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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/prospero/, 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).

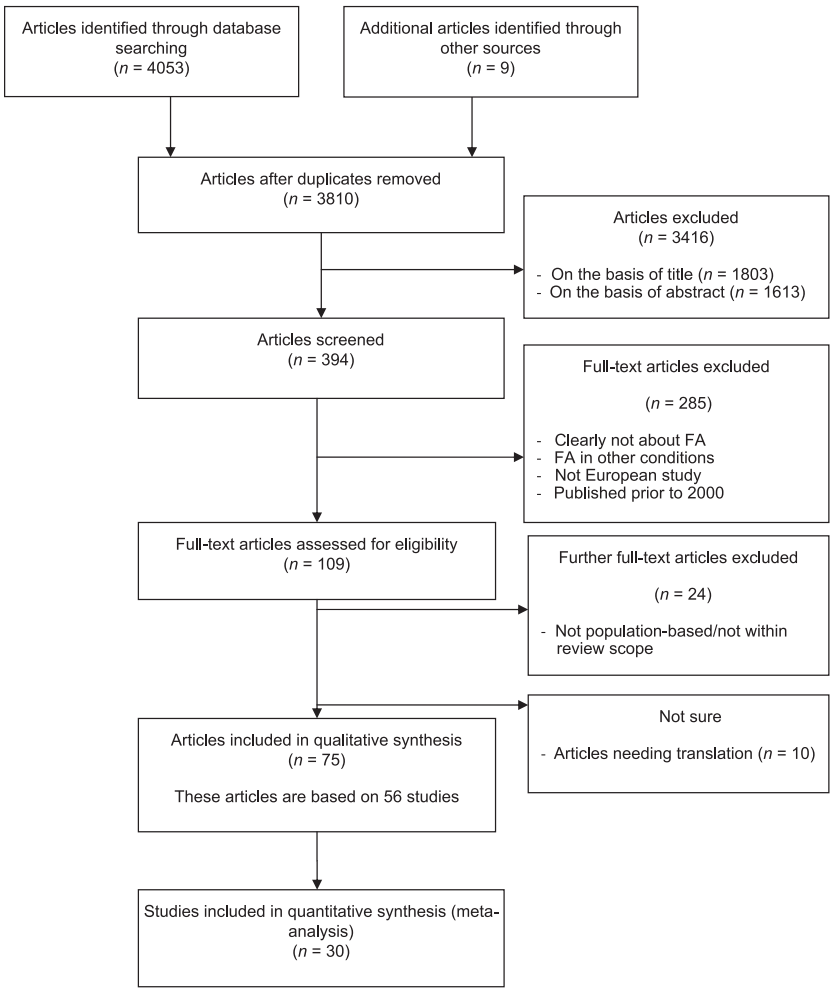

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for studies on the epidemiology of FA in Europe, January 2000–September 2012.

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							
	Point prevalence							Lifetime prevalence
	Self-report	Positive IgE	Positive SPT	Symptom plus positive IgE	Symptom plus positive SPT	Clinical history or food challenge	Food challenge	Self-report
≤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%

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

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).

Challenge-verified FA

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).

Time trends in the frequency of FA

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 and prognostic factors for FA

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

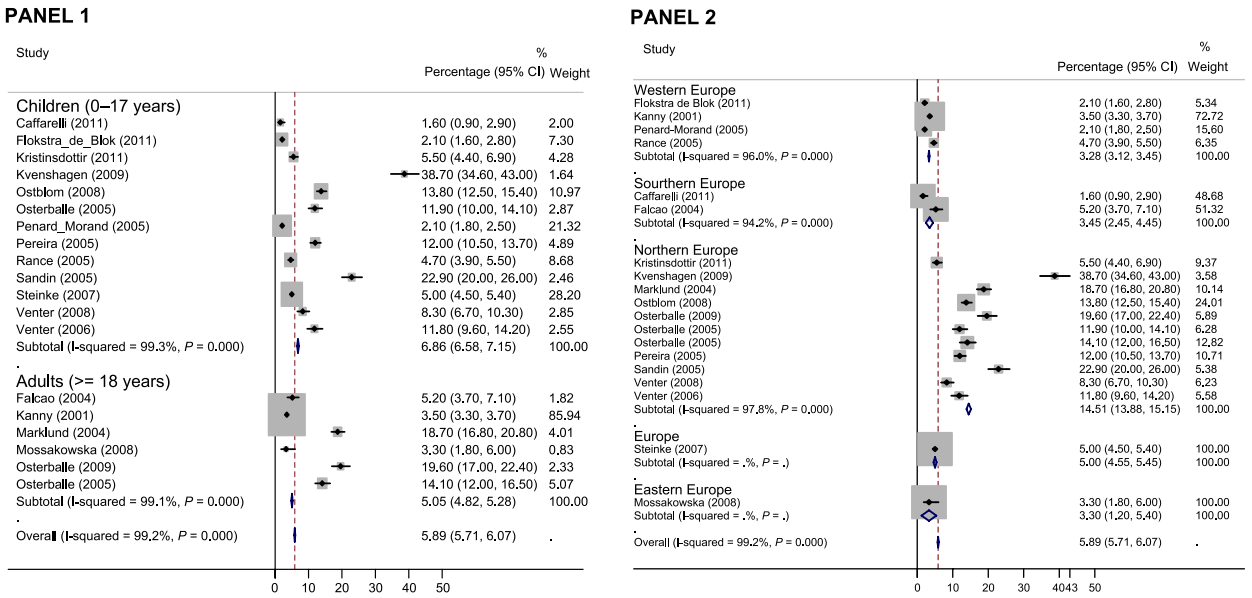

Figure 2 Pooled point prevalence of self-reported FA stratified by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI, and boxes represent the size of the study.

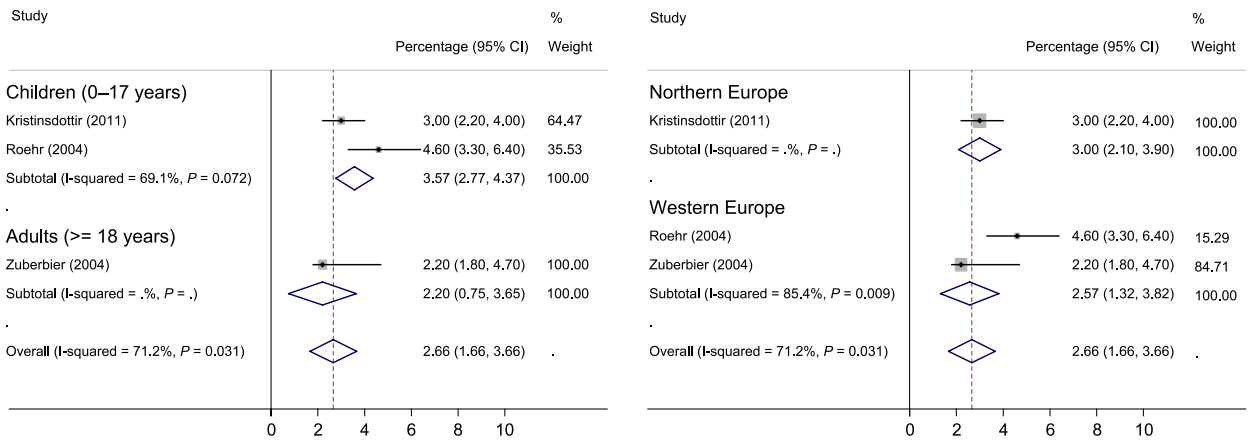

Figure 3 Pooled point prevalence of symptoms plus specific IgE positivity to at least one food allergen by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI, and boxes represent the size of the 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

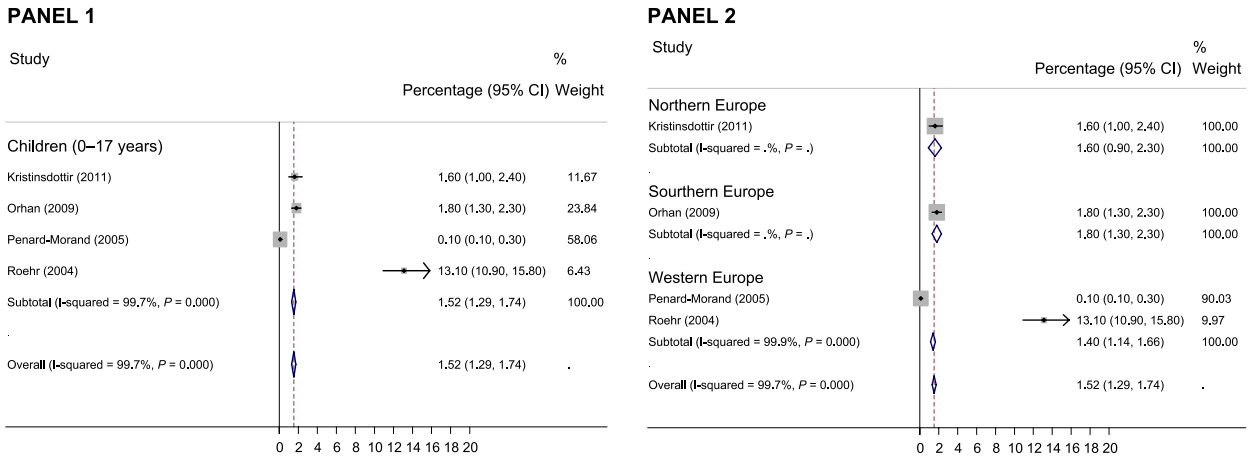

Figure 4 Pooled point prevalence of symptoms plus SPT positivity to at least one food allergen by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95%CI, and boxes represent the size of the study.

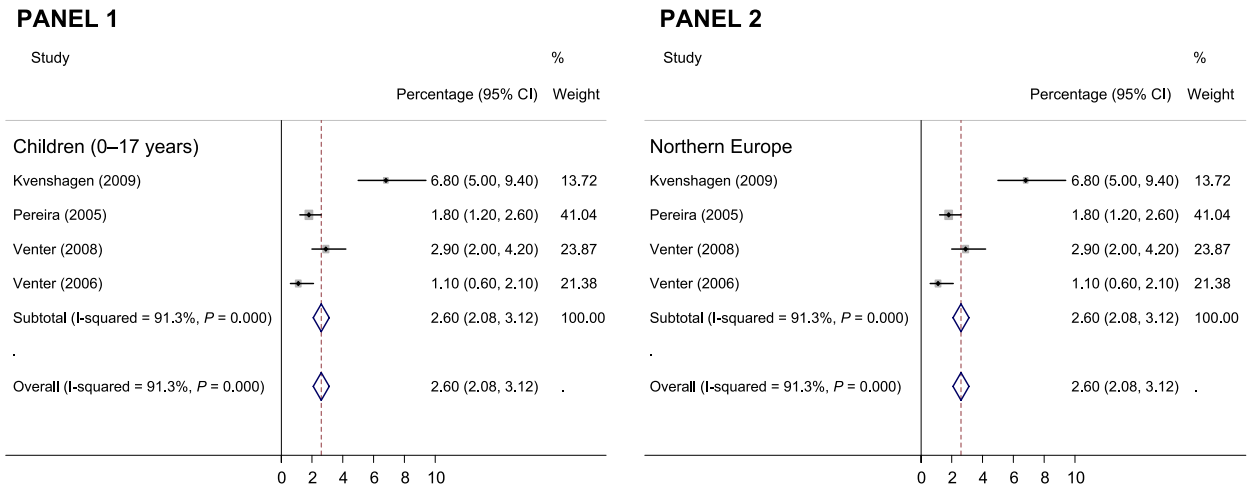

Figure 5 Pooled point prevalence of clinical history of FA or food challenge (open food challenge or double-blinded, placebo-controlled) by age (only studies among children were available) (PANEL 1) and geographical region (only studies from Northern Europe were available) (PANEL 2) in studies published 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

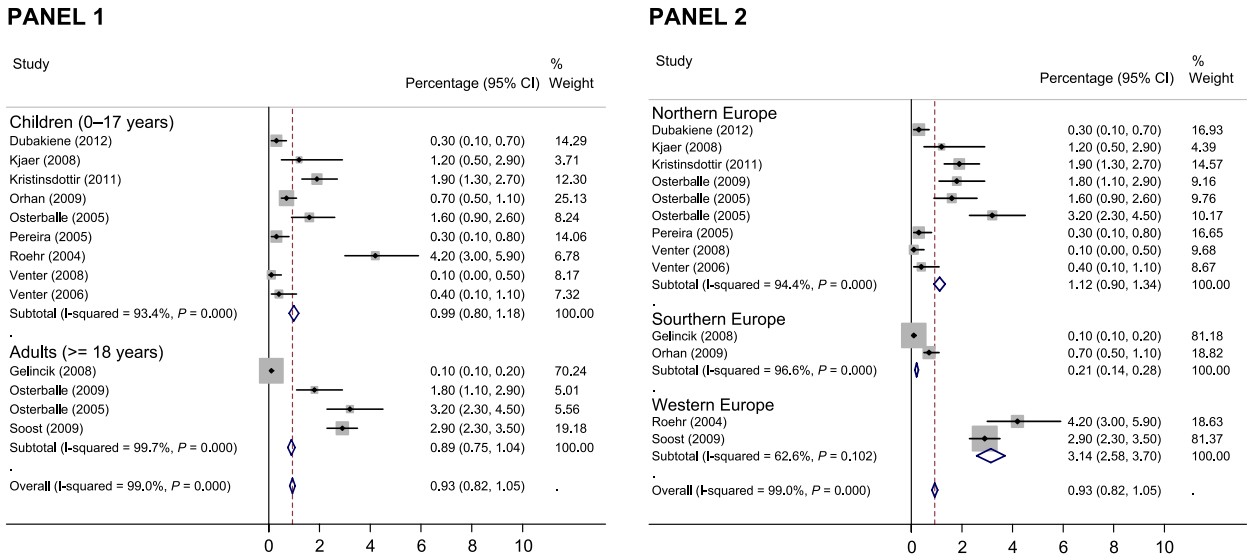

Figure 6 Pooled point prevalence of food challenge positivity (open food challenge or double-blinded, placebo-controlled) by age (PANEL 1) and geographical region (PANEL 2) in studies published in Europe between January 2000 and September 2012. Markers represent percentages and 95% CI, and boxes represent the size of the study.

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 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 scantly 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.
		Admissions rate for FA for all age groups					
		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			
		45+ age group					
		0.0	0.5	0.6			
Kotz et al. (46), UK	All ages	2001	2002	2003	2004	2005	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.
		Lifetime prevalence of doctor-diagnosed peanut allergy per 1000 patients					
		Percentage (95% CI)					
		0.24 (0.22–0.26)	0.32 (0.30–0.34)	0.39 (0.37–0.42)	0.45 (0.43–0.48)	0.51 (0.49–0.54)	
		Incidence rate of doctor-diagnosed peanut allergy per 1000 person-years					
		Percentage (95% CI)					
		0.06 (0.05–0.07)	0.08 (0.07–0.09)	0.08 (0.07–0.09)	0.08 (0.07–0.09)	0.08 (0.07–0.09)	
Venter et al. (84), UK	Children 3–4 years	1993	1998–2000	2004–2005			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.
		Point prevalence of SPT positivity to peanut allergen					
		Percentage (95% CI)					
		1.3% (0.6–1.8)	3.3% (2.4–4.4)	2.0% (1.2–3.4)			
		Point prevalence of clinician-diagnosed peanut allergy (i.e., history plus sensitization plus OFC)					
		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.
Eggesbø 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. Only the factors that were significant at the unadjusted level were included in the adjusted models
Hourihane et al. (40), UK	DBPCFC-verified peanut allergy	Breastfeeding, history of eczema and allergic rhinitis	Multiple logistic regression	DBPCFC-verified peanut allergy: ↑breastfeeding, ↑history of eczema. All these results were from adjusted models.
Kotz et al. (46), UK	Physician-diagnosed peanut allergy	Sex, age, socioeconomic deprivation	Pearson's chi-square test	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 *P*-values were reported; no modeling strategies were employed in the analysis.
Kvenshagen et al. (53), Norway	Clinician-diagnosed allergy to any food	Cesarean section, use of antibiotics	Logistic regression	Unadjusted models: →cesarean section delivery, →use of antibiotics
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	→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 weal > 8 mm. Only frequencies and *P*-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:

Box S1. Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R).

Table S1. 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.

Table S2. Quality assessment of studies included in the systematic review: included studies 1 January 2000–30 September 2012.

Table S3. Frequency of self-reported food allergy in Europe: estimates from studies published between 1 January 2000 and 30 September 2012.

Table S4. 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.

Table S5. 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.

Table S6. Frequency of objectively verified food allergy in Europe by food challenge: estimates from studies published between 1 January 2000 and 30 September 2012.

Figure S1. Pooled lifetime 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.

Figure S2. 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.

Figure S3. 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.

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