Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling

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ARTICLE SUMMARY

- Existing diagnostic testing is not predictive of severity or the threshold dose of clinical reactivity, and many patients still require an Oral Food Challenge (OFC). While OFCs are very useful for making an allergy diagnosis and determining clinical reactivity, they often cause anaphylaxis, which can increase patient anxiety. and are time and resource intensive.[1]
- An extensive validation was performed across 5 cohorts (all with confirmed oral food challenge results) across six different countries. Cohorts used: BOPI, OPIA, CAFETERIA, CoFAR6, and PEPITES with specimens from Australia, UK, US, Ireland, and Germany.
- This paper reports the first validated algorithm using two key peanut specific IgE epitopes to predict probabilities of reaction to different amounts of peanut in allergic subjects and may provide a useful clinical substitute for peanut oral food challenges.
- Using the algorithm, subjects were assigned into "high", "moderate", or "low" dose reactivity groups. On average, subjects in the "high" group were 4 times more likely to tolerate a specific dose, compared to the "low" group.[1] For example, 88% of patients in the high dose reactivity group were able to tolerate ≥ 144 mg of peanut protein whereas only 29% were able to tolerate the same amount in the low dose reactivity group.[1-2]

CLINICAL CONSIDERATIONS

- The new epitope test offers more granular information to help clinicians stratify treatment and peanut avoidance plans for their patients.
- See below for summary of clinical considerations based on threshold reactivity level.[1]

allergenis peanut diagnostic result	clinical considerations[1]
likely allergic – low dose reactor	• inform or avoid oral food challenge to reduce risk of anaphlyaxis • confirm strict avoidance of peanut • consider immunotherapy to reduce risk of reaction
likely allergic – moderate dose reactor	• consider a single oral food challenge (30 to 100 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider immunotherapy to reduce risk of reaction
likely allergic – high dose reactor	• consider a single oral food challenge (100 to 300 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider starting immunotherapy at higher doses to shorten time to maintenance dose
unlikely allergic	• oral food challenge to rule out the diagnosis of peanut allergy

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REVIEW ARTICLE

Frequency of food allergy in Europe: An updated systematic review and meta-analysis

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Abstract

Food allergy (FA) is increasingly reported in Europe, however, the latest prevalence estimates were based on studies published a decade ago. The present work provides the most updated estimates of the prevalence and trends of FA in Europe. Databases were searched for studies published between 2012 and 2021, added to studies published up to 2012. In total, 110 studies were included in this update. Most studies were graded as moderate risk of bias. Pooled lifetime and point prevalence of self-reported FA were 19.9% (95% CI 16.6–23.3) and 13.1% (95% CI 11.3–14.8), respectively. The point prevalence of sensitization based on specific IgE (sIgE) was 16.6% (95% CI 12.3–20.8), skin prick test (SPT) 5.7% (95% CI 3.9–7.4), and positive food challenge 0.8% (95% CI 0.5–0.9). While lifetime prevalence of self-reported FA and food challenge positivity only slightly changed, the point prevalence of self-reported FA,

sIgE and SPT positivity increased from previous estimates. This may reflect a real increase, increased awareness, increased number of foods assessed, or increased number of studies from countries with less data in the first review. Future studies require rigorous designs and implementation of standardized methodology in diagnosing FA, including use of double-blinded placebo-controlled food challenge to minimize potential biases.

KEYWORDS
epidemiology, Europe, food allergy, sensitization, systematic review

1 | INTRODUCTION

The frequency of food allergy (FA) in Europe has been increasingly reported over the past decades. However, the data supporting an increase are mainly anecdotal, considering that the latest systematic report on FA epidemiology was published by the European Academy of Allergy and Clinical Immunology (EAACI) in 2014 based on the articles published between 2000 and 2012.[1,2] That report provided a detailed overview of the epidemiology of FA, including estimates of the incidence, prevalence, and time trends of any FA, as well as the so-called eight big foods, i.e., cow's milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish.

It is now 10 years since the EAACI-commissioned systematic review was completed. Several studies have been published since then, indicating that an update of the previous review is now warranted. By bringing together the evidence generated from the previous systematic review together with more recent studies, we have the opportunity to make clearer estimates of the incidence, prevalence, and time trends of FA in Europe. The update will also give greater opportunity to estimate the epidemiological burden of FA across various population subgroups (e.g., age and regions). Furthermore, this update is an excellent opportunity to identify and estimate the epidemiological burden of potentially "new" and "emerging" food allergy in Europe, beyond the so-called eight big foods. The aim of the current work was to update the previously EAACI-commissioned systematic review on the incidence, prevalence, and time trends of FA in Europe by identifying, critically appraising, and synthesizing evidence from studies now published since the previous systematic review was completed (2012). The current article reports on the estimates of the frequency of any FA.

2 | METHODS

2.1 | Protocol registration

The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; reference CRD42021266657) prior to undertaking this review.

2.2 | Search strategy

The search strategy was adapted from the previously published EAACI review. The two concepts of FA and epidemiology were combined to identify all relevant literature (including both articles, conference abstracts or posters, and theses) from the electronic databases. Six databases were searched: MEDLINE, EMBASE, CINAHL, Web of Science, Cochrane Library, and Scopus. Compared with the EAACI review from 2014, Cochrane Library and Scopus were added among the databases in acknowledgement of the advancements that have occurred in the indexing of studies on the topic since the first review was done. A few more keywords were also included in the current review to ensure that it was updated with all the new and emerging keywords on FA. Experts on the topic of FA were consulted to ensure that the study identification procedure did not miss any relevant work. No language restrictions were applied in the database searches. When possible, studies published in languages different from English were translated by researchers fluent in the language to permit data extraction. When it was not possible to translate the article, but an English abstract was available, data extraction from the abstract was performed. The few cases for which neither abstract nor full article data extraction was possible have been reported. Detailed description of the search strategies employed are available in Box S1 of the Supporting Information section of the online version of this article.

2.3 | Inclusion and exclusion criteria

The studies included in the current review comprised studies published from January 1, 2000 to June 30, 2021 (i.e., studies published in the previous systematic review, and studies identified in the current update). All studies that examined subjects with suspected FA, of any age and gender, and of any European country as defined by the United Nations (see Appendix 1) were considered eligible. Studies from Greenland and Turkey were also included, similarly to what was done in the previous EAACI review. The following types of studies were considered for inclusion: systematic reviews and meta-analyses, prospective and retrospective cohort studies, cross-sectional studies, case–control studies, clinical trials, and routine

healthcare studies. Expert reviews or other reviews that are not systematic reviews, discussion papers, non-research letters and editorials, qualitative studies, case studies, case series, and animal studies were excluded from the present work.

2.4 | Study selection

All records obtained from the databases searches were exported to EndNote 20 (Clarivate Analytics, 2020) for de-duplication. Following this, all relevant articles were exported to Rayyan (https://rayyan.ai) for titles and abstracts screening, and to manage all the retrieved records. Titles and abstracts screening was performed by four independent reviewers (SN/GS and YA/MA), working in pairs. Disagreements between reviewers were resolved with consensus when possible or by consultation with the project PI (BN). The full texts of the potentially eligible studies were then assessed by the same four independent reviewers, similarly to what was done for the titles and abstracts selection. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram was used to document the screening process.

2.5 | Risk of bias assessment

Risk of bias in individual studies was independently assessed for each study by the four reviewers (SN/GS and YA/MA), working in pairs, by employing the Critical Appraisal Skills Programme (CASP; http://www.casp-uk.net) quality assessment tool. The same tool was also used in the previous EAACI systematic review. Accordingly, all studies were assigned an overall rating, along with a separate rating for each different components of the individual studies (i.e., appropriateness of the study design for the research question, risk of selection bias, exposure measurement, and outcome assessment). Any discrepancy was resolved by consensus or arbitrated by the project PI (BN).

2.6 | Data extraction

Data were collected from included studies using a customized data extraction form. All data extracted were reported in a standardized and reproducible fashion. The developed form was first piloted with a small number of included studies and approved by all reviewers before it was employed to extract data from all studies. The form was stored on a Google Drive (Alphabet Inc., Mountain View, CA, USA) repository online to make all the information promptly available to all reviewers. Similar to the selection process, the extraction of all data was performed by four reviewers, working in pairs (SN/GS and YA/MA). Each pair conducted an independent extraction of the assigned records. After cross-checking, all disagreement were addressed and further arbitrated by the project PI (BN).

2.7 | Data analysis, synthesis, and reporting

We recalculated all the frequency estimates of FA occurrence if adequate data were provided by authors. If any discrepancies were observed between our recalculated estimates and those of the authors, we reported our recalculated estimates. Our recalculated estimates were based on minimal measured events rather than the extrapolated ones. The 95% confidence intervals (95% CI) were obtained by employing the Wilson score method without continuity correction.[3] Heterogeneity was assessed using I^2 statistics. For studies that presented missing data, thus not allowing estimates recalculation, we reported the estimates provided by the authors. Where needed and possible, we contacted authors of primary studies for clarifications. Countries outside the Organization for Economic Co-operation and Development (OECD) definition of Europe were included in the systematic review but were not included in meta-analysis, similarly to what was done in the previous version of the systematic review and meta-analysis. An exception was made for Lithuania and Russia, which had recorded FA data for meta-analysis also in the previous study. According to the criteria above, Albania, Bulgaria, Croatia, and Ukraine were included in the systematic review, but not in the current meta-analysis.

Random-effects meta-analysis was performed for all studies that provided numerical data in order to derive pooled estimates across studies. The meta-analysis was conducted using the software Stata (StataCorp. 2019. Stata Statistical Software: Release 16; StataCorp LLC, College Station, TX, USA). The following outcomes were defined: 1. lifetime and point prevalence of self-reported FA; 2. lifetime and point prevalence of self-reported physician diagnosed FA (i.e., doctor-diagnosed FA reported by a subject in a questionnaire); 3. point prevalence of sIgE positivity; 4. point prevalence of SPT positivity; 5. point prevalence of symptoms plus sIgE positivity; 6. point prevalence of symptoms plus SPT positivity; 7. point prevalence of clinical history or food challenge (OFC or DBPCFC)-positivity; and 8. point prevalence of positive food challenge (OFC or DBPCFC). Meta-analysis included the studies reporting on any FA published in the previous EAACI review and those obtained from the current updated searches. As was done in the previous EAACI review, data were also stratified by age category, in children (0–17 years) and adults (18 years and over), and by European region (Northern-Eastern-Southern-Western Europe) following the classification by the United Nations (see Appendix 1). In case of overlap between the two age categories, or between groups, the estimate was included in either age group if the age distribution was skewed to that age group, following the approach used in the 2014 EAACI review. An exception was made for the United Kingdom, which was assigned to Western Europe instead of Northern Europe, as was done in the previous EAACI review. In the meta-analysis, we estimated the updated prevalence of FA for the period 2000–2021. In addition, we also performed and reported meta-analysis separately for the studies published during 2012–2021, which were compared with the estimate obtained in the previous review for the period 2000–2012.

3 | RESULTS

3.1 | Study selection and characteristics

The study selection and screening process of the current update are illustrated in the PRISMA flow chart presented in Figure 1. A total of 38,903 records were retrieved from the databases searched. After de-duplication, 33,875 records were selected for screening. Based on titles and abstracts, 33,625 records were excluded due to being clearly ineligible or not fulfilling the inclusion criteria. Out of the remaining 250 records, two full-text articles could not be retrieved, and the abstracts did not include any relevant information. They were therefore excluded. Of the remaining 248 records, 72 reports were included in this review. The new reports included were based on 54 newly identified studies, and on one study already included in the previous review but presenting updated data for the cohort enrolled in the study. Putting together the number of reports (and studies) included in the first systematic review from EAACI, with the

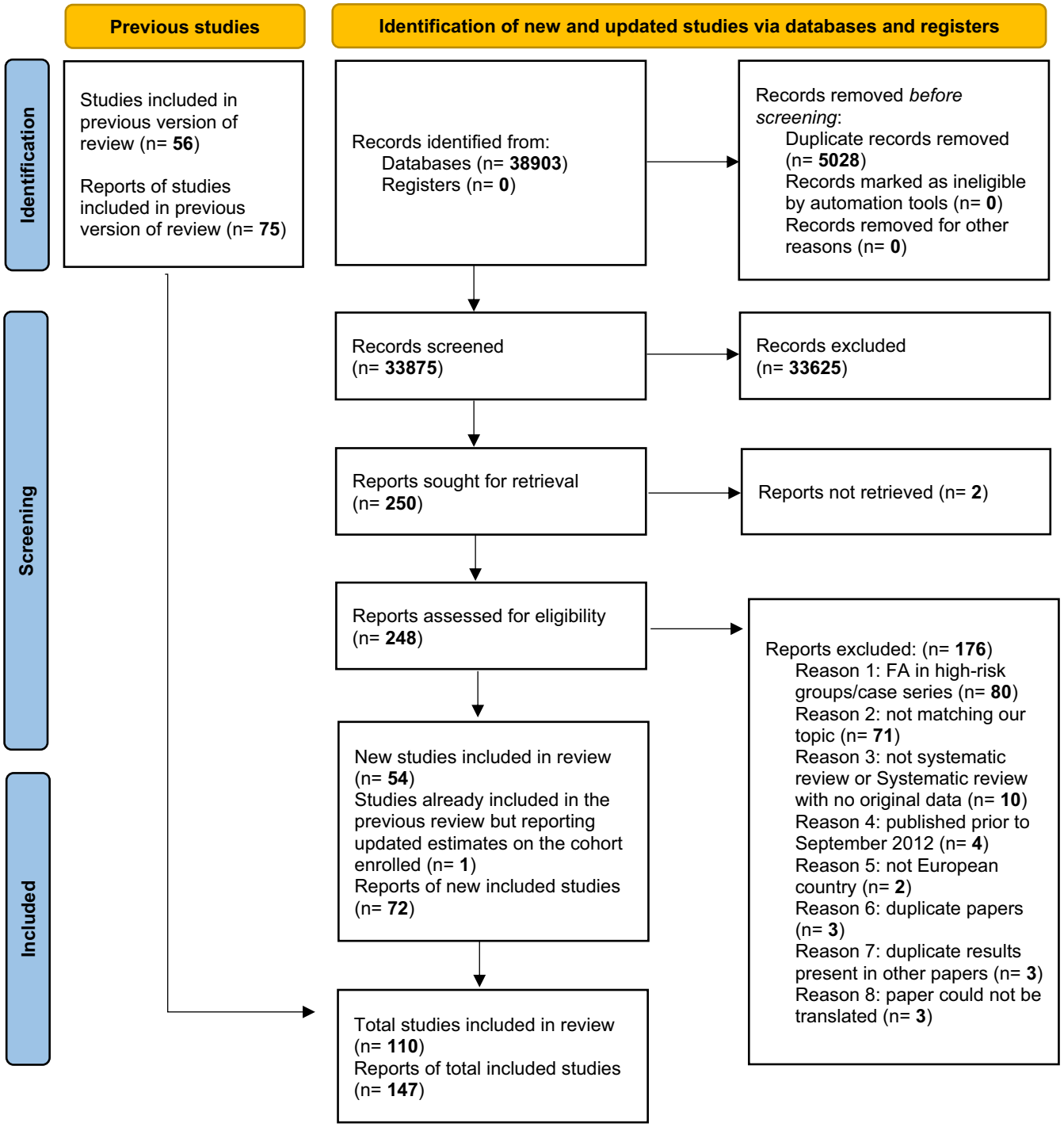

FIGURE 1 PRISMA flow diagram for updated systematic review on prevalence of food allergy in Europe, 2000–2021.

records screened and included for the current review (September 2012 to June 2021), the total number of reports included was 147, which were based on 110 studies.[4–150]

Of the 110 studies, 62 were cross-sectional studies, 41 were cohort studies, three were case-control studies (of which one nested-control), three were systematic reviews, and one was a population-based study. Most of the studies included only children (n = 76 studies). FA was investigated exclusively by self-report in 26 studies, whereas in 17 studies FA was only investigated by sIgE and/or SPT positivity. Nine studies reported only on physician/clinician diagnosed FA (in three cases, self-reported). The remaining 58 studies were a combination of self-report, self-report physician diagnosis, sIgE or SPT sensitization (with or without symptoms), clinical diagnosis/clinical history, and/or food challenge (OFC and/or DBPCFC). The majority of the studies (n = 94) reported point prevalence as the occurrence measure for assessing the frequency of FA, and in 69 of the studies point prevalence was the only occurrence measure provided. Lifetime prevalence was the second most reported type of estimate, while cumulative incidence was investigated in only 15 studies.

3.2 | Risk of bias assessment

Overall, the risk of bias assessment for individual studies graded by the CASP quality assessment tool indicated that most of the studies had a moderate risk of bias (91 out of 110 studies). Table S2 summarizes the grading of the main CASP quality assessment features for all studies.

3.3 | Frequency of any FA

The ranges of estimates for any FA categorized by age groups, and by different methods of assessment are presented in Table 1, based on the data extracted from the articles published between January 2000 and June 2021. Detailed results on the prevalence and incidence reported by each study are included in Tables S1–S6 of the Supporting Information section in the online version of this article. The pooled estimates for the prevalence of FA in Europe for the periods 2000–2021, 2000–2012, and 2012–2021 are presented in Figures 2–6 and further elaborated below. The forest plots for pooled data from studies published for the period 2000–2021, are included in the Supporting Information section of the online version of this article, along with the heterogeneity measurements for the studies included in the analysis (Figures S1–S28). As observed for the review published on data from 2000 to 2012, the heterogeneity between the studies was still significantly high ($I^2 \geq 80$ in each case) in the updated pooled data for 2000–2021, regardless of age group and European region, which reflects the variations in estimate of prevalence of FA between studies and across places.

3.3.1 | Self-reported FA

The overall pooled estimate of self-reported lifetime prevalence of any FA was 19.9% (95% CI 16.6–23.3%); 18.7% vs. 22.8% for children and adults, respectively. Self-reported point prevalence of any FA was 13.1% (95% CI 11.3–14.8%); 14.2% vs. 12.3% for children and adults, respectively. The lifetime prevalence of any FA was lowest in Southern Europe and highest in Eastern Europe. The point prevalence was lowest in Western Europe and highest in Eastern Europe. However, for both lifetime and point prevalence, Eastern Europe was also the region with the lowest number of studies reporting on FA prevalence. Overall, the lifetime prevalence did not substantially differ between the estimates in 2000–2012 (17.3%) and 2012–2021 (19.8%). However, there was almost three times increase in point prevalence between 2000 and 2012 (5.9%) and 2012 and 2021 (14.9%) (Figure 2).

3.3.2 | Self-reported physician diagnosed FA

The overall pooled estimate for self-reported physician-diagnosed lifetime prevalence of any FA was 6.6% (95% CI 5.2–7.9%); 9.3% vs. 5.0% for children and adults, respectively. Self-reported physician-diagnosed point prevalence of any FA was 4.9% (95% CI 2.7–7.1%); 3.8% vs. 6.9% for children and adults, respectively. The lifetime prevalence of any FA was lowest in Southern Europe and highest in Eastern Europe, while the point prevalence was lowest in Western Europe and highest in Southern Europe (although based on only one study). For point prevalence, no data were available on Eastern Europe. No estimates for self-reported physician-diagnosed FA were available for the previous systematic review for the period 2000–2012, thus the calculated estimates were based only on the studies obtained for the period 2012–2021 (Figure 3).

3.3.3 | Food sensitization (FS) by positive sIgE and SPT

The overall pooled estimate for point prevalence of sIgE positivity to any FA was 16.6% (95% CI 12.3–20.8%); 18.4% vs. 11.2% for children and adults, respectively, lowest in Northern Europe and highest in Western Europe. Specific IgE positivity to any FA was 10.1% during 2000–2012 and 17.4% during 2012–2021 (Figure 4).

The overall pooled estimate for point prevalence of SPT positivity to any FA was 5.7% (95% CI 3.9–7.4%); 4.5% vs. 21.4% for children and adults, respectively, lowest in Southern Europe and highest in Western Europe. No data were available for the Eastern European region. SPT positivity to any FA was 2.7% during 2000–2012 and 6.9% during 2012–2021 (Figure 4).

TABLE 1 Summary of range of estimates of the frequency of FA in Europe by self-report, self-report physician diagnosis, skin prick test (SPT) positivity, sIgE positivity, symptoms plus sIgE positivity, symptoms plus SPT positivity, clinical history or food challenge, food challenges: estimates from all the studies published between 1 January 2000 and 30 June 2021

Age bands (years) for each food allergy	Self-report	Self-report physician diagnosis	sIgE positivity	SPT positivity	Symptom plus positive sIgE	Symptom plus positive SPT	Clinical history or FC (OFC or DBPCFC)	Food challenge (OFC or DBPCFC)
Point prevalence, %								
≤1	1.7–28.5	2.1–4.9	19.4–20.3	1.8–4.3	1.3–4.6	1.6–13.1	2.7–10.0	0.3–4.2
2–5	1.6–38.7	4.9–6.6	4.1–21.5	1.8–4.5	4.6	6.8–13.1	2.1–7.7	0.0–4.2
6–17	1.6-47.5	2.3–7.6	0.1–52.0	0.1-10.2	1.4–5.6	0.1–13.1	0.2–4.2	0.1–5.7
≥18	1.7–36.3	0.5–11.3	2.0–25.5	21.4	0.3–5.9	–	–	0.1–3.2
Life–time prevalence, %								
≤1	4.1–38.4	39.3	–	–	–	–	1.0	–
2–5	4.1–38.4	–	–	–	–	–	15.0	–
6–17	4.1–41.6	2.5–27.4	–	4.1–5.9	–	–	–	–
≥18	9.5–35.0	4.7	–	–	–	–	–	–
Cumulative incidence, %								
≤1	25.8	4.7	–	–	–	–	2.4–5.0	1.5
2–5	25.5-28.1	4.7–9.8	–	5.3	–	–	5.0-6.0	3.3
6–17	11.6-21.4	4.7	47.3	–	–	–	–	3.6
≥18	11.7	–		–	–	–	–	–

Abbreviations: DBPCFC, double-bind placebo-controlled food challenge; FA, food allergy; FC, food challenge; OFC, oral/open food challenge; sIgE, specific IgE; SPT, skin prick test for sensitization to specific food allergens.

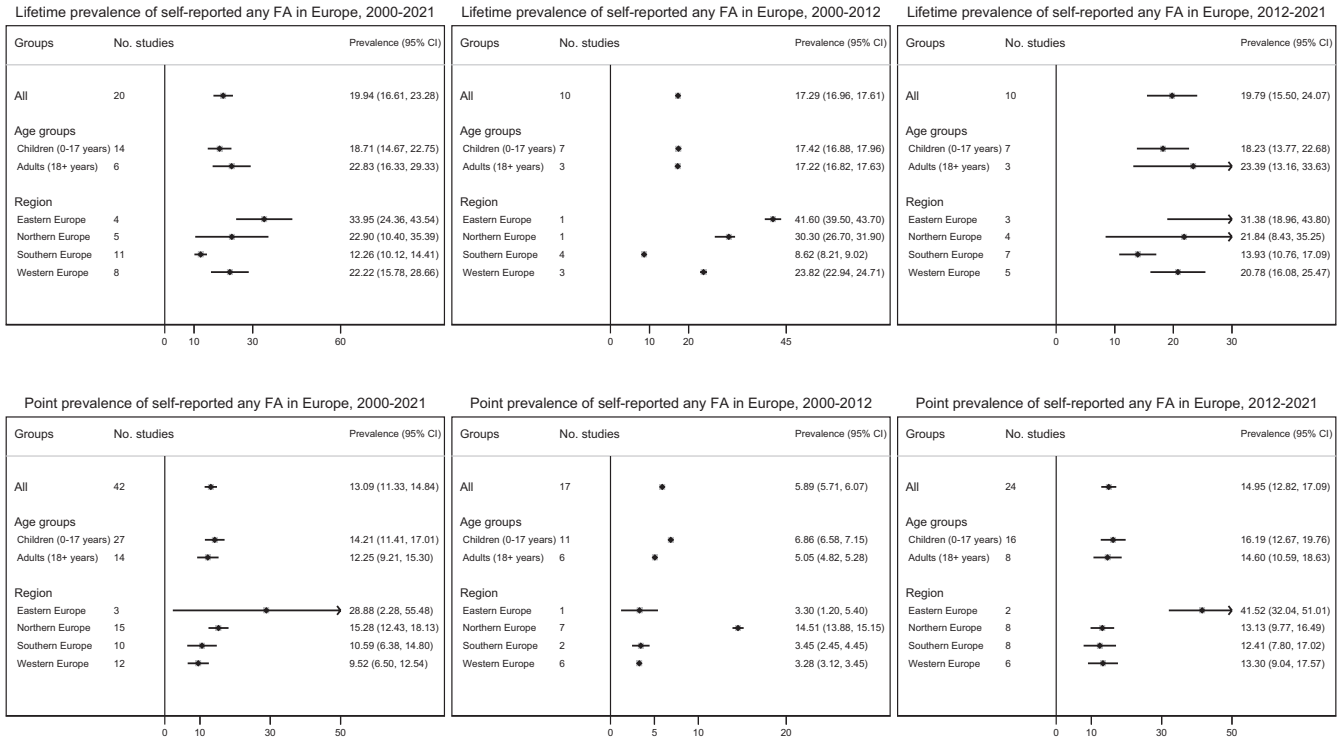

FIGURE 2 Pooled estimates for self-reported any food allergy in Europe for lifetime (top) and point prevalence (bottom) between 2000 and 2021, 2000 and 2012, and 2012 and 2021.

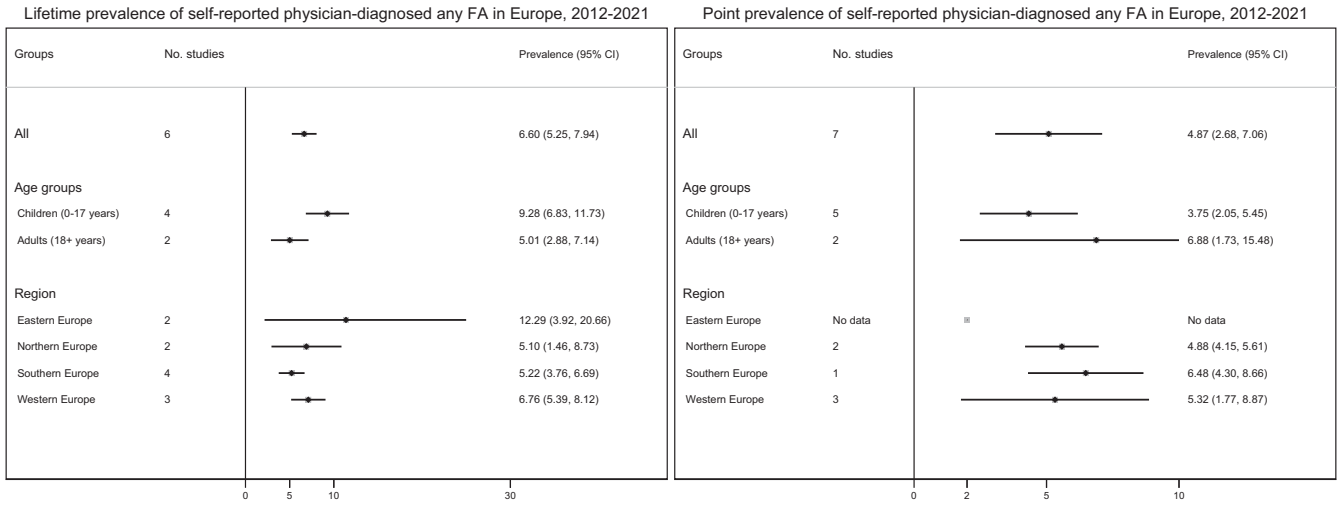

FIGURE 3 Pooled estimates for self-reported physician diagnosed any food allergy (i.e., doctor-diagnosed FA reported by a subject in a questionnaire) for lifetime (left) and point prevalence (right) between 2012 and 2021.

3.3.4 | Symptom plus sIgE or SPT positivity FA

The overall pooled estimate for prevalence of symptom plus sIgE positivity to any FA was 2.9% (95% CI 2.1–3.6%); 3.5% and 2.4% for children and adults, respectively. The prevalence was lowest in Southern Europe and highest in Eastern Europe. Estimates for symptom plus sIgE positivity to any FA was similar during 2000–2012 (2.7%) and 2012–2021 (2.9%).

The overall pooled estimate for prevalence of symptom plus SPT positivity to any FA was 2.4% (95% CI 1.3–3.4%), all studies being only available for children and none for adults. The prevalence was lowest in Southern Europe and highest in Western Europe, but data were unavailable for Eastern Europe. Estimates for symptom plus specific SPT positivity to any FA was 1.5% during 2000–2012 and 1% during 2012–2021 (Figure 5).

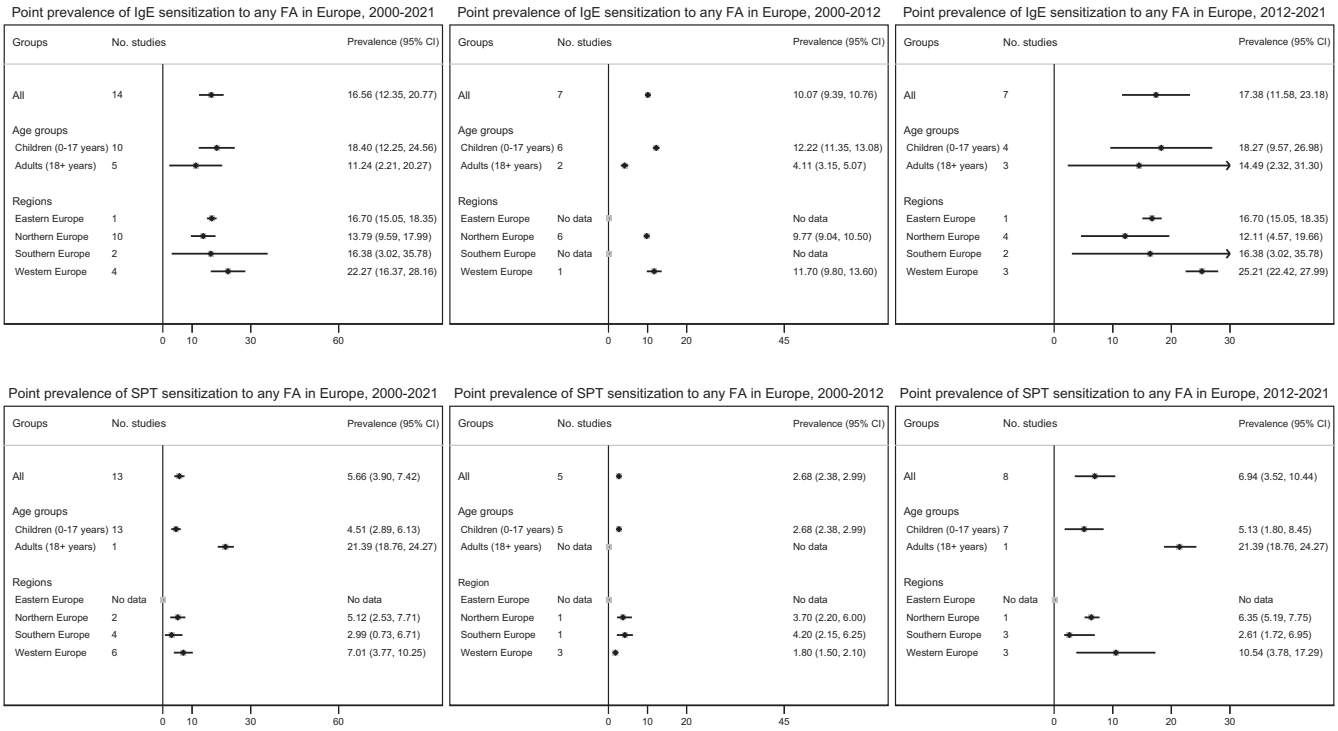

FIGURE 4 Pooled estimates for sIgE (top) or SPT (bottom) sensitization to any food allergy in Europe between 2000 and 2021, 2000 and 2012, and 2012 and 2021.

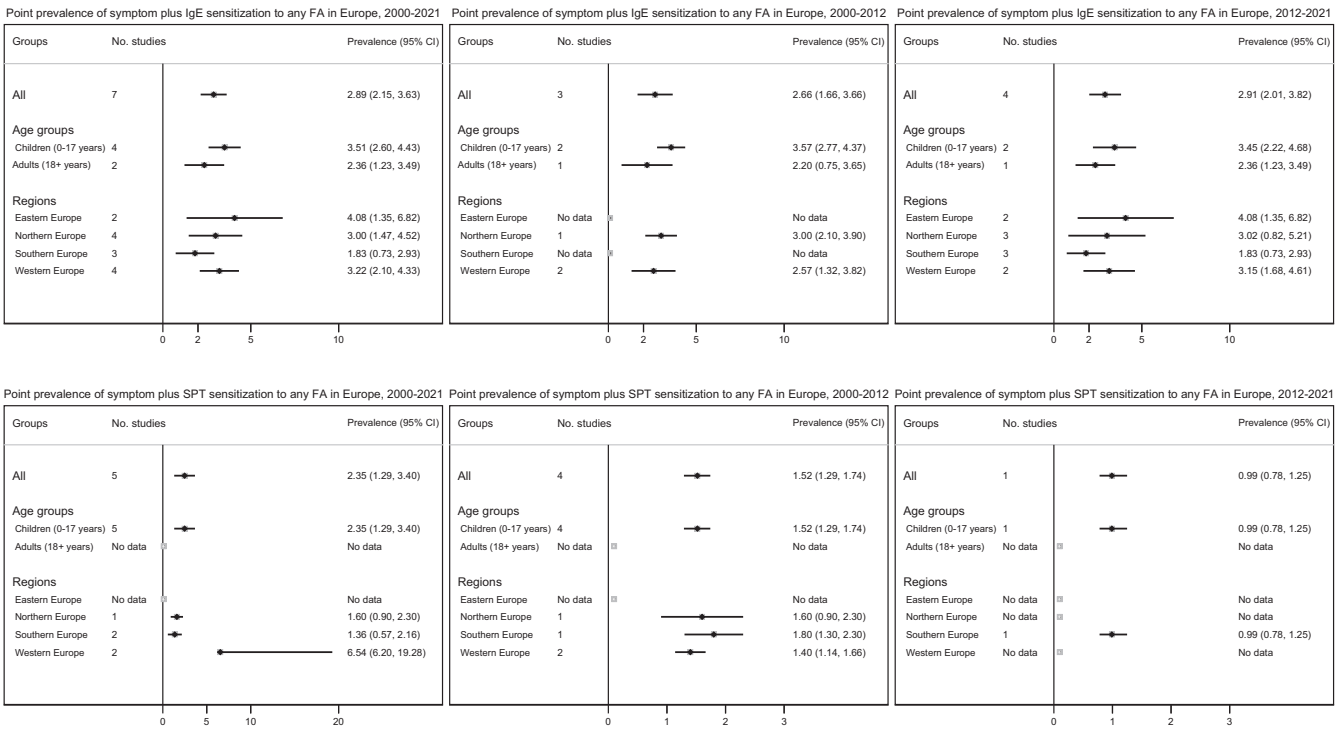

FIGURE 5 Pooled estimates for symptoms plus sIgE (top) or SPT (bottom) sensitization to any food allergy in Europe between 2000 and 2021, 2000 and 2012, and 2012 and 2021.

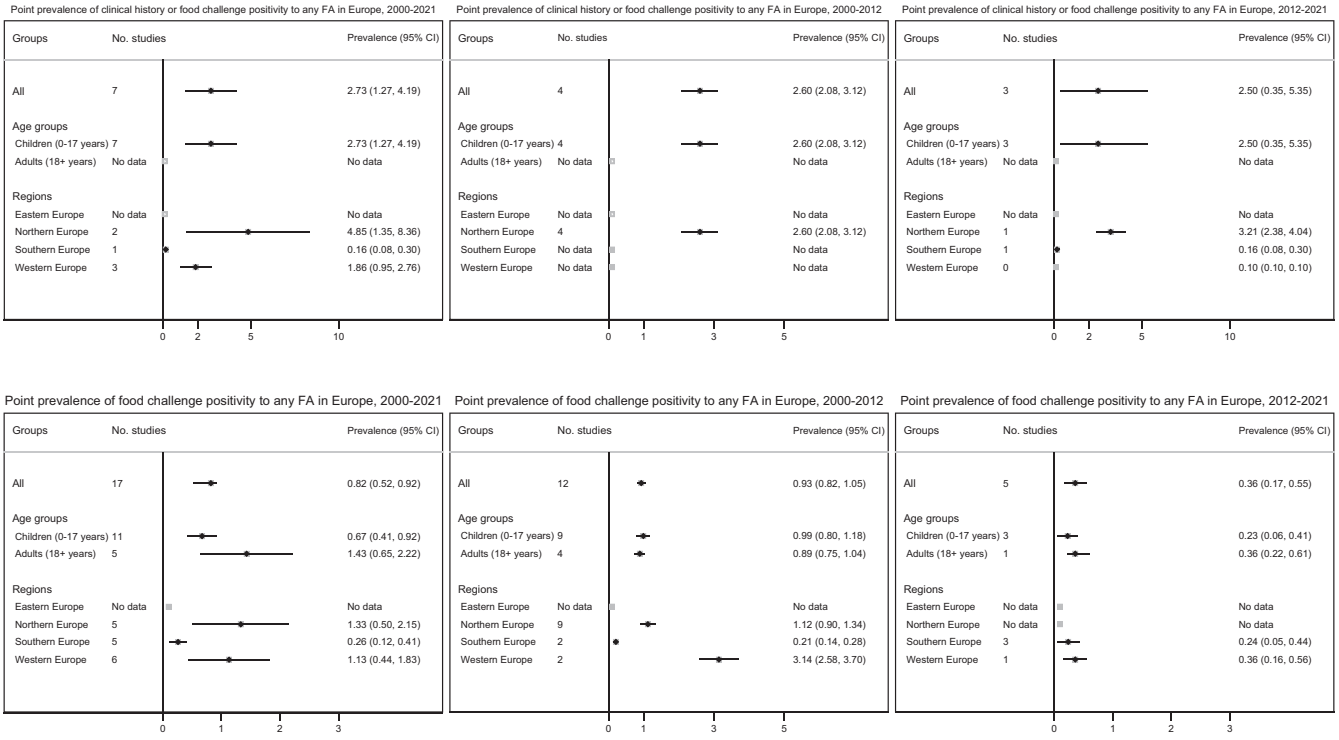

FIGURE 6 Pooled estimates for clinical history or food challenge positive any food allergy (top) and for food-challenged verified any food allergy (bottom) in Europe between 2000 and 2021, 2000 and 2012, and 2012 and 2021.

3.3.5 | FA defined by clinical history or food challenge

The overall pooled estimate for prevalence of clinical history or food challenge (OFC or DBPCFC) positivity to any FA was 2.7% (95% CI 1.3–4.2%), all studies being only available for children and none for adults. The prevalence was lowest in Southern Europe and highest in Northern Europe. No data were available for Eastern Europe region. Between 2000 and 2012 and 2012 and 2021, the prevalence of clinical history or food challenge FA was 2.6% and 2.5%, respectively (Figure 6).

3.3.6 | Food challenge-verified FA

The overall pooled estimate for prevalence of food challenge (OFC or DBPCFC) positivity to any FA was 0.8% (95% CI 0.5–0.9%); 0.7% vs. 1.4% for children and adults, respectively. The prevalence was lowest in Southern Europe and highest in Northern Europe. There were no estimates from Eastern Europe. The prevalence was 0.9% during 2000–2012 and 0.4% during 2012–2021 (Figure 6).

3.4 | Time trends of frequency of FA

Data on time trends of FA in Europe are reported in Table 2. In addition to the three studies originally reported in the previous systematic review, two more studies were identified and included in this update, giving a total of five studies.[29,55–57,65,76,136–138,141] Four out of the five studies were undertaken in the United Kingdom,[29,65,76,136–138,141] while the remaining one took place in Finland.[65] We also added updated trends on the frequency of FA for one of the studies already reported in the review from 2014.[136–138,141] Three of the studies reported trends for both any FA and specific FA. One study reported the trends of hospital admission rate for FA,[55–57] while one study reported trends for doctor-diagnosed peanut allergy.[76] While the available data remained limited to allow clear conclusion on the current time trends in the incidence or prevalence of FA, the additional data from this updated review may suggest a slight but progressive increase of clinician-diagnosed FA in the United Kingdom, with reported prevalence going from 0.6% in 2000 to 1.3% in 2015,[29] but a slight decrease in point prevalence self-reported FA, with estimates going from 8.5% to 7.2% at 1 year, from 9.2% to 8.4% at 2 years, and from 9.1% to 8.3% at 3–4 years in two birth cohort born in 1989–1990 and in 2001–2002, respectively.[136–138,141] In Finland, the prevalence of self-reported FA was not relevantly changed from 2009 to 2013 (2.7% vs. 2.5%).[65]

4 | DISCUSSION

4.1 | Statement of principal findings

The current systematic review and meta-analysis provides the most updated estimates of the frequency of FA in Europe for the period 2000–2021. We estimate that the lifetime and point prevalence of

TABLE 2 Time trends in the frequency of FA in Europe: estimates from studies published between 1 January 2000 and 30 June 2021

Reference, country	Age(s) of subjects	Frequency of FA					Comments
Diwaker et al. 2017, United Kingdom[29]	Children 0–17 years old	**Year 2000** Point prevalence of physician diagnosed FA: - any FA: 0.6% - eggs: 0.2% - nuts: 0.1%		**Year 2015** Point prevalence of physician diagnosed FA: - any FA: 1.3% - eggs: 0.3% - nuts: 0.5%			Data were extracted from a conference abstract. The abstract reports on a population study based on routine primary care data. The objective was to "estimate the trends in prevalence of General Practitioner (GP) diagnosed allergies between 2000 and 2015 among United Kingdom (UK) children (0–17 years)". To the scope, a primary care database representing 6% of the entire UK population was screened. Point prevalence of physician-diagnosed FA was also measured for the following specific foods: nuts and eggs.
Gupta et al. 2004-a, 2004-b, and 2007, United Kingdom[55-57]	All ages	**Years 1991/92** Admissions rate for FA: *All ages*: 0.5% *0–14 age group*: 1.6% *15–44 age group*: 0.5% *45+ age group*: 0.0%	**Years 2000/01** Admissions rate for FA: *All ages*: 2.9% *0–14 age group*: 11.8 *15–44 age group*: 1.1% *45+ age group* 0.5%	**Years 2003/04** Admissions rate for FA: *All ages*: 2.6% *0–14 age group*: 10.7% *15–44 age group*: 9.0% *45+ age group*: 0.6%			The increasing trends of 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.
Järvenpää et al. 2014, Finland[65]	Children 6–7 years old	**Year 2009** Point prevalence self-reported FA to: - basic foods: 2.7% (1.9–3.5) - cow's milk allergy: 1.5% (0.9–2.1) - eggs: 1.1% (0.6–1.6) - grains: 1% (0.5–1.5) - fruit and vegetables: 5.8% (4.7–7.0) - nuts: 3.1% (2.2–4.0) - legumes: 0.7% - spices: 0.6% - fish: 0.8% (0.4–1.3)		**Year 2013** Point prevalence self-reported FA to: - basic foods: 2.5% (1.9–3.4) - cow's milk: 1.3% (0.9–2.0) - eggs: 1.5% (1.0–2.2) - grains: 1% (0.6–1.6) - fruit and vegetables: 3.2% (2.5–4.2) - nuts: 1.8% (1.3–2.6) - legumes: 0.9% (0.5–1.4) - spices: 0.5% (0.3–1.0) - fish: 0.7% (0.4–1.3)			Children attending the first year of elementary school at 29 different schools in the Tampere (Finland) district were screened for the study. The objective was to assess the prevalence of self-reported FA in the Tampere district. Basic foods according to the authors' definition include milk, eggs, and grains. Point prevalence for the following specific foods was also measured: cow milk, eggs, grain, nuts, fruits and vegetables, and fish.
Kotz et al. 2011, United Kingdom[76]	All ages	Lifetime prevalence physician diagnosed peanut allergy per 1000 patients:					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 table. Only data regarding the prevalence trends of peanut allergy were reported by the authors.
		Year 2001: 0.24% (0.22–0.26)	**Year 2002:** 0.32% (0.30–0.34)	**Year 2003:** 0.39% (0.37–0.42)	**Year 2004:** 0.45% (0.43–0.48)	**Year 2005:** 0.51% (0.49–0.54)	
		Incidence rate of physician diagnosed peanut allergy per 1000 person-years:					
		Year 2001: 0.06% (0.05–0.07)	**Year 2002:** 0.08% (0.07–0.09)	**Year 2003:** 0.08% (0.07–0.09)	**Year 2004:** 0.08% (0.07–0.09)	**Year 2005:** 0.08% (0.07–0.09)	

TABLE 2 (Continued)

Reference, country	Age(s) of subjects	Frequency of FA	Comments
Venkataraman et al. 2017,[136] Venter et al. 2010,[137] Venter et al. 2008,[138] Venter et al. 2016,[141] United Kingdom	Children 0–18 years old	Point prevalence of self-reported FA, SPT positive FA, and clinical history or OFC positive FA at 1 year **Year 1990–1991** Self-reported FA: - any FA: 8.5% (7.1–10.2) SPT positive FA - peanut allergy: 0.3% **Year 1995–1997** Self-reported FA: - any FA: N/A SPT positive FA: - peanut allergy: N/A **Year 2002–2003** Self-reported FA: - any FA: 7.2% (5.7–9.1) SPT positive FA: - peanut allergy: 0.4% (0.1–1.2) Point prevalence of self-reported FA and of SPT positive FA at 2 years **Year 1991–1992** Self-reported FA: - any FA: 9.2% (7.6–10.9) SPT positive FA: - peanut allergy: 1.0% **Year 1996–1998** Self-reported FA: - any FA: N/A SPT positive FA: - peanut allergy: N/A **Year 2003–2004** Self-reported FA: - any FA: 8.4% (6.7–10.4) SPT positive FA: - peanut allergy: 2.0% (1.2–3.4) Point prevalence of self-reported FA, SPT positive FA, and of clinical history or FC positive FA at 3–4 years **Year 1993–1994** Self-reported FA: - any FA: 9.1% (7.6–10.9) SPT positive FA: - any FA 3.2% (2.2–4.5) - peanut allergy: 1.3% (0.6–1.8) Clinical history or OFC positive FA: - peanut allergy: 0.5% (0.2–1.1) **Year 1998–2000** Self-reported FA: - any FA: N/A SPT positive FA: - any FA: N/A - peanut allergy: 3.3% (2.4–4.4) Clinical history or OFC positive FA: - peanut allergy: 1.4% (0.9–2.2) **Year 2004–2005** Self-reported FA: - any FA: 8.3% (6.7–10.3) SPT positive FA: - any FA: 4.5% (3.2–6.4) - peanut allergy: 2.0% (1.2–3.4) Clinical history or OFC positive FA: - peanut allergy: 1.2% (0.7–2.2) Point prevalence of SPT positive FA at 10 years **Year 1999–2000** - any FA: 4.4% (3.4–5.9) - peanut allergy: 1.84% **Year 2004–2006** N/A **Year 2011–2012** - any FA: 2.7% (1.7–4.4) - peanut allergy: 2.4% (1.4–4.0)	The data presented come from three different birth cohorts of children, which were born in the Isle of Wight 1989–1990, 1994–1996, and 2001–2002. All three cohorts have been reviewed at 3–4 years after birth in 1993, 1998–2000, and 2004–2005, respectively. Two of the cohorts have been followed up for more years: the Isle of Wight-IOW birth cohort for subjects born in 1989–1990, and The Food Allergy and Intolerance Research-FAIR birth cohort for subjects born in 2001–2002, respectively. Overall, the prevalence of self-reported FA has slightly decreased, while the prevalence of peanut allergy sensitization seems increased in children living in the Isle of Wight.

Note: Diwakar et al. was extracted from a conference abstract.

Abbreviations: FA, food allergy; OFC, oral/open food challenge; SPT, skin prick test for sensitization to specific food allergens.

self-reported any FA currently stand at 20% and 13%, respectively. The point prevalence of sensitization as assessed by sIgE stands at 17%, skin prick test 6%, and food challenge positivity 1%. While the lifetime prevalence of self-reported FA and point prevalence of food challenge positivity only slightly changed during the period 2000–2012 and 2012–2021, the point prevalence of self-reported FA, sIgE and SPT positivity increased between the same periods. However, based on clinical history or positive food challenge (OFC or DBPCFC), FA increased from 2.6% in 2000–2012 to 3.5% in 2012–2021. Overall, there was no apparent pattern in the frequency of FA in children and adults across the different measures of assessment, nor a consistent pattern by European regions.

4.2 | Strengths, limitations, and implications of the current review update

As with the previous EAACI-led systematic review[1,2] we followed recommended rigor in undertaking this updated review, which included a comprehensive search of the extant literature and a systematic approach at every stage of the review process. Additional databases were included in the current update, more than were included in the previous review to ensure that we did not miss any relevant study given the advancement made in the literature collection over the last decade. In keeping with the previous review that included studies investigating frequency of FA using all possible methods to measure FA (e.g., self-report, specific sensitization to foods, food challenge, and their various combinations), as well as including different measures of occurrence of FA (e.g., point prevalence, lifetime prevalence, and incidence), the current review remains so far the most comprehensive in providing a clear picture of the burden of FA in Europe.

As observed in the previous review,[1] most studies in this update also failed to make any distinction between IgE or non-IgE FA phenotypes, thus it was impossible to present estimates of prevalence of FA by its IgE-mediated and non-IgE-mediated phenotypes. Overall, the quality of studies included in the review remained moderate as it was in the previous review, indicating that in going forward, the quality of the underlying evidence needs to be improved. Although the previous review highlighted the need for improved assessment of FA through increased use of the gold standard DBPCFC measurement, we did not observe such improvement in this update, regardless of the European region. This is an aspect that still requires further attention. However, OFC is traditionally more commonly used than DBPCFC, since DBPCFC can be challenging in its application. Many symptomatic individuals may be excluded from DBPCFC due to co-existing disease, labor intensity, lack of validated and blinded challenge materials, or refusal of the individuals, which usually leads to an underestimation of actual frequency of FA. In this case, we highlighted in the previous review that using estimates based on convincing clinical history or positive food challenge may represent the best objective estimates.[1] Based on these estimates, FA remained stable between 2000 and 2012 (2.6%) and 2012 and 2021 (2.5%). Still, there was no improvement over the past decade in the use and definition of FA using convincing clinical history or positive food challenge as only a negligible number of studies used it to define FA. There was also no improvement in time trends of FA as only two additional studies[29,65] were found in this update, adding to the three studies[55–57,76,137,138,141] found in the previous review. More time trend studies are required to provide a clearer picture of time trends of FA overtime.

As for the possible differences in FA between children (0–17 years) and adults (18 years and over), although in most of the cases frequency estimates for FA differed between children and adults, there was no clear pattern across the different measures of assessment by age category. For the estimates of FA across the European regions, estimates were mostly comparable for all the methods of assessment included in the analysis. However, for self-reported FA, prevalence estimates were frequently higher in Northern and Eastern regions compared with Southern and Western regions. Nevertheless, it is impossible to infer if the reported data were due to an actual increase in FA in the specific European population examined or if the higher (or lower) estimates could result from the different approaches used, framing of the questionnaire or subjective interpretation of the studied populations. This is especially true when considering that the definition of self-reported FA per se can be challenging to establish. Given that the differences in European regions were far smaller when FA outcome was defined by objective measures such as SPT or sIgE tests, the probable differences observed for self-reported FA may depend more on over or under-reporting of the phenomena across the different regions. Indeed, the observed rise in the point prevalence estimated for SPT and sIgE FA between 2000 and 2012 and 2012 and 2021 could be partially explained by the fact that more food allergens are now being investigated by sIgE testing, leading to a higher number of positive cases found.

A highly significant heterogeneity was observed in the updated review for the pooled prevalence estimates of studies published on FA in Europe in the past two decades, regardless of age and European region. While such heterogeneity may indicate inherent methodological differences across the studies regarding study implementation and definition of FA, it may also reflect the fact that indeed estimates of prevalence of FA varies across places in Europe. Consequently, harmonization of protocols, implementation, and definition of FA across studies in future studies may not resolve the heterogeneity between studies.

5 | CONCLUSIONS

This updated systematic review shows that the lifetime prevalence of FA in Europe has slightly increased since the previous review was published in 2014. Similarly, the point prevalence, especially for self-reported and sIgE positive FA increased during the same period, while clinical history and OFC or DBPCFC confirmed FA remained stable. However, the prevalence of food challenge positivity slightly decreased during this period. The observed increase may reflect a

real increase, increased awareness, increased number of food allergens assessed or increased number of studies from countries that had less data in the first review. The frequency of FA differed in children and adults, but there were no consistent patterns by age category across the outcomes investigated. Likewise, no consistent pattern was observed by European regions, although prevalence of FA was frequently higher in Northern and Eastern regions compared with Southern and Western regions. As there seemed to be important methodological and diagnostic differences within and across the European regions, interpretation of the findings requires caution, especially considering the high heterogeneity among the studies still observed in this updated review.

Overall, there was no improvement in the design of studies and diagnostic approaches used between the current update and the previous review. There is still a need to improve this evidence base in order to better understand the frequency of FA across Europe, through which its healthcare and societal burden can be clearer explained. As indicated in the previous review, future studies still require rigorous designs and implementation of standardized methodology in diagnosing FA, including use of DBPCFC to minimize potential biases.

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CONFLICT OF INTEREST

Carina Venter reports: grants (Reckitt Benckiser, Food Allergy Research and Education, and National Peanut Board) and personal fees (Reckitt Benckiser, Nestle Nutrition Institute, Danone, Abbott Nutrition, Else Nutrition, Sifter, and Before Brands). Ronald van Ree reports: consultancies (HAL Allergy BV, Citeq BV, Angany Inc., Reacta Healthcare Ltd., Mission MightyMe, and AB Enzymes), speaker's fees (HAL Allergy BV, ThermoFisher Scientific, and ALK), and stock options (Angany Inc.). Margitta Worm reports: grants and personal fees (Stallergens, HAL Allergie, Bencard Allergie, Allergopharma, ALK-Abello, Mylan Germany, Actelion Pharmaceuticals Deutschland, Biotest, AbbVie Deutschland, Lilly Deutschland Aimmune, DBV Technologies SA, Regeneron Pharmaceuticals, Sanofi Aventis, Leo Pharma, Novartis, and Viatris) outside of the submitted work and being past WAO co-chair of the anaphylaxis committee and past chair of the food allergy interest group of EAACI. Berber Vlieg-Boerstra reports: personal fees (Marfo Food Group, Nestlé, and Nutricia) and grants (Nutricia). Antonella Muraro reports: grants and speaker's fees (Aimmune), speaker's fees (DVB Technologies SA, Viatris [Mylan], ALK, and Nestlé), and being member of the Executive Committee of GA2LEN and past president of EAACI. Graham Roberts reports grants (Asthma UK and National Institutes of Health Research). Bright I, Nwaru reports unrestricted grants and personal fees from DBV Technologies and AstraZeneca, respectively. Giulia C.I. Spolidoro, Yohannes Tesfaye Amera, Mohamed Mustafa Ali, Sungkutu Nyassi, Daniil Lisik, Athina Ioannidou report fee from ACT Institutet Sweden. The other authors report no conflicting interests related to this work. The funder played no role in the content and decision to submit this manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

Geoscheme of European countries by UN			
Eastern Europe	**Northern Europe**	**Southern Europe**	**Western Europe**
Belarus	Åland*	Albania	Austria
Bulgaria	Channel Islands (Guernsey, Jersey, Sark)	Andorra	Belgium
Czech Republic	Denmark	Bosnia and Herzegovina	France
Hungary	Estonia	Croatia	Germany
Poland	Faroe Islands	Gibraltar	Liechtenstein
Moldova	Finland	Greece	Luxembourg
Romania	Iceland	Holy See (Vatican City)	Monaco
Russia	Ireland	Italy	Netherlands
Slovakia	Isle of Man	Kosovo*	Switzerland
Ukraine	Latvia	Malta	
	Lithuania	Montenegro	
	Norway	(North) Macedonia	
	Svalbard and Jan Mayen Islands*	Portugal	
	Sweden	San Marino	
	UK (England, Scotland, Wales, and Northern Ireland)	Serbia	
		Slovenia	
		Spain	
		Turkey*	
		Yugoslavia (historical)*	

Adapted version from https://cies2018.org/wp-content/uploads/List-of-Countries-by-Region-UN-Annex-II.pdf

* Appended