

REVIEW ARTICLE

The epidemiology of food allergy in Europe: a systematic review and meta-analysis

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Abstract

Food allergy (FA) is an important atopic disease although its precise burden is unclear. This systematic review aimed to provide recent, up-to-date data on the incidence, prevalence, time trends, and risk and prognostic factors for FA in Europe. We searched four electronic databases, covering studies published from 1 January 2000 to 30 September 2012. Two independent reviewers appraised the studies and qualified the risk of bias using the Critical Appraisal Skills Programme tool. Seventy-five eligible articles (comprising 56 primary studies) were included in a narrative synthesis, and 30 studies in a random-effects meta-analysis. Most of the studies were graded as at moderate risk of bias. The pooled lifetime and point prevalence of self-reported FA were 17.3% (95% CI: 17.0–17.6) and 5.9% (95% CI: 5.7–6.1), respectively. The point prevalence of sensitization to ≥ 1 food as assessed by specific IgE was 10.1% (95% CI: 9.4–10.8) and skin prick test 2.7% (95% CI: 2.4–3.0), food challenge positivity 0.9% (95% CI: 0.8–1.1). While the incidence of FA appeared stable over time, there was some evidence that the prevalence may be increasing. There were no consistent risk or prognostic factors for the development or resolution of FA identified, but sex, age, country of residence, familial atopic history, and the presence of other allergic diseases seem to be important. Food allergy is a significant clinical problem in Europe. The evidence base in this area would benefit from additional studies using standardized, rigorous methodology; data are particularly required from Eastern and Southern Europe.

Abbreviations

CASP, Critical Appraisal Skills Programme; CI, confidence intervals; DBPCFC, double-blind, placebo-controlled food challenge; EAACI, European Academy of Allergy and Clinical Immunology; FA, food allergy; IgE, immunoglobulin E; OFC, oral food challenge; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SPT, skin prick test.

During the past 50–60 years, the frequency of asthma and other atopic diseases, such as atopic eczema/dermatitis and allergic rhinitis, has increased in many Western countries. They now represent a substantial burden to healthcare systems and the society (1–5). While the incidence of these diseases may have peaked in some settings (3), it has been suggested that the frequency of food allergy (FA) appears to have increased during the last 10–20 years (6–10), leading to the thought that FA may have different risk factors (6, 8).

Despite the suggested increasing frequency of FA and the attributed public health burdens (6–10), estimates of the actual incidence and prevalence are uncertain. Relatively few epidemiological studies have utilized the gold standard of diagnosis – the double-blind, placebo-controlled food challenge (DBPCFC) in defining FA (6, 8). Most frequency estimates have been based on lay perceptions or specific immunoglobulin E (IgE) or skin prick test (SPT) sensitization to common food allergens. Both self-perception and allergic sensitization are known to substantially overestimate the actual frequency of FA (11–13).

The EAACI is developing *EAACI Guidelines for Food Allergy and Anaphylaxis*, and this systematic review is one of seven interlinked evidence syntheses that have been undertaken to provide a state-of-the-art European synopsis of the current evidence base in relation to epidemiology, prevention, diagnosis and clinical management, and impact on quality of life, which will be used to inform clinical recommendations. The aims of this systematic review were to (1) estimate the frequency of FA, (2) investigate time trends, and (3) identify potential risk and prognostic factors for the development of FA in Europe.

Methods

Protocol and registration

The protocol of this review has been published previously (14), and it is registered with the International Prospective Register of Systematic Reviews (PROSPERO; <http://www.crd.york.ac.uk/prosperto/>, reference CRD42013003704).

Search strategy

A highly sensitive search strategy was designed (see Box S1) to retrieve all articles combining the concepts of food allergy and epidemiology from electronic bibliographic databases. See Supporting Information for further details.

Inclusion and exclusion criteria

The following study designs were included: systematic reviews and meta-analyses, cohort studies, cross-sectional studies, case-control studies, and routine healthcare studies published in Europe between 1 January 2000 and 30 September 2012. These were chosen to ensure that the highest levels of European evidence were pooled based on the aims of the review. Reviews, discussion papers, nonresearch letters and editorials, case studies, and case series plus animal studies and all

randomized controlled trials were excluded. See Supporting Information for further details.

Study selection

The titles of retrieved articles were checked by two independent consultant reviewers according to our selection criteria and categorized as included, not included, and unsure. The abstracts of papers in the unsure category were retrieved and recategorized as above after further discussion. Full-text copies of potentially relevant studies were obtained, and their eligibility for inclusion was independently assessed by two reviewers (BN and LH). Any discrepancies were resolved by consensus or a third reviewer (AS) arbitrated.

Risk of bias assessment

Risk of bias in the studies was independently carried out by two reviewers (BN and LH) using adapted relevant versions of the Critical Appraisal Skills Programme (CASP) tool (<http://www.casp-uk.net/>). An overall grading was assigned to each study based on the grading obtained from the various components of the study (i.e., the appropriateness of the study design for the research question, the risk of selection bias, exposure, and outcome assessment). Discrepancies were resolved by consensus or a third reviewer (AS) arbitrated.

Analysis, synthesis, and reporting

A customized data extraction form was developed and independently used to obtain relevant data from each study by two reviewers (BN and LH). Discrepancies were resolved by discussion or arbitration by a third reviewer (AS). We recalculated all the frequency estimates of any FA occurrence if adequate data were provided by authors by using minimal measured events rather than extrapolated ones. The 95% confidence intervals (95% CI) of our recalculations were computed by the Wilson score method without continuity correction (15). We performed a random-effects meta-analysis for clinically and methodologically comparable studies to estimate the frequency of FA. We calculated the age-stratified pooled estimates for the age group 0–17 years (children) and 18 years and over (adults). We also present the pooled estimates stratified by geographical region in Europe. Statistical analysis was undertaken using STATA 11 (Stata Corp, College Station, Tx). See Supporting Information for further details.

Results

Study selection and characteristics

Figure 1 shows the PRISMA flowchart for our study selection and screening. Seventy-five papers (based on 56 primary studies) were included in the narrative synthesis (16–90), and 30 studies were included in the meta-analysis (Fig. 1).

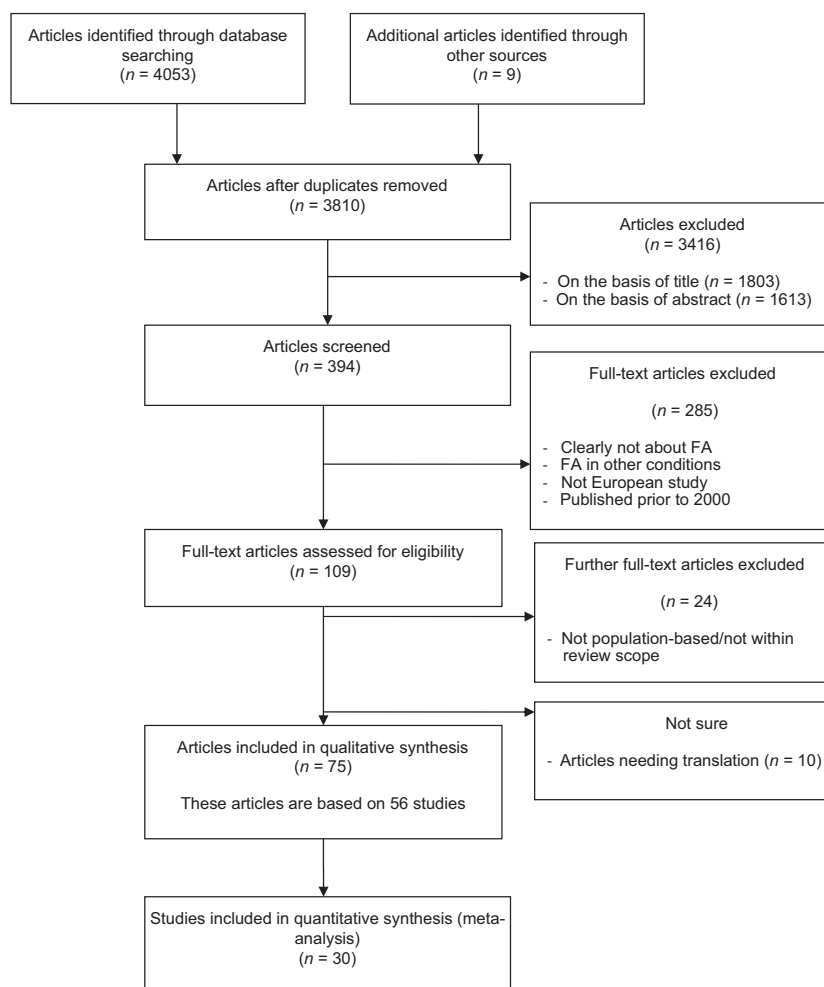


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for studies on the epidemiology of FA in Europe, January 2000–September 2012.

Further details are found in the Supporting Information (Table S1).

Risk of bias assessment of studies

The overall risk of bias grading of the studies indicated that almost all of the studies (54 of 56 studies) were graded as at 'moderate' risk of bias (Table S2).

Frequency of FA

Table 1 presents the summarized ranges of estimates for different age groups, by different assessment methods of FA, and includes the point prevalence for all FA assessment methods and lifetime prevalence only for self-reported FA. Detailed results are shown in Tables S1–S6.

Self-reported FA

The overall pooled point prevalence of self-reported FA was 5.9% (95% CI: 5.7–6.1) (Fig. 2). The pooled point prevalence

among children was higher than among adults and highest in Northern Europe than in other regions (Fig. 2). The overall pooled lifetime prevalence of self-reported FA was 17.3% (95% CI: 17.0–17.6), and this was similar in children and in adults and highest in Eastern Europe than in other regions and lowest in Southern Europe (Figure S1). High prevalence was also reported in Western and Northern Europe (Figure S1). However, even after stratification by age and region, there was still significant heterogeneity between the studies ($P < 0.001$ for I^2).

FA by positive SPT or IgE to food allergens

The overall point prevalence of positive specific IgE to at least one food was 10.1% (95% CI: 9.4–10.8) and higher among children than among adults (Figure S2). The overall point prevalence of positive SPT to at least one food was 2.7% (95% CI: 2.4–3.0) without differences between Northern and Southern Europe (Figure S3). After stratification by age and region, there was still significant heterogeneity between the studies ($P < 0.001$ for I^2).

Table 1 Summary of range of estimates of the frequency of FA in Europe by self-report, skin prick (SPT) positivity, IgE positivity, food challenges, and symptoms or clinical history: estimates from studies published between 1 January 2000 and 30 September 2012

Age bands, years	Frequency of FA							Lifetime prevalence
	Point prevalence							
	Self-report	Positive IgE	Positive SPT	Symptom plus positive IgE	Symptom plus positive SPT	Clinical history or food challenge	Food challenge	
≤1	1.7–9.8%	19.4–20.3%	2.2–4.3%	1.3–4.6%	1.6–13.1%	2.7–3.0%	0.3–4.2%	5.7–38.4%
2–5	1.6–38.7%	4.1–21.5%	3.2–4.5%	4.6%	13.1%	2.1–6.8%	0.0–4.2%	5.7–38.4%
6–10	1.6–24.4%	4.1–52.0%	1.8–6.1%	4.6%	0.1–13.1%	1.1–2.1%	0.4–4.2%	5.7–41.8%
11–17	1.6–24.4%	4.1–16.1%	1.8–6.1%	4.6%	0.1–13.1%	1.4–2.3%	0.1–5.7%	10.6–38.4%
18–60	3.5–19.6%	2.0–21.9%	–	2.2%	–	–	0.1–3.2%	9.5–35.0%
>60	3.3%	9.0–16.8%	–	2.2%	–	–	2.9%	15.5–35.0%

The overall pooled point prevalence of symptoms plus positive IgE to at least one food was 2.7% (95% CI: 1.7–3.7) and slightly higher among children than among adults (Fig. 3). The overall pooled point prevalence of symptoms plus SPT positivity to at least one food was 1.5% (95% CI: 1.3–1.7), and this was only among children (Fig. 4). Usually, the estimates for clinical history or OFC and clinical history or DBPCFC were close to each other; hence, we report the point prevalence estimates for clinical history or DBPCFC. FA-defined clinical history refers to the cases confirmed by a convincing clinical judgment by a physician, without the use of any food challenge. This was mostly done for subjects who refused food challenge or could not undergo food challenge due to other reasons. The overall pooled point prevalence of clinical history or food challenge positivity was 2.6% (95% CI: 2.1–3.1), and this was only among children from Northern Europe (Fig. 5).

The overall pooled point prevalence of food challenge (OFC or DBPCFC) was 0.9% (95% CI: 0.8–1.1) and was similar among children and adults, but highest in Western Europe, and being higher in Northern Europe than in Southern Europe (Table 1, Fig. 6).

Only three studies have investigated the time trends of FA in Europe (36–38, 46, 84) (Table 2). All these studies were from the UK, and two were primarily hospital-based studies that employed only admissions data (36–38, 46), limiting the application of the findings to the general population, although the estimates were standardized to the local populations. Two focused on peanut allergy, while one considered any FA.

In the first study (46), while the incidence of doctor-diagnosed peanut allergy remained rather stable between 2001 and 2005, the lifetime prevalence doubled during the study period. Using three different cohorts, Venter et al. (84) reported a significant increase in positive SPT to peanut allergen and clinical peanut allergy from 1993 to 1998–2000, but nonsignificantly decreased from 1998–2000 to 2004–2005 (84). Reviewing admissions rate for FA, Gupta and colleagues (36–38) observed an increased rate for all age groups between 1990 and 2004 (Table 3).

Risk factors for FA

Generally, the presence of other allergic diseases or allergic sensitization in the subjects, their parents, or siblings were strong risk factors for the development of FA (24–26, 34, 40, 58, 68–70, 73, 84–87). Increasing age appeared as a risk factor (34, 46, 69, 70). Male sex was associated with an increased risk in some studies (46, 69, 70) mainly among children, although other studies also reported no association (58). Higher socioeconomic status (46) or living in more affluent societies increased the risk (22). Cesarean section

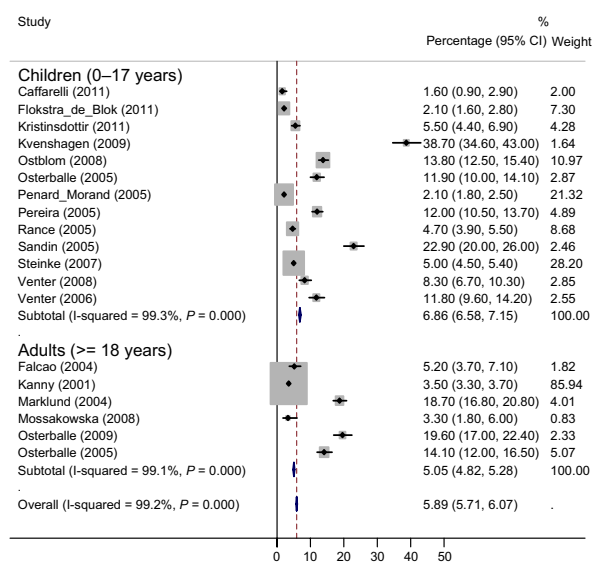
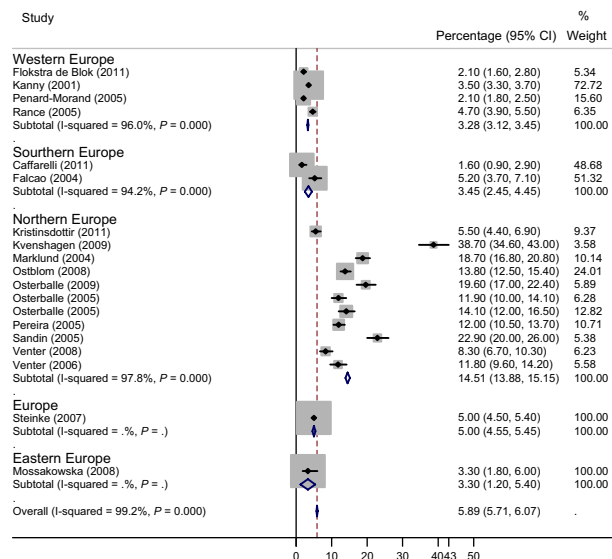
PANEL 1

Figure 2 Pooled point prevalence of self-reported FA stratified by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012.

PANEL 2

Markers represent percentages and 95%CI, and boxes represent the size of the study.

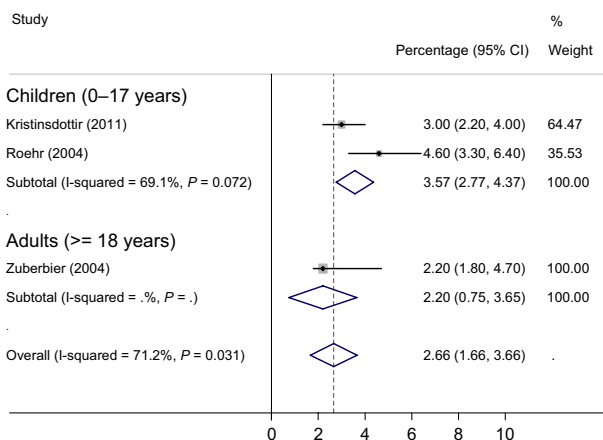
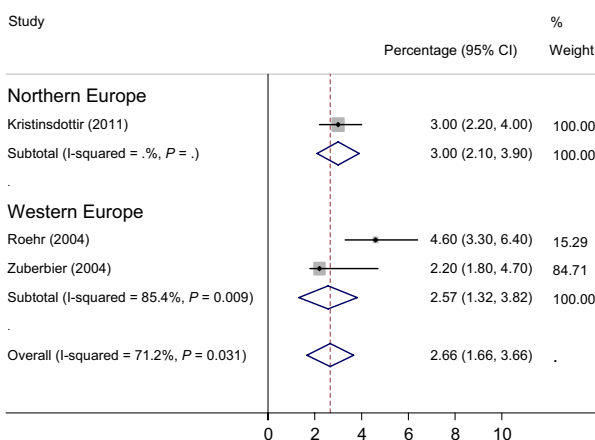
PANEL 1**PANEL 2**

Figure 3 Pooled point prevalence of symptoms plus specific IgE positivity to at least one food allergen by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between

January 2000 and September 2012. Markers represent percentages and 95%CI, and boxes represent the size of the study.

delivery and the use of antibiotics were not associated with FA (24–26, 53). In some studies, breastfeeding was not associated with the risk of FA (24–26, 58), although one study reported an increased risk (40). There was also an increased risk with the use of infant formula in one study (73). Other risk factors considered were inconsistently associated with FA across the studies.

Prognostic factors for FA

Of the various factors studied across the studies, no potential prognostic factor for the development of FA was reported,

indicating that little data exist at present to indicate the prognosis of FA. Some studies have studied outgrowing (e.g., level of specific IgE), but our search strategy would not necessarily have picked up these studies.

Discussion

Statement of principal findings

The present systematic synthesis has provided estimates of the frequency of FA across different age groups and

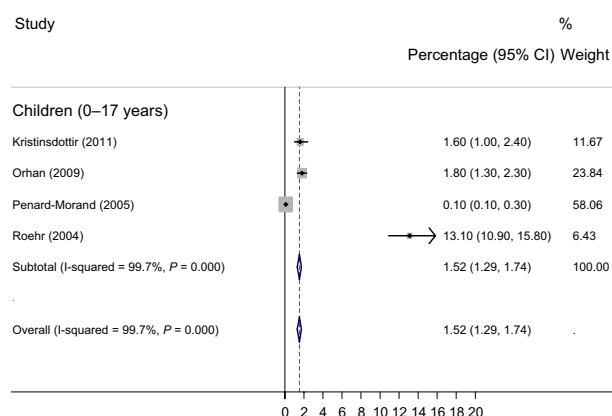
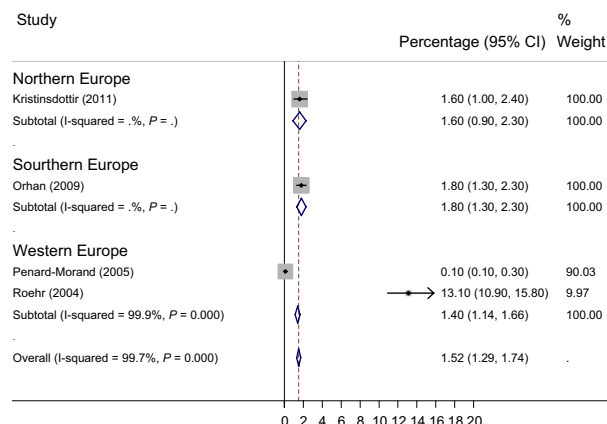
PANEL 1

Figure 4 Pooled point prevalence of symptoms plus SPT positivity to at least one food allergen by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January

PANEL 2

2000 and September 2012. Markers represent percentages and 95%CI, and boxes represent the size of the study.

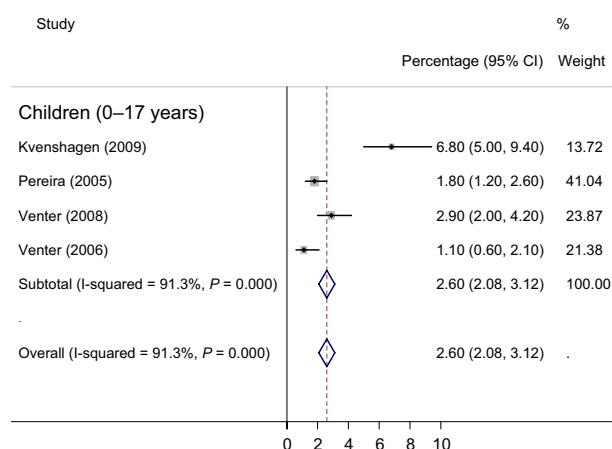
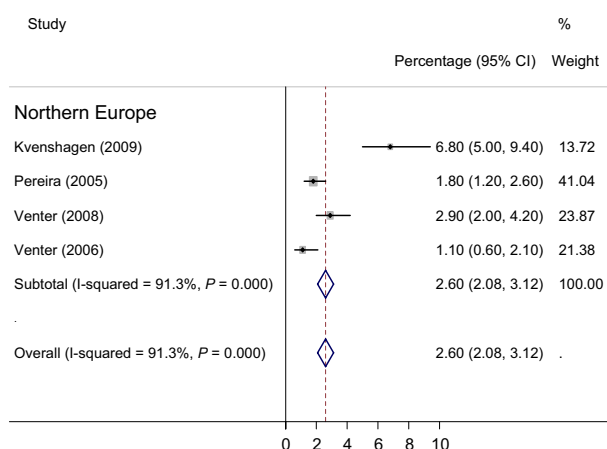
PANEL 1

Figure 5 Pooled point prevalence of clinical history of FA or food challenge (open food challenge or double-blinded, placebo-controlled) by age (only studies among children were available) (PANEL 1) and geographical region (only studies from Northern Europe were

PANEL 2

available) (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI, and boxes represent the size of the study.

geographical regions in Europe. Almost all the studies received 'moderate' overall grading. Only a few of the studies were undertaken in Eastern and Southern Europe. The overall lifetime prevalence of self-reported food allergy was 17.3% (95% CI: 17.0–17.6). Point prevalence for self-reported FA (5.9%), positive SPT to at least one food (2.7%), positive specific IgE (10.1%), and challenge-verified FA (0.9%) was lower. The highest prevalence was seen in northwestern Europe and in children compared to adults. Low prevalence of self-reported and confirmed FA was found in Southern Europe, while sensitization was similar to other regions. In Eastern Europe, a high prevalence of self-reported FA was found with lacking data about sensitization or clinical reactivity. Although data on the time trends of FA

were weak, while the incidence of FA seemed to be stable over time, the prevalence appeared to be increasing. Finally, no consistent risk or prognostic factors for the development of FA were observed, although age, sex, and the presence of other allergic diseases seem potentially important.

Strengths and limitations

Rigorous steps were undertaken in this synthesis, including a comprehensive literature search that covered the major electronic databases, no language restriction, and rigorous screening and appraisal processes undertaken. However, one of the limitations of this study is that due to the large amount of literature initially found, the review was restricted

PANEL 1

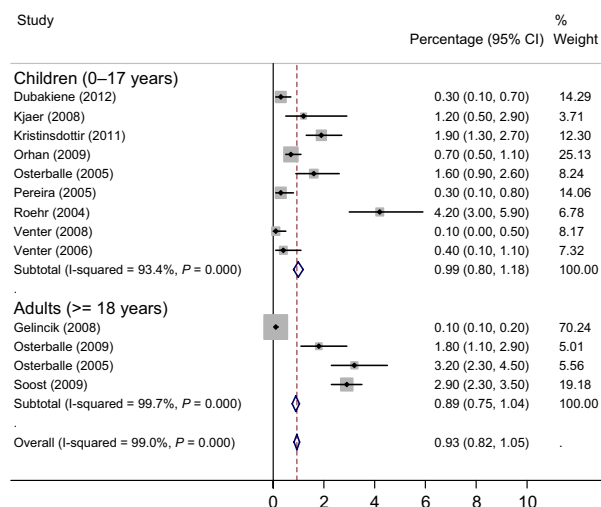


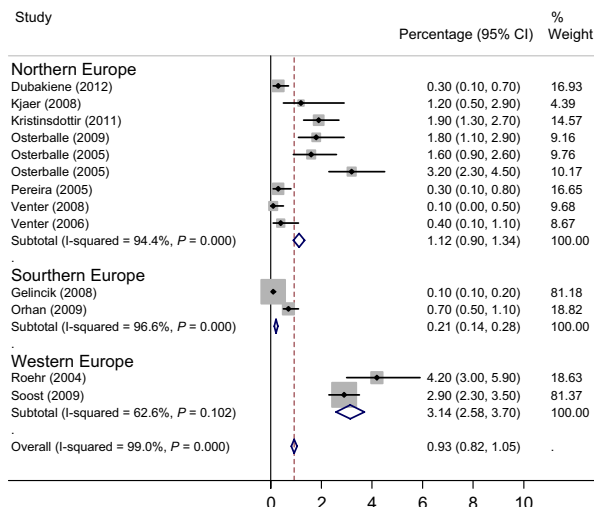
Figure 6 Pooled point prevalence of food challenge positivity (open food challenge or double-blinded, placebo-controlled) by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe

to studies published in Europe between 2000 and 2012 given the synthesis unpins the development of European Guidelines. This is so far the first study to consider the frequency of FA by geographical regions and thus sets the pace for further consideration in future studies so as to clearly understand the spatial distribution of the disease. The highly significant heterogeneity in the pooled frequency estimates points to important differences among the studies in terms of differences in protocols such as food challenge and skin prick testing methodology. These differences indicate that caution should be exercised in interpreting the pooled results. The limited number of studies from Southern and Eastern Europe could also point to the fact that a majority of the studies from these regions were published in local journals and in national languages that eventually are not indexed in the mainstream databases included in our study.

We were able to examine all possible methods that have been used to measure FA (e.g., self-report, specific sensitization, food challenges, and their various combinations) and different measures of occurrence of FA (e.g., point prevalence, lifetime prevalence incidence). We planned to additionally study case fatality and resolution, but their poor reporting made this impossible. Additionally, most studies failed to make clear whether IgE or non-IgE phenotypes were being studied. Such uncertainty, in addition to the changing definition of FA, has so far also contributed to the difficulty in estimating the actual frequency of FA.

Overall, the quality of studies included in the review was moderate. The methodological quality of future studies needs to be improved; for example, the gold standard DBPCFC should be used. However, the OFC is more often applied as DBPCFC is not yet common practice in many settings. Additionally, using DBPCFC can be problematic because many symptomatic individuals are not challenged due to co-existing

PANEL 2



between January 2000 and September 2012. Markers represent percentages and 95% CI, and boxes represent the size of the study.

disease, lack of validated and blinded challenge materials, or refusal, which could result in an underestimation of the real frequency of FA. However, the comparable DBPCFC estimates across different age groups indicate that the DBPCFC estimates obtained in this study are likely robust. Overall, using estimates where subjects with convincing clinical history and those with positive food challenge were combined as history or FC may represent the best estimates.

Due to wide variations in the definition of FA based on IgE or SPT sensitization to food allergens across the studies, comparison of estimates from studies that used these methods is also difficult. For instance, the values used for defining both positive IgE and SPT were inconsistent across a number of studies. Also, the number of specific foods tested was inconsistent across studies. Data indicate that the most common sensitized allergens are scantily represented in available commercial mixes; thus, the observed frequency of FA may be an underestimation (18). Allergies to very common inhalant allergies, such as grass pollen, house dust mites, and cockroaches, may lead to nonclinically relevant SPT or IgE positivity to cereals, peanut, and shrimp (91–93). This may inhibit valid estimation of the frequency of FA based on sensitization to specific food allergens. Finally, the diagnostic methods used to assess FA sensitization varied widely across studies, which may also reflect geographical variability in the application of diagnostic tools for defining FA sensitization.

Comparison of our findings with previous studies

We identified three previous systematic reviews that investigated the frequency of FA (16, 75, 90). Zuidmeer and colleagues focused only on the prevalence of plant food allergies and only searched the MEDLINE database, reporting estimates generally lower than our estimates (90). We

Table 2 Time trends in the frequency of FA in Europe: estimates from studies published between 1 January 2000 and 30 September 2012

Reference, country	Age(s) of subjects	Frequency of occurrence of FA					Comments
Gupta et al. (4, 36–38), UK	All ages	1990/1991	2000/2001	2003/2004			The increasing trends hospital admissions for FA between the study years were statistically significant. These admission data do not include period accident and emergency departments for observation and are therefore likely to underestimate the actual incidence or prevalence.
		<i>Admissions rate for FA for all age groups</i>					
		0.5	2.9	2.6			
		0–14 age group					
		1.6	11.8	10.7			
		15–44 age group					
		0.5	1.1	9.0			
Kotz et al. (46), UK	All ages	45+ age group					All estimates were age- and sex-standardized. During the study period, while the lifetime prevalence of peanut allergy doubled, the incidence rate of peanut allergy remained fairly stable. Sex-specific, age-specific, and SES-specific estimates are also reported in the paper.
		0.0	0.5	0.6			
		2001	2002	2003	2004	2005	
		<i>Lifetime prevalence of doctor-diagnosed peanut allergy per 1000 patients</i>					
		Percentage (95% CI)					
		0.24	0.32	0.39	0.45	0.51	
		(0.22–0.26)	(0.30–0.34)	(0.37–0.42)	(0.43–0.48)	(0.49–0.54)	
Venter et al. (84), UK	Children 3–4 years	<i>Incidence rate of doctor-diagnosed peanut allergy per 1000 person-years</i>					Three different cohorts were involved in the study, which were born in 1989, 1994–1996, and 2001–2002 and respectively reviewed (3–4 years after birth) in 1993, 1998–2000, and 2004–2005. SPT positivity to peanut allergen and clinical peanut allergy statistically significantly increased from 1993 to 1998–2000, but nonsignificantly decreased from 1998–2000 to 2004–2005.
		Percentage (95% CI)					
		0.06	0.08	0.08	0.08	0.08	
		(0.05–0.07)	(0.07–0.09)	(0.07–0.09)	(0.07–0.09)	(0.07–0.09)	
		1993	1998–2000	2004–2005			
		<i>Point prevalence of SPT positivity to peanut allergen</i>					
		Percentage (95% CI)					
1.3% (0.6–1.8)	3.3% (2.4–4.4)	2.0% (1.2–3.4)					
<i>Point prevalence of clinician-diagnosed peanut allergy (i.e., history plus sensitization plus OFC)</i>							
Percentage (95% CI)							
0.5% (0.2–1.1)	1.4% (0.9–2.2)	1.2% (0.7–2.2)					

searched four databases and had no restriction to the type of foods examined. The latest of the three systematic reviews (16) reported frequency of FA based on the estimates reported in a previous review (75), in which the prevalence of self-reported FA was around 12% in children and around 13% in adults (75). These compare to 6.9% and 5.1%, respectively, in our study. That review also reported a lower range of prevalence for positive specific IgE to at least one food (4–6%), but a higher range of positive SPT to at least one food (7–17%). The overall pooled estimate of FA by food challenge was above 2% in that study (75), twice our estimate (0.9%). The previous systematic review excluded primary studies that examined fruits, vegetables, seeds, nuts, cereals and meats, and included primary studies both from Europe and beyond. These may partly explain the differences in estimates found between our review and the previous ones. Only one of the previous studies examined the time trends in the frequency of FA and concluded that it is unclear whether the prevalence is increasing and that the observed increase over time could be attributed to increased awareness and

improved pattern of reporting and diagnosis rather than a true increase (14). We did not identify any previous systematic review that has investigated the risk or prognostic factors for FA.

Conclusions

The present evidence indicates that the lifetime prevalence and point prevalence of self-reported FA in Europe are around 17% and 6%, respectively. The point prevalence of food challenge-confirmed FA is under 1%. The frequency of FA is higher among children than among adults and highest in northwestern Europe than in other regions, while Southern Europe seems to have the lowest prevalence. Caution is required due to the heterogeneity among the studies suggesting important methodological and diagnostic differences within and across geographical regions of Europe. While the incidence of FA seems stable over time, the prevalence may be increasing, possibly reflecting changes in diagnostic practices or longer time to resolution. The risk or prognostic

Table 3 Summary of evidence on the risk/prognostic factors for FA in Europe: studies published between 1 January 2000 and 30 September 2012

Reference, country	Outcomes	Risk/prognostic factors studied	Statistical analysis method	Results and comments
Du Toit et al. (22), UK and Israel	OFC-verified peanut, sesame, tree nut, egg, and milk allergy	Country of residence (i.e., living in the UK as compared to living in Israel)	Mantel-Haenszel, Kaplan-Meier, log-rank test, multiple logistic regression	In both unadjusted and adjusted models: ↑living in the UK (compared to living in Israel) associated with peanut, sesame, tree nut, egg, and milk allergy. Early consumption of peanuts in infancy was associated with lower risk of peanut allergy, but estimates for this were not reported in the paper.
Engesbø et al. (24–26), Norway	History and OFC/DBPCFC-confirmed	Cesarean section, maternal antibiotics, child antibiotics, breastfeeding, maternal allergy, older siblings	Pearson's chi-square test, logistic regression	↑ Maternal allergy, → cesarean delivery, → maternal antibiotics, → child antibiotics, → breast feeding, → older siblings
Fox et al. (32), UK	SPT or sIgE positivity or DBPCFC	Environmental (household) peanut consumption, maternal peanut consumption during pregnancy and lactation, infant peanut consumption	Wilcoxon rank-sum test, multiple logistic regression	In adjusted models: ↑higher household peanut consumption, →maternal peanut consumption during pregnancy, →maternal peanut consumption during lactation.
Gelincik et al. (34), Turkey	DBPCFC-verified FA	Age, familial atopy, household pets, nasal allergy, itching dermatitis/urticaria, doctor-diagnosed asthma, smoking	Pearson's chi-square test, multiple logistic regression	In adjusted models: ↑age < 40 years, ↑familial atopy, ↑household pets, ↑nasal allergy, ↑itching dermatitis/urticaria, ↑doctor-diagnosed asthma.
Houriha et al. (40), UK	DBPCFC-verified peanut allergy	Breastfeeding, history of eczema and allergic rhinitis	Multiple logistic regression	Only the factors that were significant at the unadjusted level were included in the adjusted models
Kotz et al. (46), UK	Physician-diagnosed peanut allergy	Sex, age, socioeconomic deprivation	Pearson's chi-square test	DBPCFC-verified peanut allergy: ↑breastfeeding, ↑history of eczema. All these results were from adjusted models.
Kvenshagen et al. (53), Norway	Clinician-diagnosed allergy to any food	Cesarean section, use of antibiotics	Logistic regression	Incidence: ↑male sex, ↑0–4 years old, ↑being in the most affluent group Prevalence: ↑5–9 years old, being in the most affluent group Only frequencies and <i>P</i> -values were reported; no modeling strategies were employed in the analysis.
Nicolaou et al. (58), UK	History plus OFC/DBPCFC-verified peanut allergy	Sex, breastfeeding, maternal allergy, paternal allergy, current asthma/wheeze, current hay fever, current eczema, other known food allergies, median serum sIgE, peanut SPT > 8 mm	Pearson's chi-square test	Unadjusted models: →cesarean section delivery, →use of antibiotics →Male sex, →breastfed, →maternal allergic disease, →paternal allergic disease, ↑current asthma/wheeze, ↑current hay fever, ↑current eczema, ↑other known food allergies, ↑median serum sIgE to peanut, ↓median serum sIgE to grass, ↑median serum sIgE to peanut, ↑peanut SP wheal > 8 mm. Only frequencies and <i>P</i> -values were reported; no modeling strategies were employed in the analysis.

Table 3 (Continued)

Reference, country	Outcomes	Risk/prognostic factors studied	Statistical analysis method	Results and comments
Pereira et al. (68), UK	Self-reported FA	Atopic status	Binary logistic regression	Unadjusted model: †atopic children compared to nonatopic children
Pyrhönen et al. (69, 70), Finland	Physician-diagnosed FA and OFC-verified FA	Age, sex, no. of siblings, parental allergy (FA symptoms, animal allergy, hay fever, atopic rash, allergic asthma, any allergy, positivity to milk allergy, egg allergy, essential foods allergy)	Kaplan–Meier analyses and multiple Cox proportional regression	In unadjusted model: †age ≥ 1 years (compared to age 1 year), †male sex, →one or more siblings. In adjusted model: †either one or both parents having FA symptoms, † number of parental FA symptoms. The factors studied in the unadjusted model were not adjusted for and vice versa for factors studied in the adjusted model.
Roberts et al. (73) and Lack et al. (74), UK	DBPCFC-verified peanut allergy	SES, environmental tobacco smoke, maternal history of asthma, eczema, hay fever, other specific allergies, atopy; maternal intake of soybean meat, nuts during pregnancy; infant's breastfeeding status, use of soy milk or soy formula in 1st 2 years, rashes in 1st 6 months	Multiple logistic regression	Adjusted models: †consumption or formula during infancy, †rash over joints and in skin creases, †oozing, crusted rash
Venter et al. (84), UK	Physician-diagnosed and OFC/DBPCFC-verified peanut allergy	Having allergic diseases (wheeze, eczema) and increased SPT antibodies to food and inhalant allergens (house dust mite, grass, cat, milk, egg, wheat, and sesame)	Pearson's chi-square test and binary logistic regression	Unadjusted models: †ever wheeze; †wheeze in past 12 months; †ever physician-diagnosed eczema; †sensitization to house dust mite, grass, cat, milk, egg, wheat, and sesame. No adjusted models were computed for the estimates.
Venter et al. (85); Dean et al. (86); Venter et al. (87,88), UK	Physician-diagnosed and OFC/DBPCFC-verified FA	Sex, sibship, maternal and family history of atopy	Fisher's exact test, calculation of relative risk based on contingency tables	Estimates of associations between the risk factors and the endpoints not reported in the paper.

DBPCFC, double-blind, placebo-controlled food challenge; OFC, oral/open food challenge; sigE, specific immunoglobulin E test; SPT, skin prick test for sensitization to specific food allergens, †Indicates a statistically significant increased risk (risk factor); ‡Indicates a statistically significant decreased risk (protective factor); → Indicates no statistically significant association between the factor of interest and FA endpoint.

factors for the development of FA are inconsistent, although sex, age, country of residence, the presence of other allergic diseases, and familial history of allergy may be important. Clearly, there is need to improve this evidence base in order to validly estimate the putative frequency of food allergy. Future studies need to be rigorously designed using standardized methodology including DBPCFC to limit potential sources of bias that could weaken the estimates of food allergy, and more high-quality studies are needed from Eastern and Southern Europe (94, 95).

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Author contributions

AS, AM, and GR conceived this review. It was undertaken by BN and LH, with the support of SSP. BN, LH, GR, and AS led the drafting of the manuscript, and all authors critically commented on drafts of the manuscript.

Conflicts of interest

None declared.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

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1 *Long title: The epidemiology of food allergy in Europe: a systematic review and*
2 **meta-analysis**

3 *Short title: Epidemiology of food allergy in Europe: a review*

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Abbreviations:

CASP	Critical Appraisal Skills Programme
CI	Confidence intervals
DBPCFC	Double-blind, placebo-controlled food challenge
EAACI	European Academy of Allergy and Clinical Immunology
FA	Food allergy
IgE	Immunoglobulin E
OFC	Open food challenge
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SPT	Skin prick test

1 **METHODS**

3 **Search strategy**

4 Articles were retrieved using a highly sensitive search strategy implemented in four electronic
5 databases (OVID MEDLINE, OVID EMBASE, CINAHL, and ISI Web of Science). The search
6 strategy was devised on OVID MEDLINE and then adapted for the other databases (see Box 1).
7 Systematic reviews were retrieved by using the systematic review filter developed at McMaster
8 University Health Information Research Unit (HIRU)
9 (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Reviews). We also
10 adapted the search filter from York University Centre for Reviews and Dissemination
11 (http://www.york.ac.uk/inst/crd/intertasc/epidemiological_studies.html) to retrieve the
12 characteristics describing the epidemiology of FA. The McMaster filter
13 (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx#Prognosis) was applied for
14 retrieving studies on prognostic factors. Additional references were located by hand search.
15 Unpublished work and research in progress were searched through discussion with experts in the
16 field. There were no language restrictions, and where possible the literature in languages other
17 than English was translated. The literature we were unable to translate is shown in the PRISMA
18 flow diagram (Figure 1).

20 **Inclusion and exclusion criteria**

21 As per the study design, we included systematic reviews and meta-analyses, cohort studies, case-
22 control studies, cross-sectional studies, and routine healthcare studies. We excluded review and
23 discussion papers, non-research letters and editorials, case studies and case series, animal
24 studies, and all randomized controlled trials. Our initial inclusion criteria were broad by including
25 studies published worldwide between January 1990 and September 2012. However, after
26 assessing the large amount of articles, we made further restrictions to include studies published
27 only in Europe (based on the United Nations definition
28 (<http://unstats.un.org/unsd/methods/m49/m49regin.htm#europe> accessed on December 28, 2012)
29 between January 1, 2000 and September 30, 2012, with the exception of Greenland and Turkey,
30 which were included in the review because we believe they are culturally and politically more
31 European than North American and Asia, respectively.

33 **Analysis, synthesis and reporting**

34 We recalculated all the frequency estimates of FA occurrence if adequate data were provided by
35 authors. If any discrepancies were observed between our recalculated estimates and those of the
36 authors, we reported our recalculated estimates. Our recalculated estimates were based on the
37 minimal measured events rather than extrapolated estimates. In studies where inadequate data

1 were given to enable recalculation, we reported the estimates provided by the authors. Where
2 needed and possible, we contacted authors of primary studies for clarifications. The 95%
3 confidence intervals (95% CI) of our recalculations were computed by using the Wilson score
4 method without continuity correction (15). Different reports from the same primary study were
5 reported as one study. Although several specific food allergies were reported across the studies,
6 the focus of the current report is to present the estimates for 'any FA'. The other specific foods will
7 be presented in a future report. In studies reporting estimates of sensitization to food allergy
8 alongside cross-reactivity to pollen (wheat and grass), we always used the true estimates without
9 pollen cross-reactivity, where possible.

10

11 We performed a random-effects meta-analysis for clinically and methodologically comparable
12 studies to estimate the frequency of FA. The following outcomes were considered: 1. point and life-
13 time prevalence of self-reported FA; 2. point prevalence of specific IgE positivity; 3. point
14 prevalence of SPT positivity; 4. point prevalence of symptoms plus IgE positivity; 5. point
15 prevalence of symptoms plus SPT positivity; 6. point prevalence of clinical history or
16 OFC/DBPCFC-positivity; 7. point prevalence of positive response to food challenge (open food
17 challenge [OFC] or DBPCFC). For outcomes 6 and 7 above, where a study reported estimates for
18 both OFC and DBPCFC, the DBPCFC estimates were always used; otherwise OFC estimates
19 were used if DBPCFC was not done in the study. We did not present pooled estimates for
20 cumulative incidence of FA due to inconsistencies and very few data across studies.

21

22 We aimed to present stratified pooled estimates by different age groups (1 year and under, 2-5
23 years, 6–10 years, 11–17 years, 18–60 years, and older than 60 years). However, due to several
24 overlapping ages of participants across the studies, the age-stratified pooled estimates were more
25 feasibly computed for the age groups 0–17 years (children) and 18 years and over (adults). A
26 study with overlap between these two age groups was included in either age group if the age
27 distribution was skewed to that age group. For studies that gave frequency estimates at different
28 ages for the same individuals, we used the estimates for the highest age in computing the pooled
29 estimates. We also present the pooled estimates stratified by geographical region in Europe (i.e.,
30 East, West, South, North, and 'Europe'; the last group being for studies that included several
31 European countries and gave overall estimate for all the countries and in which it was not possible
32 to calculate the frequency for each country studied) using the classification by the UN
33 (<http://unstats.un.org/unsd/methods/m49/m49regin.htm#europe> accessed December, 2012). Due
34 to methodological differences across the studies investigating the risk and prognostic factors for FA
35 (varied risk and prognostic factors studied, differences in study design, differences in statistical
36 methods employed across studies, differences in factors considered for adjustment, and others),
37 we did not perform meta-analysis for these studies.

1 **RESULTS**

3 **Study characteristics**

4 The characteristics, main results, and the overall risk of bias grading of the studies included for
5 review are shown in Table S1. Of the 56 studies reviewed, 31 were cross-sectional, 19 cohort,
6 three were systematic reviews, and three case-control studies. Over 50% of the studies were
7 conducted in northern European countries. A majority of the studies (n=37) were undertaken only
8 in children. Ten studies assessed FA only by self-report, 10 only by specific-IgE or SPT positivity,
9 while the remainder was a combination of self-report, specific-IgE or SPT sensitization, and food
10 challenge. Twenty-six of the studies undertook food challenges for verifying FA, and 22 of these
11 employed DBPCFC. A majority of the studies (n=49) reported point prevalence as the occurrence
12 measure for estimating the frequency of FA. The majority of studies had a moderate risk of bias
13 (Table S2).

15 **Frequency of FA**

17 *Self-reported FA: details of studies*

18 Eighteen of the 27 studies on self-reported FA included children (i.e., < 18 years). Two studies
19 reported cumulative incidence in children: one study from Denmark reported the cumulative
20 incidence of self-reported FA by the age of 6 years as 11.6% (27-29), whereas one study from the
21 UK reported estimate of 25.8% by the age of 1 year and 28.1% by the age of 3 years (85-87). The
22 lowest (1.6%) and highest (38.7%) point prevalence of FA were reported in Italy (20) and Norway
23 (52), respectively (Figure E1). The lowest and highest life-time prevalence of FA was found in
24 Turkey (5.7%) (59) and Poland (41.8%) (53), respectively (Table E3). The range of point
25 prevalence of self-reported FA for all age groups was 1.6% to 38.7% and the highest point
26 prevalence was found in the age group 2–5 years (Table 1). The range of life-time prevalence of
27 self-reported FA for all age groups was 5.7% to 41.8% and the highest life-time prevalence was
28 found in the age group 6–10 years (Table E3).

30 *FA by positive SPT or IgE to specific food allergens: details of studies*

31 Of the 18 studies (17-19,27-29,35-42,47,50-52,61-64,67-70,76,77,81,82,85-88) that defined FA by
32 means of specific sensitization (positive SPT or IgE) to food allergens, 12 were undertaken among
33 children (Table E4). The frequency of FA as defined by positive specific-IgE was generally higher
34 than corresponding positive SPT, and often the correlation between the two types of tests was low.
35 The cumulative incidence of positive SPT or specific-IgE to at least one food by the age of 4 years
36 was reported to be 5.5% in Finland (69). The cumulative incidence of positive specific-IgE by 6
37 years was 47.3% in Denmark (27-29), while that of positive SPT was 5.3% by the age of 3 years in

1 the UK (Table E4) (85-87). The point prevalence of positive SPT to at least one food was lowest in
2 France (1.8%) (67) and highest in the UK (7.7%) (88). In general, the point prevalence of SPT
3 positivity was highest in Northern Europe than other regions (Figure E3), with only one study each
4 being undertaken in Western and Southern Europe. No study was found from Eastern Europe on
5 FA by SPT positivity to any specific food allergen. Studies on specific-IgE positivity to food
6 allergens were from only Northern and Western Europe. The point prevalence of positive specific-
7 IgE was lowest in Finland (2.0%) (41) and highest in Germany, Italy, Norway, and Denmark (each
8 country having approximately 22%) (Table E4) (18). In general, the point prevalence was higher in
9 Western than in Northern Europe (Figure E2), although only one study was undertaken in Western
10 Europe. The range of the prevalence of positive SPT positivity for all age groups was 1.8% to
11 6.1%, with the highest prevalence in the age group the 6–10 years; that of positive specific-IgE
12 ranged from 2.0% to 52.0%, the age group 6–17 also having the highest prevalence (Table 1).

13

14 *FA defined by symptoms plus allergic sensitization and by clinical history or food challenge*

15 Nine studies (23,48,53,60,67,68,78-80,85-88) defined FA based on symptoms plus sensitization
16 (SPT and IgE) to specific food allergens (n=5) or based on convincing clinical history or positivity to
17 food challenge (OFC or DBPCFC) (n=4) (Table E5). All of these studies were among children and
18 a majority from Northern Europe (n=6) (23,48,53,68,85-88). FA based on symptoms plus
19 sensitization involved subjects who were symptomatic for FA (usually by self-report) and
20 subsequently had positive results when they underwent SPT or IgE tests. On the other hand, FA
21 based on clinical history or food challenge was defined as either having a convincing clinical history
22 (without any food challenge) or being positive with food challenge.

23

24 The pooled point prevalence of symptoms plus positive IgE to at least one food was similar in
25 Northern and Western Europe (Figure 3). The lowest (2.2%) and highest (4.6%) point prevalence
26 of symptoms plus positive specific-IgE to at least one food were both found in Germany (78-80).
27 The range of the point prevalence of symptoms plus positive specific-IgE by age group was 1.3%
28 to 4.6%, those 1 year and less having the lowest frequency (Table 1).

29

30 The point prevalence of symptoms plus SPT positivity was just highest in Southern Europe
31 compared to other regions (Figure 4). The lowest point prevalence was found in France (0.1%) (66)
32 and the highest in Germany (13.1%) (77-79). The range of the point prevalence of symptoms plus
33 positive SPT by age group was 0.1% to 13.1%, the age groups 6–10 and 11–17 years having the
34 lowest estimates.

35

36 The overall pooled point prevalence of clinical history or food challenge positivity was lowest in the
37 UK (1.1%) (87) and highest in Norway (6.8%) (53) (Table E5). The range of the point prevalence

of clinical history or food challenge by age group was 1.1% to 6.8%, the age group 2–5 years having the highest frequency (Table 1). Differences may be explained by the use of OFC versus DBPCFC.

There was significant heterogeneity between the studies ($P < 0.05$ for I^2) despite stratification by age and region.

Challenge-verified FA: details of studies

Of the 12 primary studies (23,27-29,34,48,60,65,66,68-70,78-80,85-88) that assessed FA by performing food challenge (OFC or DBPCFC), eight only included children (23,27-29,48,60,68-70,85-88) and nine came from Northern Europe (23,27-29,48,65,66,68-70,85-88), two from Southern Europe (34,60), and one from Western Europe (78-80) (Table E6). Three of the studies reported cumulative incidence of challenge positive FA by 1 year (1.5% [95% CI 0.9-2.5]) (27-29), by 4 years (3.3% [95% CI 2.8-3.9]) (69,70), and by 6 years (3.6% [95% CI 2.3-5.4]) (85-87). The lowest point prevalence of challenge-verified FA was found in the UK (almost zero per cent) (85-87) while the highest was found in Germany (5.7%) (78-80) (Table E6). The range of the point prevalence of challenge-verified FA was from 0% to 5.7%, with the age group 11–17 having the highest frequency (Table 1). There was significant heterogeneity between the studies ($P < 0.05$ for I^2) even after stratification by age and region.

Cumulative incidence

Only one of the nine studies in these categories reported estimates for cumulative incidence (84-86), showing that the cumulative incidence of FA by the age of 3 years was 6.0% (95% CI 4.6-6.7) based on clinical history or OFC positivity and 5.0% (95% CI 3.8-6.5) based on clinical history or DBPCFC positivity.

Risk and prognostic factors for FA

Although a number of the reviewed studies examined the risk and prognostic factors for self-reported FA and sensitization to specific food allergen, a priori, we were interested in studying the risk and prognostic factors for clinician-diagnosed or objectively-verified FA, which is expected to give stronger evidence for causality and would be more meaningful for clinical intervention. Thirteen studies (22,24-26,32,34,40,46,53,58,68-70,73,84-87) were found of which 11 were among children (Table 3). Due to several methodological differences between the studies, they were not combined in a meta-analysis.

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Box E1: Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Search Strategy:

1 exp Food Hypersensitivity/
2 food allerg*.mp.
3 food hypersensitivity.mp.
4 food hypersensitivities.mp.
5 allergy, food.mp.
6 (rat or rats or cow or cows or chicken? or horse or horses or mice or
7 mouse or bovine or animal\$).ti.
8 exp animals/ not humans.sh.
9 6 or 7

10 *Incidence/
11 *Prevalence/
12 (incidence or prevalence or epidemiol\$).ti.
13 epidemiologic methods/

14 *cohort studies/
15 controlled clinical trial.pt.
16 *case-control studies/
17 exp Food Hypersensitivity/ep [Epidemiology]
18 exp Hospitalization/
19 exp Hospitalization/sn, td [Statistics & Numerical Data, Trends]
20 exp Mortality/sn, td [Statistics & Numerical Data, Trends]
21 exp Epinephrine/ad, tu, th [Administration & Dosage, Therapeutic Use,
22 Therapy]
23 exp "Cause of Death"/
24 ((adrenaline or epinephrine) adj3 (dispens\$ or prescrib\$)).tw.
25 or/9-22
26 or/1-5
27 23 and 24
28 25 not 8
29 limit 26 to yr="1990 - 2012"

Table E1: The main features, main results of frequency of FA, and overall risk of bias assessment of the studies included in the systematic review on the epidemiology of FA in Europe: studies published 1 January 2000 – 30 September 2012

Reference, country	Study design	Study population N (children/adults; source of study population)		Age of subjects	Outcome studied and assessment method		Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Overall risk of bias assessment
		Number approached	Number participated		Outcome(s) studied	Method of outcome assessment ¹			
Bant et al. 2008, Poland	Cross-sectional study	Not indicated	156	18-27 years old	Any food allergen	SPT, sIgE	Point prevalence	Point prevalence of sIgE positivity to at least one FA: 11%	Moderate
Burney et al. 2010; Woods et al. 2001, Europe, United States of America, Australia, New Zealand	Cross-sectional study	Not indicated	17280	20-44 yrs old	Any FA, fish, egg, cow's milk, mustard, melon, poppy seed, soya, sunflower, walnut, banana, peanut, buckwheat, rice, tomato, corn, celery, kiwifruit, carrot, sesame, apple, wheat, shrimp, peach, hazelnut	Self-reported, sIgE	Point and life-time prevalence	Point prevalence of sIgE positivity to at least one FA for all countries 12.3%	Moderate
Caffarelli et al. 2011, Italy	Cross-sectional study	900	625	5-14 years old	Any FA, cow's milk, egg, tomato, peanut, wheat, chocolate, kiwi, strawberry, melon, orange, hazelnut, sesame	Self-reported	Point and life-time prevalence	Point prevalence of self-reported FA: 1.6% (0.9-2.9)	Moderate
Chafen et al. 2010, World-wide	Systematic review	12378 studies identified	72 studies included	All age groups	Cow's milk, egg, peanut, fish, shellfish	Self-reported, physician-diagnosis, SPT, sIgE, OFC, DBPCFC	Point, period, life-time prevalence; cumulative incidence, incidence rate	The same frequency estimates as given in Rona et al. 2007	Strong
Colver et al. 2005, United Kingdom and Ireland	Cross-sectional study	13028933	13028933	Children < 16 years	Any food allergic reaction	Physician diagnosis	Point prevalence	Frequency estimates not obtainable from the study	Moderate
Du Toit et al. 2008, United Kingdom and Israel	Cross-sectional study	10786	8826	4-18 years old	Peanut, sesame, tree nuts, egg, milk	Self-reported, clinical history, OFC	Point prevalence	Point prevalence of DBPCFC-confirmed peanut allergy: 0.4% (0.3-0.6) in United Kingdom and Israel	Moderate
Dubakiene et al. 2012, Lithuania	Cohort study	1558	1558	6-12 months old	Any FA, milk, egg, wheat, peanut, potato, and fish	Self-reported, SPT, sIgE, DBPCFC	Point prevalence	Point prevalence of DBPCFC-confirmed FA: 0.3% (0.1-0.7)	Moderate
Eggesbø et al. 2003, 2001a and 2001b, Norway	Cohort study	4973	3754	2.5 years old	Any FA, cow's milk, hen's egg, fish, nuts, cereals, chocolate, fruits, vegetables	Self-reported, physician diagnosis, SPT, sIgE, OFC,	Point prevalence, cumulative incidence	Point prevalence of OFC/DBPCFC-confirmed egg allergy 0.3% (0.2-0.6) and milk allergy 0.4% (0.2-	Moderate

						DBPCFC		0.7)	
Eller et al. 2009, Kjaer et al. 2008, Johnke et al. 2006, Denmark	Cohort study	1095	562	6 years old	Any FA, cow's milk, hen's egg, peanut, wheat, codfish, soy, shrimp, hazelnut, Brazil nut, celery	Self-reported, SPT, sIgE, OFC, DBPCFC	Point prevalence, cumulative incidence	Point prevalence of OFC/DBPCFC-confirmed FA at 6 years: 1.2% (0.5-2.9)	Moderate
Falcaõ et al. 2004, Portugal	Cross-sectional study	1565	659	>39 years old	Any FA, fresh fruits, meat, fish, eggs, octopus and squid, chocolate, milk, spices, legumes	Self-reported	Point prevalence	Point prevalence of self-reported FA: 5.2% (3.7-7.1)	Moderate
Flokstra-de Blok et al. 2011, The Netherlands	Cross-sectional study	No information	2284	11-20 years old	Any FA	Self-reported	Point prevalence	Point prevalence of self-reported FA: 2.1% (1.6-2.8)	Weak
Fox et al. 2009, United Kingdom	Case-control study	133 cases, 310 controls	133 cases, 310 controls	< 4 years	Peanut allergy	SPT, sIgE, DBPCFC	Point prevalence	Case-control study: frequency estimates not given	Moderate
Frongia et al 2005, Italy	Cross-sectional study	5040	4602	1-2 years old	Any FA, peanut, egg, milk, tomato	Self-reported	Lifetime prevalence	Lifetime prevalence of FA: 7.8% (7.0-8.6)	Moderate
Gelincik et al. 2008, Turkey	Cross-sectional study	17064	11816	≥ 18 years old	Any FA, any non-allergic food hypersensitivity, tomatoes, hen's egg, cacao, orange, eggplant, peanut, strawberry, carrot, banana, hazelnut, pear, spinach, red chili, black pepper, food additives, chocolate, walnut, potato, fish	Self-reported, SPT, sIgE, DBPCFC	Point and life-time prevalence	Point prevalence of DBPCFC-confirmed FA: 0.1% (0.1-0.2)	Moderate
Grundy et al. 2002, United Kingdom	Cohort study	2858	1273	3-4 years old	Peanut allergy	Self-report, SPT, OFC	Point prevalence	Point prevalence of OFC-confirmed peanut allergy: 0.6% (0.3-1.2)	Moderate
Gupta et al. 2007, 2004, 2003, United Kingdom	Cross-sectional study	Not indicated	Not indicated	All age groups	Any FA	Physician diagnosis	Cumulative incidence	Please see results in Table 7 (time trends)	Moderate
Høst et al. 2002, Denmark	Cohort study	1758	1749	15 years old	Any FA, cow's milk allergy	SPT, sIgE, OFC, DBPCFC	Point prevalence	Point prevalence of history or OFC/DBPCFC-confirmed milk allergy 2.2% (1.6-3.0)	Moderate
Hourihane et al. 2007, United Kingdom	Cross-sectional study	5072	1125	4-5 years old	Peanut allergy	SPT, sIgE, DBPCFC	Point prevalence	Point prevalence of DBPCFC-confirmed peanut allergy: 1.4% (0.8-2.3)	Moderate
Isolauri et al. 2004, Finland	Cross-sectional study	400	400	7, 27, 47, 67 years	Any FA, milk	Self-reported, sIgE	Lifetime prevalence and point prevalence	Point prevalence of sIgE positivity to at least one FA at 67 years: 9% (5-18)	Moderate
Johansson et al. 2005, Sweden and Norway	Cross-sectional study	Not indicated	Sweden 1002; Norway 500	Adults	Any FA, peanut, soya bean, egg white, cow's milk, cod fish, wheat flour, penicilloyl G, suxamethonium, latex, hazel nut	sIgE	Point prevalence	Point prevalence of sIgE positivity to at least one FA for both Norway and Sweden 3.6% (2.8-4.7)	Moderate
Julge et al. 2001,	Cohort	455	298	5 years	Egg white, cow's milk	SPT, sIgE	Point prevalence	Point prevalence of SPT	Moderate

Vasar et al. 2000, Estonia	study							positivity to egg at 5 years 0% and sIgE positivity to egg at 5 years 2.4%	
Kanny et al. 2001, France	Cross-sectional study	44000	31110	≤ 60 years	Any FA	Self-reported	Point prevalence	Point prevalence of self-reported FA 3.5% (3.3-3.7)	Moderate
Kotz et al. 2011, United Kingdom	Cohort study	2958366	2958366	All age groups	Peanut allergy	Physician diagnosis	Life-time prevalence, incidence rate	Please see results in Table 7 (time trends)	Moderate
Krause et al. 2002, Greenland	Cross-sectional study	1213	1068	5-18 years old	Any FA, egg, milk, fish, peanut, wheat, soy	sIgE	Point prevalence	Point prevalence of sIgE positivity to at least one FA: 4.1% (3.0-5.5)	Moderate
Kristinsdottir et al. 2011, Iceland	Cohort study	No information	1341	1 year old	Any FA, hen's egg, cow's milk, peanut, fish, wheat, soy, shrimp, cranberry, potato, pineapple, almond, nutramigen, green peas	Self-reported, SPT, specific sIgE, DBPCFC	Point prevalence	Point prevalence of DBPCFC-confirmed FA: 1.9% (1.3-2.7)	Moderate
Kucukosmanoglu et al. 2008, Turkey	Cross-sectional study	1415	1015	8-18 months	Egg allergy	SPT	Point prevalence	Point prevalence of SPT positivity to egg 1.9% (1.2-2.9)	Moderate
Kurulaaratchy et al. 2005, Arshad et al. 2001, Tariq et al. 2000, United Kingdom	Cohort study	1536	1456	4 years old	Any FA, milk, egg, peanut, cod, wheat, soya	SPT	Point prevalence, cumulative incidence	Point prevalence of SPT positivity to at least one FA: 3.5%	Moderate
Kvenshagen et al. 2009, Norway	Cohort study	Not indicated	609	2 years old	Any FA, egg, milk, peanut, hazelnut	Self-reported, SPT, sIgE, OFC, DBPCFC	Point prevalence	Point prevalence of Clinical history or OFC/DBPCFC FA 6.8% (5.0-9.4)	Moderate
Majkowska-Wojciechowska et al. 2009, Poland	Cross-sectional study	3260	2148	7-10 years old	Any FA, milk, chocolate, dairy, strawberries, eggs, tomatoes, cocoa, nuts, fruits, oranges	Self-reported	Life-time prevalence	Life-time prevalence of FA 41.6% (39.5-43.7)	Moderate
Marklund et al. 2004, Sweden	Cross-sectional study	2064	1488	13-21 years old	Any food hypersensitivity	Self-reported	Point prevalence	Point prevalence of self-reported FA: 18.7% (16.8-20.8)	Moderate
Matricardi et al. 2007, Germany	Cohort study	7609	1314	2-10 years old	Cow's milk, hen's egg, soy, and wheat	sIgE	Point prevalence	Point prevalence of sIgE positivity to at least one FA at 10 years: milk 1.0% (0.5-2.3), egg 0.9% (0.4-2.0), soy 6.1% (4.4-8.3), wheat 8.8% (6.8-11.4)	Moderate
Mossakowska et al. 2008, Poland	Cross-sectional study	Not indicated	301	>100 years old	Strawberries, bananas, oranges, eggs, pepper, garlic, chamomile, ice cream	Self-reported	Point prevalence	Point prevalence of FA: 3.3% (1.8-6.0)	Moderate
Nicolaou et al. 2010, United Kingdom	Cohort study	1499	1085	8 years old	Peanut, milk, egg, fish, tree nut	Self-reported, SPT, sIgE, OFC, DBPCFC	Point and lifetime prevalence	Point prevalence of OFC-confirmed peanut allergy: 0.7% (0.3-1.4)	Moderate

Niggemann et al. 2011, Germany	Cross-sectional study	26787	17641	0-17 years old	Peanut allergy	slgE	Point prevalence	Point prevalence of slgE positivity to peanut allergen 10.9%	Moderate
Orhan et al. 2009, Turkey	Cross-sectional study	3500	2739	6-9 years old	Any FA, cocoa, hen's egg, beef, cow's milk, fish, tomato, hazelnut, kiwi, black pepper, chickpea, peanut, walnut, corn, banana, strawberry, potato	Self-reported, SPT, OFC, DBPCFC	Life-time and point prevalence	Point prevalence of DBPCFC-confirmed FA 0.7% (0.5-1.1)	Moderate
Östblom et al. 2008a, 2008b, 2008c and Almqvist et al. 2005, Sweden	Cohort study	7221	4089	4-8 years old	Any FA, cow's milk, citrus, peanut, tree nuts/almond, hen's egg, stone fruit, chocolate, fish, pea, soy bean, wheat, banana, cod fish	Self-reported, slgE	Point and period prevalence	Point prevalence of slgE positivity to at least one FA at 8 years: 13.8% (12.5-15.4)	Moderate
Osterballe et al. 2009, Denmark	Cross-sectional study	1094	843	Mean age 22 years	Any FA, additives, codfish, cow's milk, hen's egg, octopus, peanut, shrimp, soy, wheat, beer, cheese, red wine (other secondary food allergies also reported in the paper)	Self-reported, SPT, OFC, DBPCFC	Point prevalence	Point prevalence of OFC/DBPCFC-confirmed FHS: 1.8% (1.1-2.9)	Moderate
Osterballe et al. 2005, Denmark	Cohort study	Not indicated	1834	Children and adults	Any FA, additives, codfish, cow's milk, hen's egg, peanut, shrimp, soy, wheat, fruit/vegetables	Self-reported, physician diagnosis, SPT, slgE, OFC, DBPCFC	Point prevalence	Point prevalence of OFC/DBPCFC-confirmed FHS: at 3 years 2.3% (1.3-4.0); adults 3.2% (2.3-4.5)	Moderate
Penard-Morand et al. 2005, France	Cross-sectional study	9615	7781	9-11 years old	Any FA, nuts, fruits or vegetables, egg, milk, peanut, fish, seafood	Self-reported, SPT	Point prevalence	Point prevalence of symptoms plus SPT positivity to at least one FA: 0.1% (0.1-0.3)	Moderate
Pereira et al. 2005, United Kingdom	Cross-sectional study	3144	1532	11 and 15 year old	Any FA, milk, egg, wheat, fish, peanut, sesame, tree nuts, additives, shellfish	Self-reported, physician diagnosis, SPT, OFC, DBPCFC	Point prevalence	Point prevalence for all children: OFC-confirmed FA 2.3% (1.6-3.2) DBPCFC-confirmed 1.8% (1.2-2.6)	Moderate
Pyrhönen et al. 2011 and 2009, Finland	Cohort study	5973	3899	0-4 years old	Any FA, milk, egg, wheat, barley or rye, nut, fish, citrus fruit	Self-reported, physician-diagnosis, SPT, slgE, OFC	Life-time prevalence, cumulative incidence	Lifetime prevalence of self-reported physician-diagnosed FA 30.3% (28.7-31.9) Cumulative incidence of OFC-confirmed FA by 4 years: 3.3% (2.8-3.9)	Moderate
Pyziak and Kamer 2011, Poland	Cross-sectional study	115	83	6-17 years old	Any FA, cow's milk, hen's egg, soy, pork, beef	Self-reported, slgE, SPT, OFC	Point prevalence	Frequency estimates not given in the study	Moderate
Rance et al. 2005, France	Cross-sectional study	3500	2716	Mean age 8.9 years	Any FA, cow's milk, egg, kiwi, peanut, fish, tree nut, shrimp	Self-reported	Point and life-time prevalence	Point prevalence of self-reported FA: 4.7 (3.9-5.5)	Moderate

Roberts et al. 2005 and Lack et al. 2003, United Kingdom	Cohort study	13971	12090	0-7 years	Egg, milk, cod fish, soya, sesame, peanut, tree nut, cashew, almond, walnut, hazelnut, brazil nut, pecan nut	Self-reported, SPT, DBPCFC	Point Prevalence	Point prevalence of DBPCFC-confirmed peanut allergy: 0.2% (0.1-0.3)	Moderate
Rona et al. 2007, World-wide	Systematic review	934 studies identified	Number of studies included in review not indicated	All age groups	Any FA, cow's milk, hen's egg, peanut, fish, shellfish	Self-reported, physician-diagnosis, SPT, sIgE, OFC, DBPCFC	Point, period, life-time prevalence, cumulative incidence and incidence rate	Range of prevalence of SPT or sIgE to at least one FA: 2%-5% SPT only: 7%-17% IgE only: 4%-6%	Moderate
Ronchetti et al. 2008, Italy	Cross-sectional study	Not indicated	380	9 and 13 years old	Any FA, cow's milk, hen's egg, tomato, wheat flour	SPT	Point prevalence	Point prevalence of SPT positivity to at least one FA for all children 4.2% (2.6-6.7)	Moderate
Sandin et al. 2005, Sweden and Estonia	Case-control study	All 985 Sweden 645 Estonia 340	All 770 Sweden 483 Estonia 287	10-11 years old	Any FA; apple, peach, kiwi, or carrot; nut or peanut; orange, mandarin or tomato; milk, egg, fish or wheat	Self-report, sIgE	Point prevalence	Point prevalence of sIgE positivity to at least one FA for Estonia and Sweden 13.9% (11.3-16.9)	Moderate
Schäfer et al. 2001, Germany	Nested case-control study	2539	1537	25-74	Any FA	Self-reported, SPT	Point prevalence, lifetime prevalence	Point prevalence of SPT positivity to at least one FA in the population of the allergy MONICA study: 16.8%	Moderate
Schnabel et al. 2010, Germany	Cohort study	3097	1082	6 years old	Any FA	Self-reported, sIgE	Point prevalence	Point prevalence of sIgE positivity to at least one FA at 6 years: 11.7% (10.0-13.8)	Moderate
Soost et al. 2009 and Zuberbier et al. 2004, Roehr et al. 2004, Germany	Cross-sectional study	13300	All: 4093 Age 0-17 years: 739 Age 18-79 years: 3227	0-79 years old	Any FA, vegetables, legumes, soy, spices, fish, cereals, meat and fat, stonefruit, chocolate/sweets, cow's milk, hen's egg, pipfruit, nuts, vegetable oil, carrot, celery, sesame, apple, apple, hazelnut, potato, wheat, peanut, walnut, shrimp	Self-reported, physician diagnosis, SPT, sIgE, OFC, SBPCFC, DBPCFC	Point and life-time prevalence	Point prevalence of OFC/DBPCFC-confirmed FA: All: 2.8% (2.4-3.4) Children: 4.2% (3.0-5.9) Adults: 2.9% (2.3-3.5)	Moderate
Steinke et al. 2007, Europe	Cross-sectional study	Not indicated	40426	< 18 years	Any FA, fish, seafood, wheat, meat, eggs, milk, fruits, legumes, vegetables, nuts	Self-reported	Point prevalence	Point prevalence of self-reported FA: All countries: 5.0% (4.5-5.4)	Moderate
Venter et al. 2010, United Kingdom	Cohort study	5283	3382	3-4 years old	Peanut allergy	Physician diagnosis, SPT, sIgE, OFC, DBPCFC	Point prevalence	Point prevalence of OFC-confirmed peanut allergy: 0.3% (0.1-1.0)	Moderate
Venter al 2008; Dean et al. 2007; Venter et al. 2006,	Cohort study	1063	969	3 years old	Any FA, milk, egg, fish, peanut, sesame, wheat	Self-report, SPT, OFC, DBPCFC	Point and period prevalence, cumulative	Point prevalence of OFC-confirmed FA at 3 years: 0.8% (0.4-1.6)	Moderate

United Kingdom							incidence		
Venter et al. 2006, United Kingdom	Cross-sectional study	1440	798	6 years old	Any FA, milk, peanut, egg, additives & colourings, tree nuts, wheat, strawberry, sesame, fish, chocolate, banana	Self-report, SPT, OFC, DBPCFC	Point prevalence	Point prevalence of OFC-confirmed FA 1.3% (0.7-2.3) and DBPCFC-confirmed FA 0.4% (0.1-1.1)	Moderate
von Hertzen et al. 2006, Finland and Russia	Cross-sectional study	Finland: 546 child-mother pairs	Finland: 413 children, 409 mothers	7-16 years children	Fish, egg, wheat, cow's milk, peanut, hazelnut	SPT	Point prevalence	Point prevalence of SPT positively to peanut allergen: children: 8.2% (5.8-11.5), mothers: 10.1% (7.4-13.6)	Moderate
Zuidmeer et al. 2008, World-wide	Systematic review	396 studies identified	33 studies included	All age groups	Fruits, vegetables, tree nuts, soy, wheat	Self-reported, physician-diagnosis, SPT, sIgE, OFC, DBPCFC	Point, period, and life-time prevalence	Point prevalence of DBPCFC-confirmed allergy to vegetables: 1.4%	Moderate

¹DBPCFC: double-blind, placebo-controlled food challenge; OFC: oral/open food challenge; sIgE: specific immunoglobulin E test; SPT: skin prick test for sensitization to specific food allergens

Table E2: Quality assessment of studies included in the systematic review: included studies 1 January 2000 – 30 September 2012

Reference, country	Overall risk of bias assessment	Components of risk of bias assessment			
		Study design	Selection bias	Exposure assessment	Outcome assessment
Bant et al. 2008, Poland	Moderate	Strong	Weak	Not applicable	Moderate
Burney et al. 2010; Woods et al. 2001, Europe, United States of America, Australia, New Zealand	Moderate	Moderate	Moderate	Moderate	Moderate
Caffarelli et al. 2011, Italy	Moderate	Strong	Moderate	Moderate	Weak
Chafen et al. 2010, World-wide	Strong	Strong	Moderate	Not applicable	Strong
Colver et al. 2005, United Kingdom and Ireland	Moderate	Moderate	Weak	Moderate	Moderate
Du Toit et al. 2008, United Kingdom and Israel	Moderate	Moderate	Moderate	Moderate	Strong
Dubakiene et al. 2012, Lithuania	Moderate	Strong	Moderate	Moderate	Strong
Eggesbø et al. 2003, 2001a, 2001b, Norway	Moderate	Strong	Moderate	Moderate	Strong
Eller et al. 2009, Kjaer et al. 2008, Johnke et al. 2006, Denmark	Moderate	Strong	Moderate	Not applicable	Strong
Falcaõ et al. 2004, Portugal	Moderate	Strong	Moderate	Not applicable	Weak
Flokstra-de Blok et al. 2011, The Netherlands	Weak	Strong	Weak	Not applicable	Weak
Fox et al. 2009, United Kingdom	Moderate	Strong	Moderate	Moderate	Strong
Frongia et al 2005, Italy	Moderate	Strong	Moderate	Not applicable	Weak
Gelincik et al. 2008, Turkey	Moderate	Moderate	Weak	Moderate	Strong
Grundy et al. 2002, United Kingdom	Moderate	Strong	Moderate	Not applicable	Strong
Gupta et al. 2007, 2004, 2003, United Kingdom	Moderate	Strong	Weak	Not applicable	Moderate
Høst et al. 2002, Denmark	Moderate	Strong	Moderate	Not applicable	Strong
Hourihane et al. 2007, United Kingdom	Moderate	Moderate	Weak	Moderate	Strong
Isolauri et al. 2004, Finland	Moderate	Strong	Moderate	Moderate	Moderate
Johansson et al. 2005, Sweden and Norway	Moderate	Moderate	Weak	Not applicable	Moderate
Julge et al. 2001, Vasar et al. 2000, Estonia	Moderate	Strong	Moderate	Moderate	Moderate
Kanny et al. 2001, France	Moderate	Strong	Moderate	Moderate	Weak
Kotz et al. 2011, United Kingdom	Moderate	Moderate	Moderate	Moderate	Moderate
Krause et al. 2002, Greenland	Moderate	Strong	Moderate	Not applicable	Moderate
Kristinsdottir et al. 2011, Iceland	Moderate	Strong	Moderate	Not applicable	Strong
Kucukosmanoglu et al. 2008, Turkey	Moderate	Strong	Moderate	Not applicable	Moderate
Kurulaarachy et al. 2005, Arshad et al. 2001, Tariq et al. 2000, United Kingdom	Moderate	Strong	Moderate	Not applicable	Moderate
Kvenshagen et al. 2009, Norway	Moderate	Strong	Moderate	Moderate	Strong
Majkowska-Wojciechowska et al. 2009, Poland	Moderate	Strong	Moderate	Not applicable	Weak
Marklund et al. 2004, Sweden	Moderate	Strong	Moderate	Not applicable	Weak
Matricardi et al. 2007, Germany	Moderate	Strong	Moderate	Not applicable	Moderate
Mossakowska et al. 2008, Poland	Moderate	Strong	Moderate	Not applicable	Weak
Nicolaou et al. 2010, United Kingdom	Moderate	Strong	Moderate	Moderate	Strong
Niggemann et al. 2011, Germany	Moderate	Strong	Moderate	Not applicable	Moderate
Orhan et al. 2009, Turkey	Moderate	Strong	Moderate	Not applicable	Strong
Östblom et al. 2008a, 2008b, 2008c; Almqvist et al. 2005, Sweden	Moderate	Strong	Moderate	Not applicable	Moderate

Osterballe et al. 2009, Denmark	Moderate	Strong	Moderate	Not applicable	Strong
Osterballe et al. 2005, Denmark	Moderate	Strong	Moderate	Not applicable	Strong
Penard-Morand et al. 2005, France	Moderate	Moderate	Moderate	Moderate	Moderate
Pereira et al. 2005, United Kingdom	Moderate	Strong	Moderate	Not applicable	Strong
Pyrhönen et al. 2011 and 2009, Finland	Moderate	Moderate	Moderate	Moderate	Strong
Pyziak and Kamer 2011, Poland	Moderate	Moderate	Weak	Moderate	Strong
Rance et al. 2005, France	Moderate	Strong	Moderate	Not applicable	Weak
Roberts et al. 2005 and Lack et al. 2003, United Kingdom	Moderate	Strong	Moderate	Moderate	Strong
Rona et al. 2007, World-wide	Moderate	Strong	Moderate	Not applicable	Strong
Ronchetti et al. 2008, Italy	Moderate	Moderate	Moderate	Not applicable	Moderate
Sandin et al. 2005, Sweden and Estonia	Moderate	Moderate	Moderate	Not applicable	Moderate
Soost et al. 2009 and Zuberbier et al. 2004, Roehr et al. 2004, Germany	Moderate	Moderate	Moderate	Moderate	Strong
Schnabel et al. 2010, Germany	Moderate	Strong	Moderate	Moderate	Moderate
Schäfer et al. 2001, Germany	Moderate	Strong	Moderate	Not applicable	Moderate
Steinke et al. 2007, Europe	Moderate	Strong	Moderate	Not applicable	Weak
Venter et al. 2010, United Kingdom	Moderate	Strong	Moderate	Moderate	Strong
Venter et al. 2008; Dean et al. 2007; Venter et al. 2006, United Kingdom	Moderate	Strong	Moderate	Moderate	Strong
Venter et al. 2006, United Kingdom	Moderate	Strong	Moderate	Not applicable	Strong
von Hertzen et al. 2006, Finland and Russia	Moderate	Moderate	Moderate	Moderate	Moderate
Zuidmeer et al. 2008, World-wide	Moderate	Strong	Weak	Not applicable	Strong

The overall risk assessment was based on the component risk assessments (i.e., on the suitability of the study design for the research question, potential for selection bias, methods of exposure assessment, and methods of outcome assessment).

For the study design, all cross-sectional and cohort studies that studied only the prevalence of food allergy received a “strong” grading.

Only case-control and cohort studies (and not cross-sectional studies) received a “strong” grading when the research question was on the risk/prognostic factors for food allergy.

Table E3: Frequency of self-reported food allergy in Europe: estimates from studies published between 1 January 2000 and 30 September 2012

Reference, country	Age(s) of subjects	Frequency of occurrence food allergy			Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)	Lifetime Prevalence Percentage (95% CI)	
Burney et al. 2010 and Woods et al. 2001 Europe, USA, Australia	Adults 20-44 years			all countries 19.2% (18.6-19.8)	USA, Australia and New Zealand are included in the overall figure. Our own calculation with the given data is 19.2% (18.6-19.8); authors' calculation 12.2% (12-13).
Caffarelli et al. 2011, Italy	Children 5-14 years		1.6% (0.9-2.9)	10.6% (8.4-13.2)	Data also reported for milk, egg, wheat, peanut, sesame, hazelnut, tomato, chocolate and different fruits in the paper
Eller et al. 2009, Kjaer et al. 2008, Johnke et al. 2006, Denmark	Children 6 years	By age 6 years 11.6% (9.2-14.5)			
Falcaõ et al. 2004, Portugal	Adults >39		5.2% (3.7-7.1)		Data also reported for fruits, meat, fish, egg, octopus and squid, chocolate, milk, spices, and legumes
Flokstra-de Blok et al. 2011, Netherlands	Adolescents 11-20 years		2.1% (1.6-2.8)		These are minimal reported estimates. Extrapolated estimates are reported in the paper.
Frongia et al 2005, Italy	Children 1-2 years			7.8% (7.0-8.6)	Data also reported for peanut, egg, milk, and tomato in the paper
Gelincik et al. 2008, Turkey	Adults >18			9.5% (8.9-10.0)	Estimates for different age bands reported in the paper
Kanny et al. 2001, France	Population < 61years		3.5% (3.3-3.7)		
Kristinsdottir et al. 2011, Iceland	Children at 1 year		5.5% (4.4-6.9)		Data also reported for milk, egg, fish, wheat, peanut, and soya in the paper
Kvenshagen et al. 2009, Norway	Children at 2 years		38.7% (34.6-43.0)		
Majkowska-Wojciechowska et al. 2009, Poland	Children 7-10 years			Parental reported adverse reactions to any food: 41.6% (39.5-43.7) Parental reported DD of food allergy 27.4% (25.6-29.4)	Insufficient data given in the paper to understand authors' calculations and to enable the calculation of the confidence intervals around the point estimates and
Marklund et al. 2004. Sweden	Adolescents 14-21 years		18.7% (16.8-20.8)		
Mossakowska et al. 2008, Poland	Adults >100		3.3% (1.8-6.0)		

Orhan et al. 2009, Turkey	Children 0-6 years			5.7% (4.8-6.6)	Data also reported for egg, milk, fish, tomato, hazelnut, kiwi, black pepper, chickpea, peanut, walnut, corn, banana, strawberry, potato, beef, cocoa
Östblom et al. 2008a, 2008b, 2008c; Almqvist et al. 2005, Sweden	Children 1-8 years		Parental report of FHS At 1 year: 9.8 (8.7–10.8) At 2 years: 9.5% (8.4-10.5) At 4 years: 10.9% (9.5-12.4) At 8 years: 13.8% (12.5-15.4) Parental report of DD of FHS At 1 year: 3.1% (2.5-3.7) At 2 years: 4.4% (3.7-5.1) At 4 years: 4.9% (3.9-5.9) At 8 years 7.6% (6.4-8.9)		
Osterballe et al. 2009, Denmark	Young adults Mean 22		Primary FHS: 19.6% (17.0-22.4)		Data also reported for additives, codfish, milk, egg, octopus, peanut, shrimp, soy, wheat Primary FHS was defined as being independent of pollen sensitization, whereas secondary FHS was defined as reactions to pollen related fruits and vegetables in pollen allergic patients.
Osterballe et al. 2005, Denmark	Children at 3 years and adults		All: 13.0% (11.6-14.7) Adults: 14.1% (12.0-16.5) Children: 11.9% (10.0-14.1)		Siblings (younger and older) and adults of the children from the DARC birth cohort were examined
Penard-Morand et al. 2005, France	Children 9-11 years		2.1% (1.8-2.5)		Data also reported for milk, egg, fish, seafood, fruits and vegetables, peanuts, nuts,
Pereira et al. 2005, United Kingdom	Children at 11 and 15 years		All: 12.0% (10.5-13.7) Age 11years: 11.6% (9.5-14.1) Age 15 years: 12.4% (10.3-15.0)		Data also reported for milk, egg, fish, wheat, peanut, sesame. Tree nut, Shellfish, Additives
Pyrhönen et al. 2011 and 2009, Finland	0-4 years old			30.3% (28.7-31.9)	Prevalence of parental-perceived and parental report of physician-diagnosed FA
Rance et al. 2005, France	Children Mean age 8.9 years		4.7 (3.9-5.5)	6.7% (5.8-7.7)	Data also reported for milk, egg, fish, shrimp, peanut and tree nut
Rona et al. 2007, World-wide	All ages		Range of prevalence of self - reported FHS to any food: 3%-35%		Include also non-European studies. There was significant heterogeneity among the studies. Data is also reported for milk, egg, fish, shellfish and peanut
Sandin et al. 2005, Sweden and Estonia	Children 10-11 years		All: 22.9% (20.0-26.0) Estonia: 20.2% (16.0-25.2) Sweden: 24.4% (20.8-28.5)		Data also reported for peach, kiwi, or carrot; nut or peanut; orange mandarin or tomato; milk, egg, fish, or wheat
Schäfer et al. 2001, Germany	Adults 25-74 years			Population of the allergy MONICA study: 15.5%	MONICA is the base population for the nested case-control study population. Insufficient data given in the paper to enable the

					calculation of the confidence intervals around the point estimates. Data also reported for other foods, such as milk, egg, flour, fish, meat, tomatoes, etc.
Schnabel et al. 2010, Germany	Children 2-6 years		Self-report of doctor diagnoses of FA At 2 years 6.6% At 5 years 3.9% At 6 years 3.9%		Insufficient data given in the paper to enable the calculation of the confidence intervals around the point estimates.
Soost et al. 2009 and Zuberbier et al. 2004 and Roehr et al. 2004, Germany	0-79			Suspected adverse reactions to any food Population 0-79: 53.9% (52.4-55.5) Adults 18-79: 55.7% (54.0-57.4) Children 0-17 years: 61.6% (58.0-65.0) Still suspected after second contact 0-79 years: 35.0% (33.6-36.5) 18-79 years: 34.9% (33.2-36.5) Children 0-17 years: 38.4% (35.0-42.0)	
Steinke et al. 2007, Europe	Children < 18 years		Overall in all countries: 5.0% (4.5-5.4) Austria: 1.7% ; Belgium: 4.9% ; Denmark: 2.5% ; Finland: 11.7% ; Germany: 3.0% ; Greece: 4.8% ; Italy: 3.9% ; Poland: 8.3% ; Slovenia: 4.6% ; Switzerland: 3.1%		Our own calculation for all countries is 4.96%, different from authors' calculation of 4.7%.
Venter et al. 2008 and 2006, Dean et al. 2007, United Kingdom	Children 1-6 years	By age 1 year Any food: 25.8% (23.1-28.6) By age 3 years: 28.1% (25.3-31.0)	At 1 year: 7.2% (5.7-9.1) At 2 years: 8.4% (6.7-10.4) At 3 years: 8.3% (6.7-10.3)		
Venter et al. 2006, United Kingdom	Children at 6 years		11.8% (9.6-14.2)		Data is also reported for milk, egg, fish, peanut, tree nut, wheat and sesame

Table E4: Frequency of sensitization (positive skin prick test [SPT], immunoglobulin E [IgE]) to at least one food allergen in Europe: estimates from studies published between 1 January 2000 and 30 September 2012

Reference, country	Age(s) of subjects	Frequency of occurrence of SPT and IgE positivity to at least one food allergen		Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)	
Bant et al. 2008, Poland	Adults 18-27 years		slgE positivity 11%	Food allergens measured: milk, egg, wheat, soya, fish, and peanuts. Insufficient data given in the paper to enable the calculation of the confidence intervals around the point estimates.
Burney et al. 2010 and Woods et al. 2001 Europe, USA, Australia	Adults 20-39 years		slgE positivity: All countries: 12.3% Germany: 21.8% ; Italy: 21.9% ; France: 14.1% ; Belgium: 16.8% ; Spain: 11.1% ; Norway: 21.7% ; Sweden: 17.2% ; United Kingdom: 14.5% ; Iceland: 7.7%	Country-specific estimates include birch positivity which is excluded in the all countries estimate. Insufficient data given in the paper to enable the calculation of the confidence intervals around the point estimates. Data incomplete for Switzerland and Iceland Food allergens measured: milk, egg white, fish, soya bean, peanut and wheat, sesame, buckwheat, corn and rice, hazelnut, walnut, celery, tomato and carrot, mustard, shrimp, sunflower seed, poppy seed and lentil, banana, kiwi, apple, peach and melon. Data also reported for fish, egg, milk, soya, walnut, peanut, sesame, wheat, shrimp hazelnut.
Eller et al. 2009, Kjaer et al. 2008, Johnke et al. 2006, Denmark	Children 0-6 years	slgE positivity by 6 years: 47.3%	SPT positivity At 6 month: 3.1% At 12 month: 4.3% At 18 month: 3.2% At 6 years: 3.7% (2.2-6.0) slgE positivity At 6 month: 19.4% At 12 month: 20.3% At 18 month: 21.5% At 6 years 15.1% (11.7-19.2)	Food allergens measured: milk, egg and fresh milk. Food allergens tested for slgE: codfish, milk, Egg, peanut, wheat, soy, shrimp, hazelnut, Brazil nut, and celery root. Insufficient data given in the papers to enable the calculation of the confidence intervals around the point estimates at age 6, 12 and 18 month.
Isolaure et al. 2004, Finland	Children at 7 years and adults 27, 47 and 67 years		slgE positivity to at least one food allergen 7 years: 52.0% (41.0-62.0) 27 years: 9.0% (5.0-18.0) 47 years: 2.0% (0.1-7.0) 67 years: 9.0% (5.0-18.0)	These estimates are only approximates as the authors presented the estimates only in a figure, so we did not have the actual numbers to enable the actual calculations. Data also reported for milk
Johansson et al. 2005, Sweden	Adults		slgE positivity All 3.6% (2.8-4.7) Sweden: 3.9% (2.9-5.3) Norway: 3.0% (1.8-4.9)	Food allergens measured: milk, egg white, cod fish, soya bean, peanut, wheat flour. Data also reported for milk, egg, fish, peanut wheat and sesame
Krause et al. 2002, Greenland	Children 5-18 years		slgE positivity: 4.1% (3.0-5.5)	Food allergens measured: egg, milk, fish, wheat, peanut and soy. Data also reported for different age bands, both sexes, origin and for egg, milk, fish, peanut, wheat, and soy
Kurukulaaratchy et al. 2005, Arshad et al. 2001, Tariq et al.	Children 2-4 years		SPT positivity at 4 years: 3.5%	The estimates were presented in a figure, so actual numbers were not shown to enable the calculation of confidence limits around the estimates.

2000, United Kingdom				Data is also reported for the single allergens. Food allergens measured: milk, egg, soya, cod fish, wheat, and peanut
Östblom et al. 2008a, 2008b, 2008c; Almqvist et al. 2005, Sweden	Children 4-8 years		slgE positivity At 4 years: 13% to 16% At 8 years: 13.8% (12.5-15.4)	In their reports the authors present different prevalence estimates for the same study at the age of 4 years because of different denominators used for calculations. Food allergens measured: milk, egg white, codfish, peanut, soybean and wheat.
Penard-Morand et al. 2005, France	Children 9-11 years		SPT positivity: 1.8% (1.5-2.1)	Food allergens measured: egg, cod fish, peanut Data also reported for egg, cod fish, and peanut
Pereira et al. 2005, United Kingdom	Children at 11 and 15 years		SPT positivity All 5.0% (4.0-6.3) Age 11 years: 5.2% (3.7-7.0) Age 15 years: 4.9% (3.5-6.9)	The estimates here are SPT sensitization without cross-reactivity to pollen Food allergens measured: milk, egg, wheat, fish, peanut and sesame
Pyrhönen et al. 2011 and 2009, Finland	Children by 4 years	slgE or SPT positively 5.5% (4.8-6.3)		Food allergens measured not stated in the paper Data also reported for milk, egg and food essentials
Rona et al. 2007, United Kingdom	All ages		Range of prevalence of SPT and IgE positivity SPT or slgE: 2%-5% SPT only: 7%-17% IgE only: 4%-6%	Results include non-European populations There was significant heterogeneity among the studies. Food allergens measured: depends on the different studies included Data is also reported for milk, egg, fish, shellfish and peanut
Ronchetti et al. 2008, Italy	Children 9 and 13 years		SPT positivity for all 4.2% (2.6-6.7) SPT positivity At 9 years: 2.2% (0.8-5.5) At 13 years: 6.1% (3.5-10.4)	Food allergens measured: fresh food allergens (whole milk, whisked egg, tomato and wheat flour Data also reported for milk, egg, tomato, wheat
Sandin et al. 2005, Sweden and Estonia	Children 10-11 years		slgE positivity: All 13.9% (11.3-16.9) Estonia 8.0% (4.7-13.2) Sweden 16.1% (12.9-19.9)	Food allergens measured: egg white, milk, soya bean, fish, wheat and peanut.
Schäfer et al. 2001, Germany	Adults 25-74 years		IgE positivity: from the population of the allergy MONICA study 16.8%	MONICA is the base population for the nested case-control study population. Insufficient data given in the paper to enable the calculation of the confidence intervals around the point estimates. Food allergens measured: milk, egg, peanut, pork, mackerel, celery, hazelnut, wheat, soy, and crab.
Schnabel et al. 2010, Germany	Children 2-6 years		slgE positivity : At 2 years: 9.4% (7.8-11.3) At 6 years: 11.7% (10.0-13.8)	Food allergens measured: egg, milk, peanut, soybean, wheat flour and codfish. Data also reported for milk, egg and peanut, soya, wheat, codfish
Venter et al. 2008 and 2006, Dean et al. 2007, United Kingdom	Children 1-3 years	SPT positivity by 3 years of age: 5.3% (3.9-7.1)	SPT positivity At 1 year: 2.2% (1.4-3.5) At 2 years: 3.8% (2.6-5.5) At 3 years: 4.5% (3.2-6.4)	The authors reported different prevalence estimates from the same study because of different denominators used for calculations. Dean et al. 2007 calculated the estimates based on children who underwent SPT on all 3 occasions. Food allergens measured: milk, egg, wheat, peanut, sesame and fish Data also reported for milk, egg, wheat, fish, peanut, sesame
Venter et al. 2006, United Kingdom	Children at 6 years		SPT positivity 3.6% (2.3-5.2)	Food allergens measured: milk, egg, wheat, codfish, peanut and sesame

Table E5: Frequency of clinician diagnosed food allergy (based on symptoms and sensitization and convincing clinical history or food challenge in Europe: estimates from studies published between 1 January 2000 and 30 September 2012

Reference, country	Age(s) of subjects	Frequency of occurrence of any food allergy (FA)		Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)	
Dubakiene et al. 2012, Lithuania	Children 0-1 years		Symptoms + SPT or sIgE positivity: At 6 months: 1.3 (0.8-2.0) At 1 year: 2.8 (2.1-3.7)	Food allergens measured not stated in the paper Data also reported for milk, egg fish, peanut potato and wheat
Kristinsdottir et al. 2011, Iceland	Children at 1 year		Symptoms + SPT positivity: 1.6% (1.0-2.4) Symptoms + sIgE positivity: 3.0% (2.2-4.0) Symptoms + SPT or sIgE: 3.3% (2.5-4.4)	Food allergens measured not stated in the paper Data also reported for milk, egg, fish, wheat, peanut, soya available
Kvenshagen et al. 2009, Norway	Children at 2 years		Clinical history or OFC/DBPCFC Any food: 6.8% (5.0-9.4) IgE-mediated any food 1.8% (0.9-3.3) Non-IgE-mediated any food 5.3% (3.7-7.6)	Food allergens measured: milk, egg, cod fish, hazelnut, peanut, wheat and soya. Children with a history of an immediate reaction to a food allergen, a positive SPT and an elevated IgE to that food allergen were not challenged
Orhan et al. 2009, Turkey	Children 6-9 years		Symptoms + SPT positivity 1.8% (1.3-2.3)	Food allergens measured: milk, egg, soy, wheat, peanut, fish, and hazelnut Data also reported for egg, milk, fish, hazelnut, peanut, walnut, beef, cocoa, etc.
Penard-Morand et al. 2005, France	Children 9-11 years		Symptoms + SPT positivity: 0.1% (0.1-0.3)	Food allergens measured: egg, cod fish, peanut Data also reported for egg, cod fish, and peanut
Pereira et al. 2005, United Kingdom	Children at 11 and 15 years		All: Clinical history or OFC: 2.3 (1.6-3.2) Clinical history or DBPCFC: 1.8 (1.2-2.6) At 11 years: Clinical history or OFC: 2.3% (1.5-3.6) Clinical history or DBPCFC: 1.4% (0.8-2.5) At 15 years: Clinical history or OFC: 2.2% (1.4-3.6) Clinical history or DBPCFC: 2.1% (1.3-3.4)	Unchallenged children with a clear history of adverse reactions in the presence of a positive SPT or sIgE responses or with a physician diagnosis of FA were included as having FA.
Soost et al. 2009 and Zuberbier et al. 2004 and Roehr et al. 2004, Germany	Children (0-17 years) and adults		Children Symptoms + SPT positivity: 13.1% (10.9-15.8) Symptoms + sIgE positivity: 4.6% (3.3-6.4) Total population: Symptoms + sIgE positivity: 2.2% (1.8-2.7)	Food allergens measured: milk, egg, wheat, soy, carrot and peanut
Venter et al. 2008 and 2006, Dean et al. 2007, United Kingdom	Children 1-6 years	Clinical history or OFC-confirmed any FA by 3 years: 6.0% (4.6-6.7) Clinical history or DBPCFC-confirmed any FA by 3 years: 5.0% (3.8-6.5)	At age 1 year: Clinical history or OFC: 3.0% (2.1-4.3) Clinical history or DBPCFC: 2.7% (1.8-3.9) At age 2 years: Clinical history or OFC: 2.4% (1.6-3.7) Clinical history or DBPCFC: 2.1% (1.3-3.3) At age 3 years:	Cumulative incidence also given for age 1 and 2 years in the paper. Not clear what the authors used as a convincing clinical history.

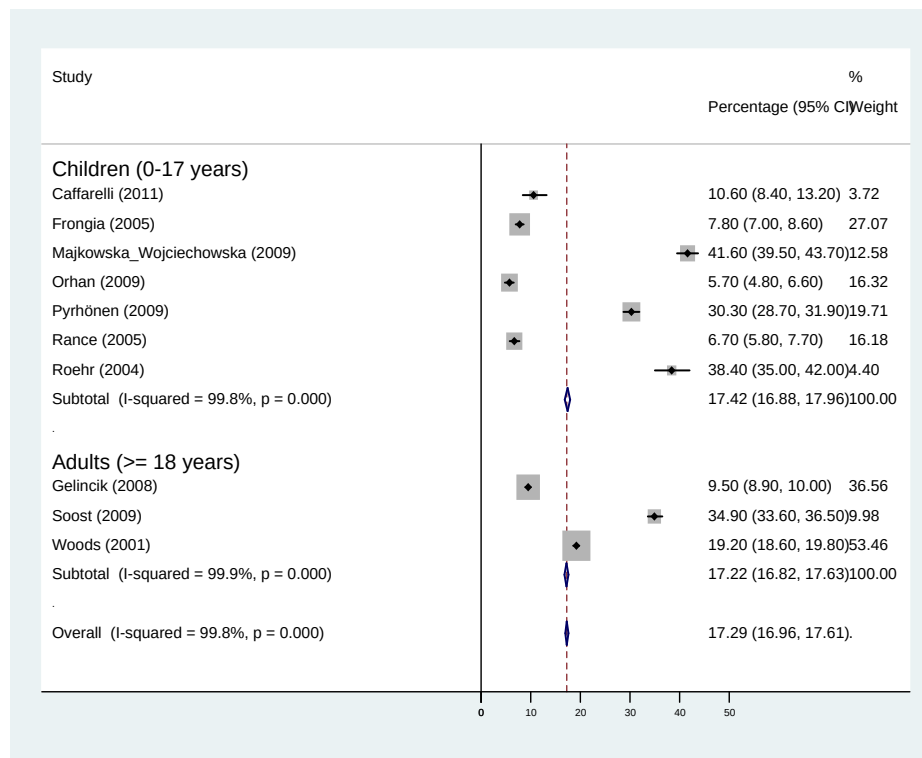
			Clinical history or OFC: 3.0% (2.1-4.4) Clinical history or DBPCFC: 2.9% (2.0-4.2)	
Venter et al. 2006, United Kingdom	Children at 6 years		Clinical history or OFC 2.1% (1.3-3.4) Clinical history or DBPCFC 1.1% (0.6-2.1)	Unchallenged children with prior hospital diagnosis of food allergy or a history of inadvertent reaction with positive skin test were included as having FA.

Table E6: Frequency of objectively verified food allergy in Europe by food challenge: estimates from studies published between 1 January 2000 and 30 September 2012

Reference, country	Age(s) of subjects	Frequency of occurrence of any food allergy (FA)		Comment
		Cumulative incidence Percentage (95% CI)	Point prevalence Percentage (95% CI)	
Dubakiene et al. 2012, Lithuania	Children at 6 month		DBPCFC-confirmed FA: 0.3% (0.1-0.7)	Data also reported for milk, egg and wheat
Eller et al. 2009, Kjaer et al. 2008, Johnke et al. 2006, Denmark	Children 0-6 years	OFC/ DBPCFC-confirmed any FA by 6 years: 3.6% (2.3-5.4)	OFC/ DBPCFC-confirmed FA: Age 6 months: 0.4% (0.1-1.5) Age 1 year: 1.3% (0.6-2.8) Age 3 years: 3.0% (1.7-5.0) ; Age 6 years: 1.2% (0.5-2.9)	Data also reported for peanut, egg, and milk confirmed challenges. At 3 years authors reported an estimate of 3.4% while our own calculation shows 3.0%.
Gelincik et al. 2008, Turkey	Adults >18		DBPCFC-confirmed FA/NAFA: 0.1% (0.1-0.2) DBPCFC-confirmed FA: 0.1% (0.1-0.2) DBPCFC-confirmed NAFA: 0.1% (0.1-0.2)	Data also reported for tomato, egg, orange, eggplant, peanut, strawberry, carrot, banana, hazelnut, pear, spinach, red chili, black pepper, food additives, chocolate, walnut, potato, fish
Kristinsdottir et al. 2011, Iceland	Children at 1 year		DBPCFC-confirmed FA: 1.9% (1.3-2.7)	Data also reported for milk, egg, fish, wheat, peanut, soya
Orhan et al. 2009, Turkey	Children 6-9 years		DBPCFC-confirmed FA 0.7% (0.5-1.1)	Data also reported for egg, milk, fish, hazelnut, peanut, walnut, beef, cocoa. Authors used number of positive challenges (22) instead of number of children (20) as the numerator. Our estimates are based on number of positive children.
Osterballe et al. 2009, Denmark	Young adults mean 22		OFC/DBPCFC-confirmed FHS: 1.8% (1.1-2.9)	Data also reported for fish, milk, peanut, shrimp, soy
Osterballe et al. 2005, Denmark	Children and adults		OFC/DBPCFC-confirmed primary food hypersensitivity All: 2.4% (1.8-3.2) Children: 1.6% (0.9-2.6) Age 3 years: 2.3% (1.3-4.0) Age <3 years: 0.0% (0.0-3.3) Age >3 years: 1.0% (0.3-2.9) Adults: 3.2% (2.3-4.5)	Children from the DARC birth cohort and their siblings (younger and older) and adults were examined
Pereira et al. 2005, United Kingdom	Children at 11 and 15 years		All: OFC-confirmed FA 1.0% (0.6-1.7) DBPCFC-confirmed 0.3% (0.1-0.8) At 11 years: OFC-confirmed FA: 1.0% (0.5-2.0) DBPCFC-confirmed FA: 0.1% (0-0.7) At 15 years OFC-confirmed FA: 1.1% (0.5-2.1) DBPCFC-confirmed FA: 0.5% (0.2-1.4)	
Pyrhonen et al. 2011 and 2009,	Children by 4 years	OFC-confirmed any FA by 4 years: 3.3% (2.8-3.9)		

Finland				
Rona et al. 2007, United Kingdom	All ages		Range of prevalence of allergy to any food based on food challenge: 1%-10.8%	Results include also non-European studies Estimates presented if at least 4 studies of the food item were available There was significant heterogeneity among the studies. Data is reported available for milk, egg, fish, shellfish and peanut
Soost et al. 2009 and Zuberbier et al. 2004 and Roehr et al. 2004, Germany	Children and adults 0-79 years		OFC/DBPCFC-confirmed FA: Total population (0-79 years): 2.8% (2.4-3.4) 2.6% (2.1-3.2) (weighted for Germany) Adults 18-79 years: All 2.9 (2.3-3.5) IgE mediated 1.9% (1.4-2.4) Non IgE mediated 1.0% (0.7-1.4) Children: 0-17 years: 4.2% (3.0-5.9) 0-14 years: 3.8% (2.6-5.7) 15-17 years: 5.7% (2.9-10.8) IgE-mediated (0-17 years): 3.5% (2.4-5.1) Non-IgE-mediated (0-17 years): 0.7% (0.3-1.6)	Food allergy was confirmed by DBPCFC in adults and OFC or one blinded FC or DBPCFC in children.
Venter et al. 2008 and 2006, Dean et al. 2007, United Kingdom	Children 1-6 years	OFC-confirmed any FA by 1 year: 3.6% (2.5-5.0) DBPCFC-confirmed any FA by 1 year: 1.5% (0.9-2.5)	At age 1 year: OFC-confirmed FA: 2.8% (1.9-4.1) DBPCFC-confirmed FA: 1.3% (0.8-2.3)) At age 2 years: OFC-confirmed FA: 1.0% (0.6-2.0) DBPCFC-confirmed FA : 0.1% (0.0-0.7) At age 3 years: OFC-confirmed FA: 0.8% (0.4-1.6) DBPCFC-confirmed FA: 0.0%	Cumulative incidence also given for age 1 and 2 years in the paper.
Venter et al. 2006, United Kingdom	Children at 6 years		OFC and DBPCFC-confirmed food allergy OFC-confirmed FA: 1.3% (0.7-2.3) DBPCFC-confirmed FA : 0.4% (0.1-1.1)	

PANEL 1



PANEL 2

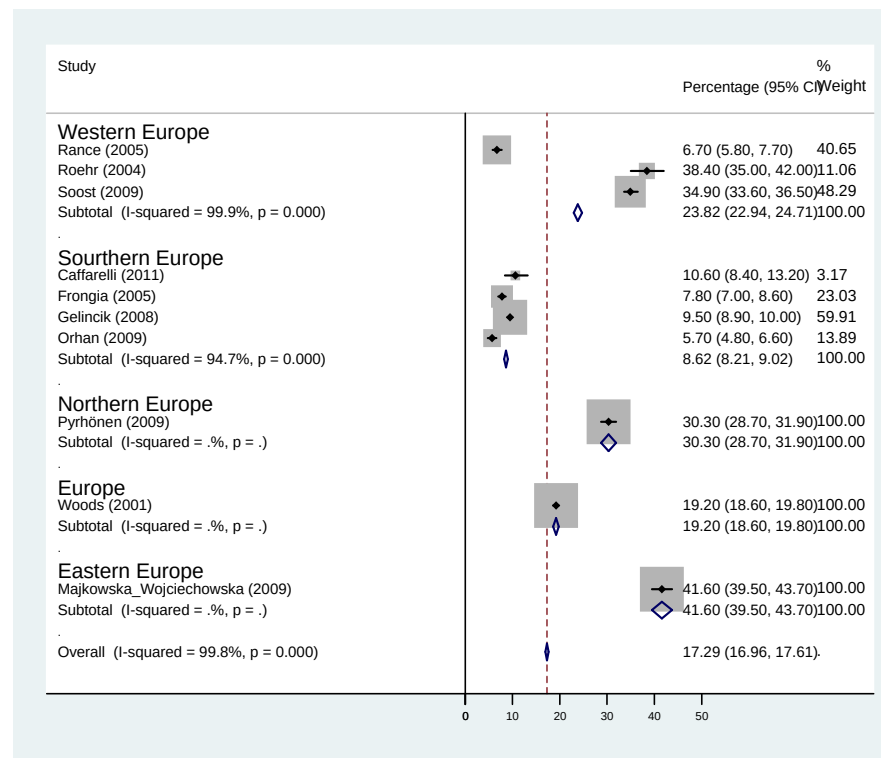
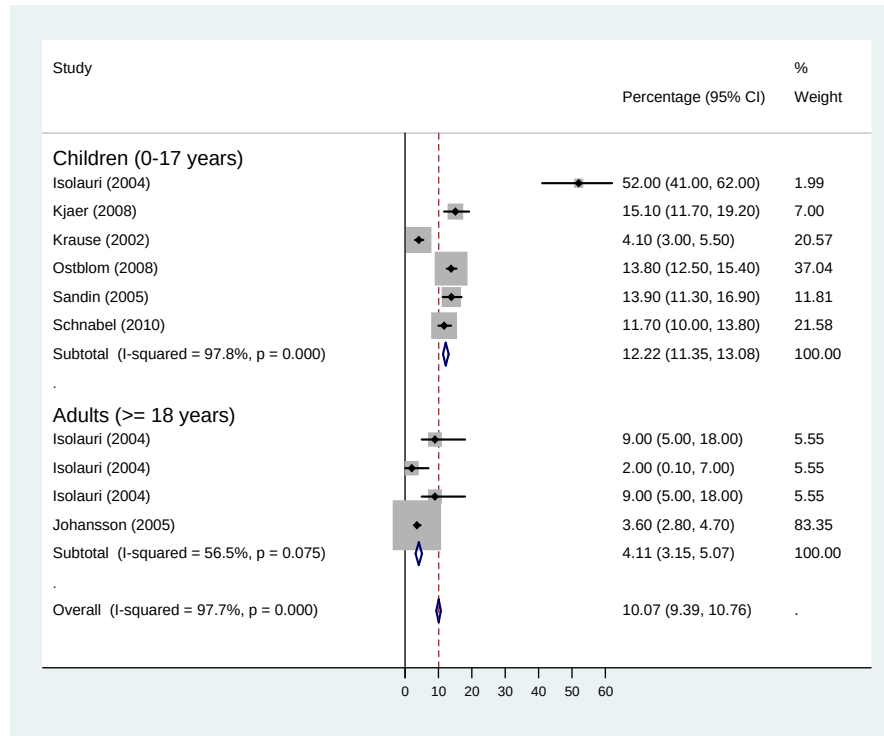


Figure E1: Pooled life-time prevalence of self-reported food allergy stratified by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the size of the study

PANEL 1



PANEL 2

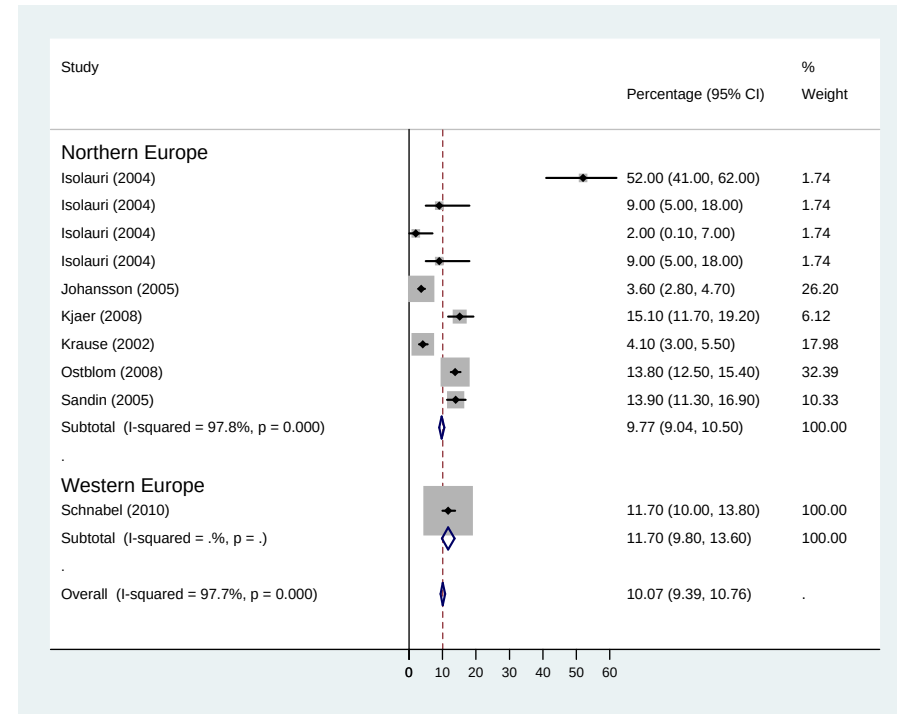
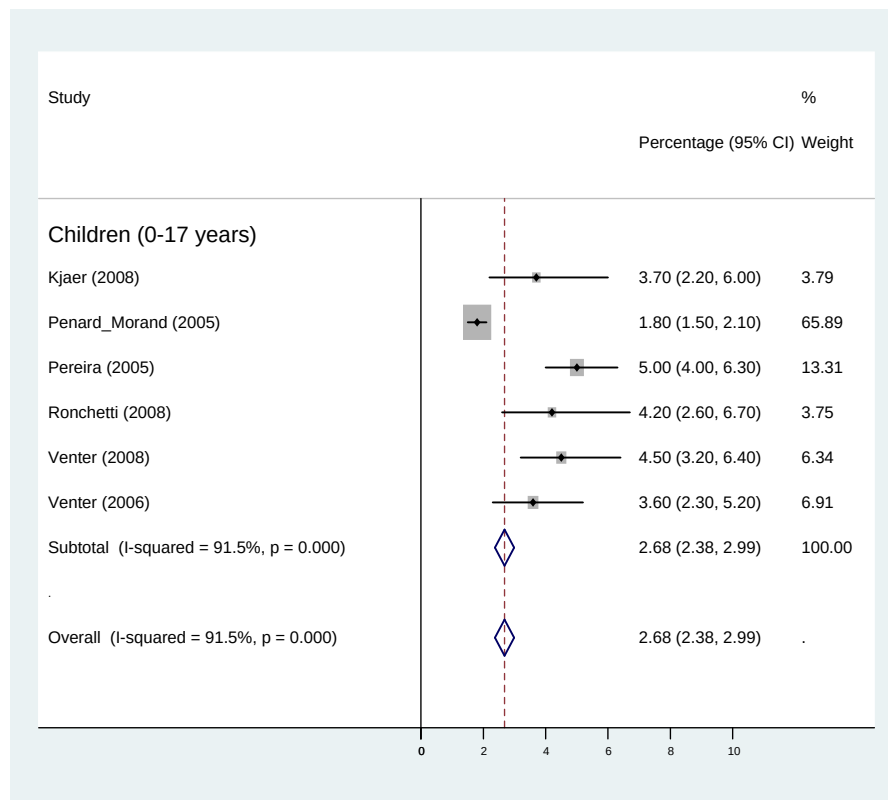


Figure E2: Pooled point prevalence of specific immunoglobulin E (IgE) positivity to at least one food allergen stratified by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the size of the study

PANEL 1



PANEL 2

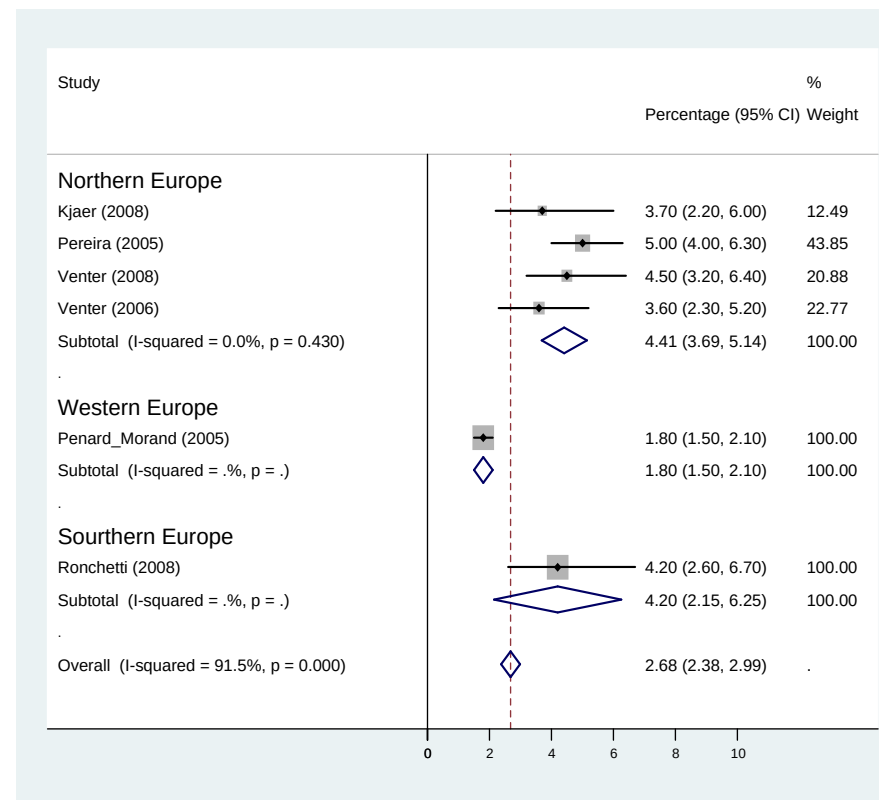


Figure E3: Pooled point prevalence of skin prick test (SPT) positivity to at least one food allergen stratified by age (only studies among children were available) (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI and boxes represent the size of the study