevalence of current FA of 1.4% (of 6,105 children, Figure 4). Furthermore, considering the high similarity between those who participated only in the questionnaire assessment and those who were lost to follow-up by school-age, a lower-limit prevalence of current FA for the whole cohort would be 0.8% (88 of 10,563). Note that these estimates rely on a simple group-wise extrapolation approach only.

# Discussion

*Key results.* In 17 of 2,097 completely assessed school age children from this European birth cohort study, food allergy (FA) to at least one allergen source was confirmed, yielding an average raw prevalence of 0.8% across all eight countries involved, as a lower limit estimate. Extrapolating to all children who completed the eligibility assessment, we estimated an adjusted FA prevalence between 1.4% (extrapolated to all children with questionnaire data) and 3.8% (extrapolated to those with completed eligibility assessment). Most of the positively challenged children reacted only mildly or moderately, except for five children with severe signs or symptoms during DBPCFC. However, more severe reactions might have been observed if those eligible but refusing to undergo the challenge were actually challenged. The most common allergens responsible for FA in school-age and for allergic sensitization assessed by skin tests were hazelnut and peanut.

The low absolute numbers per study centre hampered valid regional comparisons.

*Comparison with other studies.* Previous prevalence surveys were conducted only as single centre studies, and used different approaches hampering inter-country comparisons. As our measures were highly standardized, this is the first European multicentre study to report comparable estimates for the prevalence of FA in primary school-age. Results of our study were in line with the few previous studies of children with comparable age from Turkey with a prevalence of 0.7% at 6-9 years,[4] and 1.4% for 6,[8] and 1.3% for 10 year olds from the UK[10] though these studies did not report adjusted estimates. However, the MAAS study in the UK reported peanut allergy prevalence alone of about 2% at age 8 years of age.[11] The prevalence of FA in the HealthNuts study in Australia was estimated higher at 3.8% but in pre-school children at 4 years of age; however early life FAs against cow's milk and hen's egg are still more prevalent than among school-age children who have mostly become tolerant against these foods.[18] Compared to the previous studies from Europe we did not find an indication for an increase in the prevalence of FA in school-age.

*Strengths and Limitations.* Our birth cohort study that has been conducted in various European regions is the largest and first multi-national population-based investigation of DBPCFC-confirmed FA in childhood worldwide. However, the generalizability of the initial sample to the whole (regional or whole-country) populations has not been formally assessed. Due to a stringent, standardized, clinically-based methodology, it allows better comparisons of confirmed FA occurrence and influential factors in eight European countries than previous single-centre/-country studies. The diagnostic work-up included several possible approaches to identify suspected FA, also capturing measures of disease severity and impact. It

also focussed on the need to thoroughly adjust for the different types of non-response, particularly the refusal of a clinically indicated DBPCFC.[19]

The local consumption habits influence the likelihood that a dormant potential to react to a certain allergen presents as an apparent reaction. This limits the comparability, e.g. of different regions and parent-reported symptoms. We focussed the standardized assessment of consumption and sensitization to a core list of major allergen sources and only for these foods the current prevalence estimates yield valid results. For all other foods, for which the consumption history and sensitization assessments were only available for children whose families reported problems ever, we cannot present valid denominators for measures of disease frequency. We cannot exclude allergy to these foods in participants who may not be consuming them. Furthermore, groups of foods containing similar (potentially allergenic) food allergens, e.g., cow's milk in bakery products, would need to be differentiated in more detail. Including more and more foods in the consumption and sensitization assessment would be likely to increase the number of identified yet unnoticed food allergies and thus increase the estimated frequencies.

The overall participation in the questionnaire assessment was comparable to other birth cohorts on allergy in Europe. There was considerable attrition in all stages of the assessment, form the questionnaire and clinical assessment to the final diagnostic step. We thoroughly assessed the potential for differential non-response and weighted after investigating a large set of background characteristics, potentially giving a range of estimates that closer reflect the actual prevalence in the whole population, including those not assessed. Compared to other one-time surveys, this prevalence assessment took place in a sample of children recruited at birth and followed until 30 months and later until school-age for incident FA. This sample's families are likely to be more aware of this specific disease and also far more examined and assessed during infancy in search for food reactions.

A major weakness of the study was that a considerable number of families did not participate in the food challenges, which would have been necessary (based on the predefined eligibility criteria) to confirm or rule out FA. The willingness to undergo a time-consuming and stressful food challenge of at least two days is much lower without the (felt) burden of the affected child and its family, usually the key trigger to consent to this procedure in regular care.

In one approach, we extrapolated the proportion of food allergic children of all challenged to those children who refused to undergo the procedure. There are many possible reasons for such refusal. Our prevalence estimates would be too low if severe reactions and previously challenge-proven food allergy were the main reason for the parents' hesitancy to allow food challenge. Thus, we reported a range of

frequency estimates reflecting several probably extreme but justifiable sets of assumptions. Providing a single and robust point estimate supported by a reliable measure of precision would require a close to complete assessment of a population-based sample. As the uncertainty due to other factors than random error are likely to outweigh the potential variation due to chance/sampling, we explicitly refrained from calculating confidence intervals (which mainly address random error) for extrapolated frequencies.

*Conclusions.* The occurrence of FA in European school children was estimated between 1-4%, depending on the strategy for weighting attrition, which was considerably lower than suspected from information based on parental reports. The prevalence of food allergy of the children who only completed the online questionnaire could only be estimated. Assuming they had the same prevalence of food allergy than those seen in the study centre likely overestimated the true frequency at 3.8%, whereas assuming they are all non-allergic certainly yields too low estimates (1.4%). The true prevalence is probably within this interval. The most common allergens responsible for FA and sensitization were peanut and hazelnut.

**Declaration of interests**

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# Tables

**Table 1**

Response at school age and lifetime prevalence (raw % and n) of parent-reported symptoms after food consumption and parent-reported physician diagnosed food allergy, based on online questionnaire (n=6,069).

Symptoms after consumption of "core foods" were asked specifically, all other foods are labelled "non-core foods".

*Only the most frequently reported non-core foods are listed here, rarely reported non-core foods are presented in e-Table 2.

| | Reykjavik Iceland | Southampton UK | Amsterdam NL | Berlin Germany | Lodz Poland | Vilnius Lithuania | Madrid Spain | Athens Greece | Total |
|---|---|---|---|---|---|---|---|---|---|
| **Baseline [n]** | **1,341** | **1,140** | **976** | **1,570** | **1,513** | **1,556** | **1,387** | **1,080** | **10,563** |
| Response [%] | 70.5 | 39.8 | 66.8 | 63.8 | 54.1 | 61.0 | 49.6 | 51.9 | 57.5 |
| | **945** | **454** | **652** | **1,001** | **819** | **949** | **688** | **561** | **6,069** |
| **n** | **% (n)** | **% (n)** | **% (n)** | **% (n)** | **% (n)** | **% (n)** | **% (n)** | **% (n)** | **% (n)** |
| **Parent-reported symptoms** | | | | | | | | | |
| **Any food** | **20.1 (190)** | **20.7 (94)** | **19.8 (129)** | **17.2 (172)** | **22.0 (180)** | **12.3 (117)** | **11.2 (77)** | **4.1 (23)** | **16.2 (982)** |
| **"Core foods"** | **18.0 (170)** | **14.3 (65)** | **15.5 (101)** | **12.0 (120)** | **16.5 (135)** | **7.9 (75)** | **7.8 (54)** | **3.0 (17)** | **12.1 (737)** |
| Cow's milk | 14.1 (133) | 8.8 (40) | 11.8 (77) | 8.2 (82) | 12.8 (105) | 4.5 (43) | 2.9 (20) | 1.2 (7) | 8.4 (507) |
| Hen's egg | 3.8 (36) | 4.2 (19) | 4.1 (27) | 1.9 (19) | 5.5 (45) | 3.1 (29) | 3.5 (24) | 0.7 (4) | 3.3 (203) |
| Wheat | 1.6 (15) | 3.3 (15) | 0.8 (5) | 1.0 (10) | 1.2 (10) | 1.8 (17) | 1.2 (8) | 0.0 (0) | 1.3 (80) |
| Soy | 1.0 (9) | 1.3 (6) | 0.6 (4) | 0.2 (2) | 0.6 (5) | 0.5 (5) | 0.1 (1) | 0.0 (0) | 0.5 (32) |
| Peanut | 1.6 (15) | 2.2 (10) | 2.0 (13) | 1.4 (14) | 2.4 (20) | 1.1 (10) | 1.6 (11) | 0.5 (3) | 1.6 (96) |
| Hazelnut | 1.0 (9) | 0.9 (4) | 1.1 (7) | 1.9 (19) | 3.5 (29) | 1.3 (12) | 1.2 (8) | 0.2 (1) | 1.5 (89) |
| White fish | 1.8 (17) | 0.4 (2) | 0.6 (4) | 0.1 (1) | 0.6 (5) | 0.6 (6) | 1.0 (7) | 0.9 (5) | 0.8 (47) |
| Oily fish | 0.8 (8) | 0.2 (1) | 0.0 (0) | 0.4 (4) | 0.2 (2) | 0.4 (4) | 0.7 (5) | 0.5 (3) | 0.4 (27) |
| Crustaceans | 1.0 (9) | 0.7 (3) | 0.6 (4) | 0.1 (1) | 0.0 (0) | 0.5 (5) | 0.4 (3) | 0.4 (2) | 0.4 (27) |
| **"Non-core foods"*** | **5.6 (53)** | **9.7 (44)** | **6.3 (41)** | **8.7 (87)** | **10.7 (88)** | **6.5 (62)** | **5.7 (39)** | **1.8 (10)** | **7.0 (424)** |
| Nuts (except hazelnut) | 0.5 (5) | 0.7 (3) | 0.9 (6) | 0.8 (8) | 0.1 (1) | 0.1 (1) | 2.0 (14) | 0.7 (4) | 0.7 (42) |
| Tomato | 0.3 (3) | 1.8 (8) | 1.2 (8) | 0.5 (5) | 0.7 (6) | 0.3 (3) | 0.0 (0) | 0.0 (0) | 0.5 (33) |
| Kiwi | 0.3 (3) | 0.4 (2) | 0.9 (6) | 0.2 (2) | 0.9 (7) | 0.1 (1) | 1.0 (7) | 0.0 (0) | 0.5 (28) |
| Strawberry | 0.0 (0) | 0.7 (3) | 0.6 (4) | 0.9 (9) | 1.1 (9) | 0.2 (2) | 0.0 (0) | 0.0 (0) | 0.4 (27) |
| Apple | 0.1 (1) | 0.2 (1) | 0.3 (2) | 0.7 (7) | 1.0 (8) | 0.3 (3) | 0.0 (0) | 0.0 (0) | 0.4 (22) |
| Citrus fruits, not specified | 0.2 (2) | 0.2 (1) | 0.2 (1) | 0.5 (5) | 1.2 (10) | 0.6 (6) | 0.0 (0) | 0.0 (0) | 0.4 (25) |
| **Parent-reported doctors-diagnosed food allergy** | **8.7 (82)** | **8.8 (40)** | **10.6 (69)** | **5.1 (51)** | **14.4 (118)** | **7.2 (68)** | **7.7 (53)** | **2.5 (14)** | **8.2 (495)** |
| **"Core foods"** | **8.0 (76)** | **8.1 (37)** | **10.0 (65)** | **4.6 (46)** | **12.1 (99)** | **5.7 (54)** | **5.8 (40)** | **2.1 (12)** | **7.1 (429)** |
| Cow's milk | 4.9 (46) | 5.3 (24) | 7.4 (48) | 2.1 (21) | 9.8 (80) | 3.4 (32) | 1.9 (13) | 1.1 (6) | 4.4 (270) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Hen's egg | 3.7 (35) | 3.3 (15) | 3.7 (24) | 1.3 (13) | 4.6 (38) | 2.7 (26) | 3.3 (23) | 0.5 (3) | 2.9 (177) |
| Wheat | 0.4 (4) | 1.1 (5) | 0.6 (4) | 0.4 (4) | 0.7 (6) | 1.6 (15) | 0.6 (4) | 0.0 (0) | 0.7 (42) |
| Soy | 0.8 (8) | 0.9 (4) | 0.3 (2) | 0.2 (2) | 0.6 (5) | 0.5 (5) | 0.1 (1) | 0.0 (0) | 0.4 (27) |
| Peanut | 1.4 (13) | 1.8 (8) | 0.8 (5) | 1.2 (12) | 1.2 (10) | 0.6 (6) | 1.6 (11) | 0.4 (2) | 1.1 (67) |
| Hazelnut | 0.6 (6) | 0.7 (3) | 0.5 (3) | 0.8 (8) | 2.7 (22) | 0.8 (8) | 1.0 (7) | 0.2 (1) | 1.0 (58) |
| White fish | 1.4 (13) | 0.0 (0) | 0.3 (2) | 0.1 (1) | 0.2 (2) | 0.6 (6) | 0.7 (5) | 0.9 (5) | 0.6 (34) |
| Oily fish | 0.4 (4) | 0.0 (0) | 0.0 (0) | 0.2 (2) | 0.0 (0) | 0.3 (3) | 0.3 (2) | 0.5 (3) | 0.2 (14) |
| Crustaceans | 0.6 (6) | 0.4 (2) | 0.2 (1) | 0.0 (0) | 0.0 (0) | 0.3 (3) | 0.4 (3) | 0.0 (0) | 0.2 (15) |
| **"Non-core foods"*** | **1.8 (17)** | **2.0 (9)** | **0.9 (6)** | **1.6 (16)** | **6.0 (49)** | **2.4 (23)** | **3.8 (26)** | **0.7 (4)** | **2.5 (150)** |
| Nuts (except hazelnut) | 0.4 (4) | 0.7 (3) | 0.6 (4) | 0.8 (8) | 0.1 (1) | 0.1 (1) | 1.9 (13) | 0.7 (4) | 0.6 (38) |
| Tomato | 0.0 (0) | 0.2 (1) | 0.2 (1) | 0.0 (0) | 0.5 (4) | 0.2 (2) | 0.0 (0) | 0.0 (0) | 0.1 (8) |
| Kiwi | 0.2 (2) | 0.0 (0) | 0.2 (1) | 0.1 (1) | 0.4 (3) | 0.0 (0) | 0.6 (4) | 0.0 (0) | 0.2 (11) |
| Strawberry | 0.0 (0) | 0.2 (1) | 0.0 (0) | 0.2 (2) | 0.5 (4) | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.1 (7) |
| Apple | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.7 (6) | 0.3 (3) | 0.0 (0) | 0.0 (0) | 0.1 (9) |
| Citrus fruits, not specified | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.0 (0) | 0.7 (6) | 0.2 (2) | 0.0 (0) | 0.0 (0) | 0.1 (8) |

**Table 2**

Parent-reported history of symptoms and consumption, eligibility assessment as judged by the supervising study physician, and results of food challenge tests. Percentages not adjusted for non-response.

Number of questions Q1-Q4 referring to Figure 2.

| | | Cow's milk | Hen's egg | Wheat | Soy | Peanut | Hazelnut | White fish | Oily fish | Crusta-ceans | Core foods | Any food |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Parent-reported history of symptoms and consumption** (based on interviews, n=2,322) | | | | | | | | | | | | |
| Never symptoms (Q1) + Currently consumed (Q2) | n | 2,008 | 2,183 | 2,274 | 857 | 1,863 | 2,019 | 2,131 | 1,846 | 1,043 | - | - |
| Ever symptoms (Q1) + Tolerated again (Q4) + Currently consumed (Q2) | n | 202 | 80 | 13 | 7 | 13 | 10 | 9 | 4 | 2 | - | - |
| Never symptoms (Q1) + Currently not consumed (Q2) | n | 10 | 16 | 17 | 1,448 | 402 | 245 | 162 | 463 | 1,265 | - | - |
| Ever symptoms (Q1) + Tolerated again (Q4) + Currently not consumed (Q2) | n | 2 | 2 | 0 | 1 | 4 | 0 | 0 | 0 | 1 | - | - |
| Ever symptoms (Q1) + Never tolerated (Q4) | n | 100 | 41 | 18 | 9 | 40 | 48 | 20 | 9 | 11 | 214 | 290 |
| **Eligibility assessment for food challenge as judged by physician** (n=2,289) | | | | | | | | | | | | |
| Currently consumed | **No** (Type A) No food allergy | n | 2,199 | 2,166 | 2,255 | 918 | 1,886 | 1,831 | 2,130 | 1,866 | 1,119 | - | - |
| Never symptoms, not consumed, SPT- | **No** (Type B) Food allergy possible | n | 44 | 82 | 22 | 1,360 | 338 | 388 | 139 | 417 | 1,144 | - | - |
| Never symptoms, not consumed, SPT+ | **Yes** (Type C) Food allergy possible | n | 4 | 6 | 3 | 8 | 36 | 42 | 8 | 2 | 17 | 186 | 238 |
| Ever symptoms, not consumed | **Yes** (Type D) Food allergy likely | n | 42 | 35 | 9 | 3 | 29 | 28 | 12 | 4 | 9 | | |
| **Eligible** (Type C + D) | | **%** | **2.0** | **1.8** | **0.5** | **0.5** | **2.8** | **3.1** | **0.9** | **0.3** | **1.1** | **8.1** | **10.4** |
| **Food challenge** (fully completed assessments n=2,097) | | | | | | | | | | | | |
| Conducted | | n | 6 | 7 | 0 | 0 | 15 | 16 | 2 | 1 | 7 | 39 | 46 |
| Positive | | n | 0 | 1 | 0 | 0 | 3 | 7 | 1 | 1 | 2 | 13 | 17 |
| **Challenge-proven food allergy** | | **%** | **0** | **0.05** | **0** | **0** | **0.14** | **0.33** | **0.05** | **0.05** | **0.10** | **0.62** | **0.81** |

**Table 3**

Basic characteristics of all recruited birth cohort participants, by follow-up status. Testing similarity between groups, Chi-square p-values.

*asthma, allergic rhinitis, or eczema.

#Cow's milk, Hen's egg, Wheat, Soy, Peanut, Hazelnut, White fish, Oily fish, Crustaceans

| | Lost to follow-up | Questionnaire only | Eligible but not challenged | Eligible and challenged | Not eligible | Lost to follow-up vs. Questionnaire only | Questionnaire only vs. Not eligible | Elig. not challenged vs. Elig. Challenged |
|---|---|---|---|---|---|---|---|---|
| **n** | **4.458** | **3.816** | **192** | **46** | **2.051** | | | |
| **Group number** | **1** | **2** | **3** | **4** | **5** | **1 vs. 2** | **2 vs. 5** | **3 vs. 4** |
| | **%** | **%** | **%** | **%** | **%** | p-value | p-value | p-value |
| **Birth & Family (assessed shortly after birth)** | | | | | | | | |
| Male sex | 51,3 | 51,6 | 54,2 | 65,1 | 51,5 | 0,792 | 0,986 | 0,191 |
| Cesarean section | 22,7 | 23,1 | 24,6 | 14,6 | 23,8 | 0,713 | 0,537 | 0,168 |
| Month of birth Jun-Nov | 47,4 | 47,9 | 44,8 | 39,5 | 44,7 | 0,608 | 0,019 | 0,530 |
| Antibiotics in first week | 16,9 | 12,0 | 11,5 | 4,8 | 17,1 | <0.001 | <0.001 | 0,195 |
| Older siblings | 48,3 | 48,0 | 45,0 | 37,2 | 48,6 | 0,727 | 0,631 | 0,350 |
| Mother smokes | 15,2 | 10,2 | 7,8 | 4,7 | 10,3 | <0.001 | 0,898 | 0,469 |
| University/college degree father and/or mother | 39,8 | 56,4 | 59,2 | 67,4 | 53,2 | <0.001 | 0,018 | 0,315 |
| Smoking in pregnancy | 13,4 | 8,9 | 6,3 | 4,7 | 9,5 | <0.001 | 0,415 | 0,689 |
| Cat or dog in household | 29,8 | 28,6 | 22,4 | 14,0 | 24,4 | 0,241 | <0.001 | 0,218 |
| **Family's allergies (assessed shortly after birth)** | | | | | | | | |
| Self-reported physician's diagnosed allergy* (mother) | 25,0 | 24,3 | 35,9 | 60,5 | 32,7 | 0,463 | <0.001 | 0,003 |
| Self-reported food allergy/hypersensitivity (mother) | 13,3 | 14,8 | 18,8 | 16,7 | 17,4 | 0,042 | 0,011 | 0,752 |
| Self-reported physician's diagnosed allergy* (father) | 19,6 | 19,4 | 29,1 | 34,9 | 24,9 | 0,814 | <0.001 | 0,456 |
| Self-reported food allergy/hypersensitivity (father) | 7,7 | 8,3 | 15,5 | 19,0 | 10,7 | 0,354 | 0,002 | 0,573 |
| **Child: 0-3 years (data from EuroPrevall)** | | | | | | | | |
| Eczema | 34,5 | 32,2 | 61,4 | 66,7 | 44,8 | 0,041 | <0.001 | 0,526 |
| Challenge-proven FA (any) | 1,3 | 1,6 | 14,9 | 31,7 | 1,6 | 0,355 | 0,998 | 0,012 |
| ...cow's milk allergy | 0,4 | 0,5 | 4,0 | 15,0 | 0,7 | 0,765 | 0,464 | 0,009 |
| ...hen's egg allergy | 0,8 | 0,9 | 8,6 | 26,8 | 1,0 | 0,695 | 0,571 | 0,001 |
| …peanut allergy | 0,1 | 0,1 | 1,2 | 7,5 | 0,0 | 0,786 | 0,204 | 0,017 |
| **Child: 6-10 years (assessed by online questionnaire)** | | | | | | | | |
| Parent-reported asthma (in previous 12 months) | | 6,4 | 27,7 | 11,6 | 9,2 | | <0.001 | 0,027 |
| Parent-reported allergic rhinitis (in previous 12 months) | | 17,8 | 50,8 | 46,5 | 28,8 | | <0.001 | 0,613 |
| Parent-reported eczema (in previous 12 months) | | 17,8 | 47,1 | 37,2 | 28,6 | | <0.001 | 0,238 |
| Ever any reaction to food | | 12,7 | 74,9 | 62,8 | 16,2 | | <0.001 | 0,108 |
| Consumed cow's milk in last 3 months | | 98,7 | 96,9 | 93,0 | 97,1 | | <0.001 | 0,234 |
| Consumed hen's egg in last 3 months | | 98,6 | 91,1 | 95,3 | 96,9 | | <0.001 | 0,361 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Consumed peanut in last 3 months | 82,0 | 62,5 | 53,5 | 76,4 | <0.001 | 0,274 |
| **Child: 6-10 years (assessed by face-to-face interview)** | | | | | | |
| Likely current FA (any food) | | 83,9 | 83,3 | 4,0 | | 0,934 |
| SPT positive (any core food#) | | 59,1 | 71,8 | 5,2 | | 0,140 |
| Eligible for cow's milk challenge | | 19,8 | 18,6 | | | 0,859 |
| Eligible for hen's egg challenge | | 16,1 | 20,9 | | | 0,451 |
| Eligible for peanut challenge | | 24,0 | 44,2 | | | 0,007 |

**Table 4**

Food-specific characteristics of challenge-eligible children, by challenge conduct. Only foods with more than 5 conducted challenges.

| | challenge conducted | challenge not conducted |
|---|---|---|
| **Eligible for cow's milk challenge (n = 47)** | **6** | **41** |
| of these… | | |
| …cow's milk SPT positive | 17% | 18% |
| …symptoms in previous 12m | 83% | 56% |
| …earlier physician's diagnosis | 83% | 39% |
| …current avoidance of cow's milk | 50% | 17% |
| **Eligible for hen's egg challenge (n = 42)** | **7** | **35** |
| of these… | | |
| …hen's egg SPT positive | 0% | 57% |
| …symptoms in previous 12m | 14% | 20% |
| …earlier physician's diagnosis | 43% | 77% |
| …current avoidance of hen's egg | 43% | 40% |
| **Eligible for peanut challenge (n = 66)** | **15** | **51** |
| of these… | | |
| …peanut SPT positive | 85% | 88% |
| …symptoms in previous 12m | 0% | 2% |
| …earlier physician's diagnosis | 36% | 39% |
| …current avoidance of peanut | 64% | 49% |
| **Eligible for hazelnut challenge (n = 70)** | **16** | **54** |
| of these… | | |
| …hazelnut SPT positive | 80% | 73% |
| …symptoms in previous 12m | 7% | 7% |
| …earlier physician's diagnosis | 33% | 33% |
| …current avoidance of hazelnut | 47% | 46% |
| **Eligible for crustacean challenge (n = 26)** | **7** | **19** |
| of these… | | |
| …crustacean SPT positive | 71% | 88% |
| …symptoms in previous 12m | 0% | 5% |
| …earlier physician's diagnosis | 14% | 21% |
| …current avoidance of crustaceans | 43% | 37% |

# Figure legends

**Figure 1**

Number of children participating assessments and diagnostic steps and number of children lost to follow-up.

**Figure 2**

Decision tree used to define current food allergy status, using peanut as an example (absolute numbers refer to peanut reactions).

**Figure 3**

Skin Prick Test (SPT) including allergens from the core food list in 2,188 European children aged 6-10 years. A total of 223 (10.2%) children had a positive SPT. Error bars indicate 95% confidence intervals for the proportion of positive tests (≥3 mm).

**Figure 4**

Adjusted prevalence of challenge-proven food allergy, by follow-up status.

Lost to follow-up at school age (Group 1) were 4,458 out of 10,563 subjects recruited at birth in 8 centres.

Adjustment as follows, based on similarity of groups regarding baseline and follow-up information as outlined in Table 3:

(i) disease frequency of those challenged (Group 4) as substitute for those eligible but refusing the challenge (Group 3), with an additional estimated number of 71 cases;

(ii) disease frequency of those not eligible (Group 5) as substitute for those who only answered the questionnaire (no estimated cases added);

Extrapolated numbers rounded to the next integer.

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**Figure 1**

Number of children participating assessments and diagnostic steps and number of children lost to follow-up.

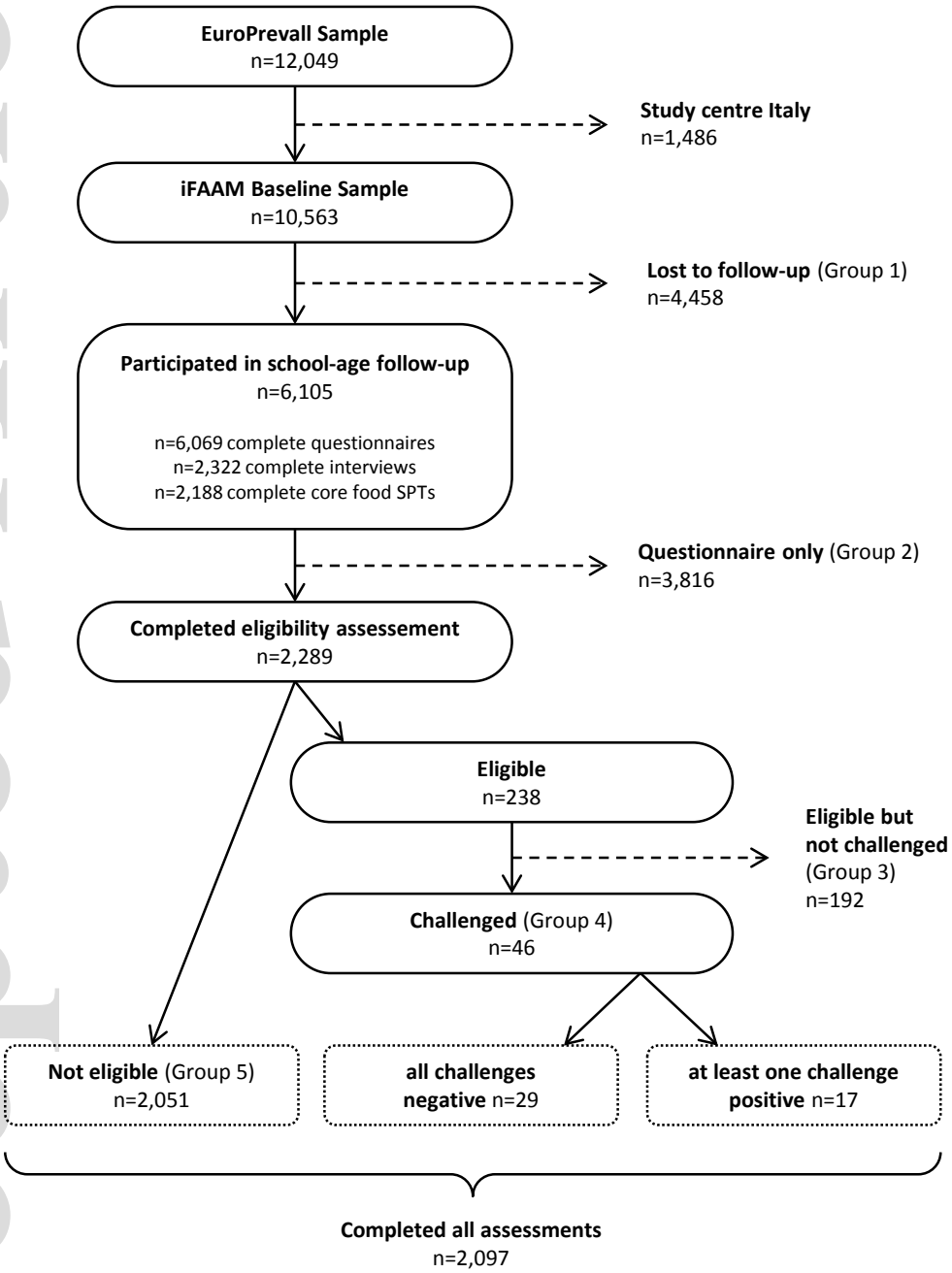

**Figure 2**

Decision tree used to define current food allergy status, using peanut as an example (absolute numbers refer to peanut reactions).

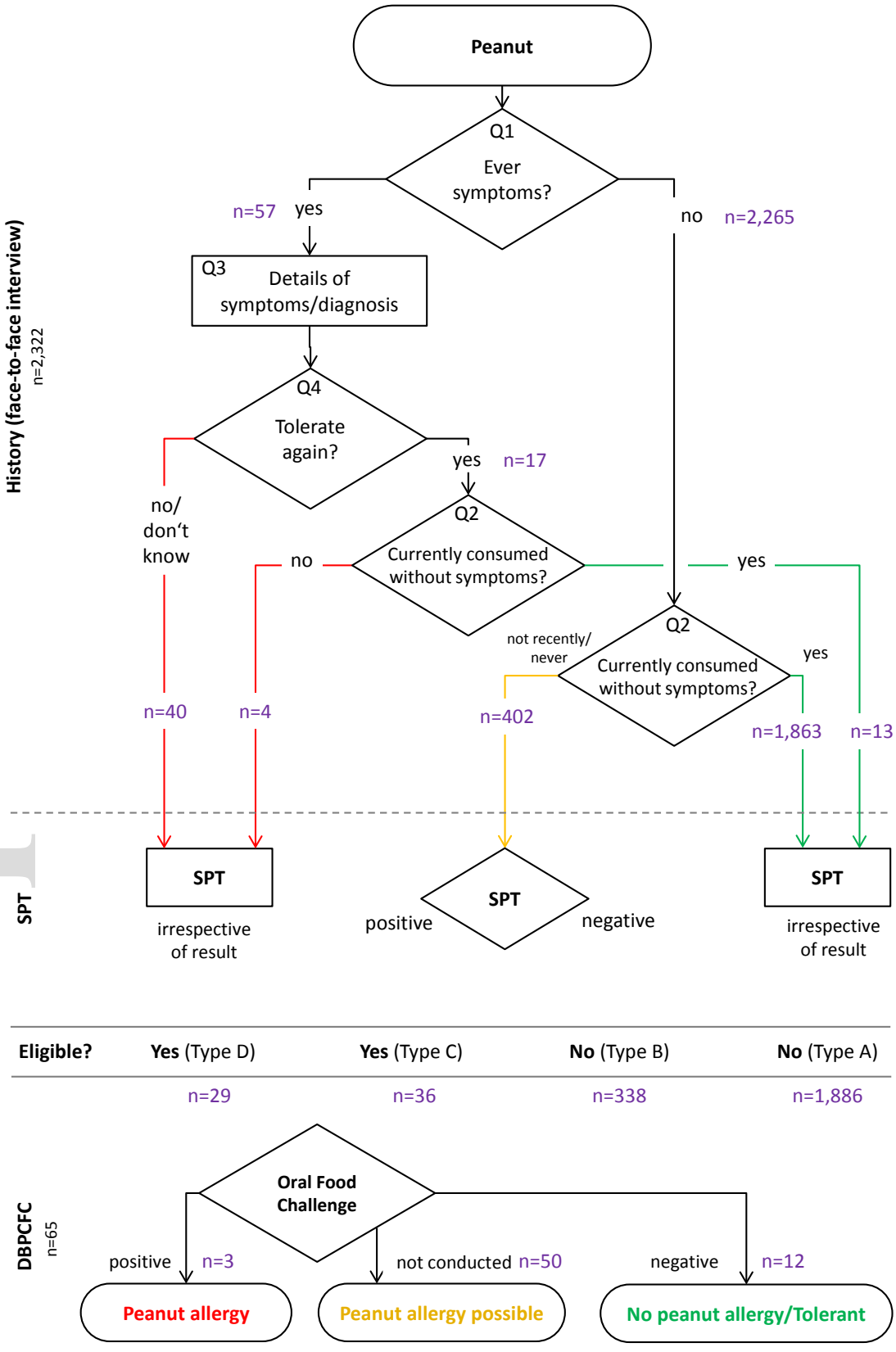

**Figure 3**

Skin Prick Test (SPT) including allergens from the core food list in 2,188 European children aged 6-10 years. A total of 223 (10.2%) children had a positive SPT. Error bars indicate 95% confidence intervals for the proportion of positive tests (≥3 mm).

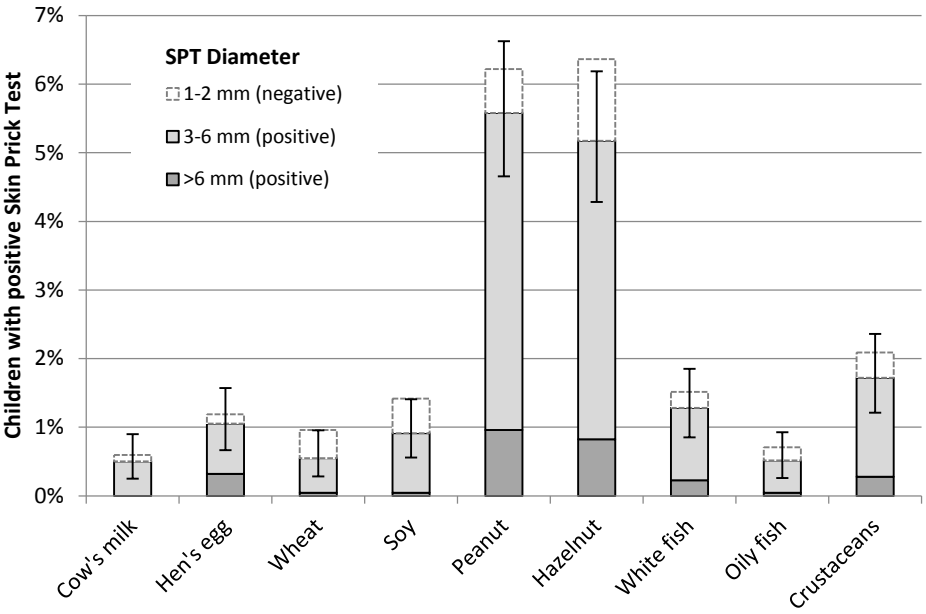

**Figure 4**

Adjusted prevalence of challenge-proven food allergy, by follow-up status.

Lost to follow-up at school age (Group 1) were 4,458 out of 10,563 subjects recruited at birth in 8 centres.

Adjustment as follows, based on similarity of groups regarding baseline and follow-up information as outlined in Table 3:

(i) disease frequency of those challenged (Group 4) as substitute for those eligible but refusing the challenge (Group 3), with an additional estimated number of 71 cases;

(ii) disease frequency of those not eligible (Group 5) as substitute for those who only answered the questionnaire (no estimated cases added);

Extrapolated numbers rounded to the next integer.