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REVIEW

Prevalence of tree nut allergy in Europe: A systematic review and meta-analysis

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Abstract

In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) published the first systematic review that summarized the prevalence of food allergy (FA) and food sensitization in Europe for studies published 2000–2012. However, only summary estimates for tree nut allergy (TNA) were feasible in that work. In the current update of that systematic review, we summarized the prevalence of tree nut allergy/sensitization to individual tree nuts. Six databases were searched for relevant papers published 2012–2021 and 17 eligible studies were added to the 15 studies already identified between 2000 and 2012, giving a total of 32 studies. Of the investigated tree nuts, meta-analysis was possible for hazelnut, walnut, almond, and in few cases, for cashew, and Brazil nut. The lifetime self-reported prevalence was 0.8% (95% CI 0.5–1.1) for hazelnut and 0.4% (0.2–0.9) for walnut. The point self-reported prevalence was 4.0% (2.9–5.2) for hazelnut, 3.4% (2.0–4.9) for Brazil nut, 2.0% (1.1–2.9) for

almond, and 1.8% (1.1–2.5) for walnut. Point prevalence of food challenge-confirmed TNA was 0.04% (0.0–0.1) for hazelnut and 0.02% (0.01–0.1) for walnut. Due to paucity of data, we could not identify any meaningful and consistent differences across age groups and European regions.

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

1 | INTRODUCTION

In 2014, the European Academy of Allergy and Clinical Immunology (EAACI) published the first systematic review and meta-analysis on the frequency of food allergy (FA; i.e., immune response on exposure to specific foods resulting in adverse health effects) and food sensitization (i.e., specific immunoglobulin E and/or skin prick test positivity to a food allergen) in Europe.[1,2] We have recently updated the frequency estimates on FA/sensitization in Europe, including summary estimates for tree nut allergy (TNA) and sensitization, up to 2021.[3,4] According to the updated estimates, the prevalence of any TNA varies from 0.9% and 2.4% for self-reported lifetime and point prevalence, respectively, to 0.04% for food challenge (FC) confirmed TNA.

The prevalence of allergies to individual tree nuts may vary substantially as they are not homogenous groups. There are potential differences in prevalence of individual tree nut allergies between age groups and European regions, which are important to explore to guide clinical care/research priorities. Although cross-reactivity exists between different tree nuts, many subjects with one TNA can tolerate other tree nuts.[5]

In the current work, we present the prevalence estimates for specific TNA/sensitization, including hazelnut, walnut, almond, Brazil nut, cashew nut, pistachio, chestnut, pecan nut, and pine nut based on data published between 2000 and 2021. There were no available data on macadamia nut allergy.

2 | METHODS

2.1 | Protocol registration, search strategies, and study identification and selection

The protocol for this study was registered with the International Prospective Register of Systematic Reviews prior to performing the systematic review (PROSPERO; registration number CRD42021266657).

The search strategy was adapted from the methodology used in the 2014 EAACI review.[1,2] We searched six electronic databases (MEDLINE, EMBASE, CINAHL, Web of Science, Cochrane Library, and Scopus) for relevant studies (papers or conference abstracts) published between September 2012 and June 2021. Eligible studies were then added to the studies included in the systematic review published in 2014, which was based on papers published between January 2000 and September 2012. For the search strategy we maintained all keywords previously employed in the 2014 EAACI review and added new keywords to ensure the inclusion of all relevant studies, as well as to account for developments that have occurred in the respective databases over the last 10 years.

No language restriction was employed in searching the databases. In case of papers or conference abstracts published in a language other than English, we consulted with researchers who were fluent in the language used in the study. When no expert was available to translate the text, we extracted data on FA from the English abstract, while at the same time employed Google Translate to translate the main text. The types of studies eligible for this review included systematic reviews, cross-sectional, cohort, and case control studies, clinical trials, and routine healthcare studies. Narrative reviews, discussion papers, non-research letters or editorials, case-series, case-studies, and animal studies were excluded.

All eligible studies were first screened by title and/or abstract, and later by full text by two pairs of independent reviewers (SN/GS and YA/MA). Disagreement between the pairs was resolved either by consensus or by consulting the project PI (BN). We employed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram for reporting the screening procedure. The full search strategy and screening procedure have been reported previously.[3,4]

2.2 | Outcomes

All types of tree nuts were investigated in the review, that is, hazelnut, walnut, almond, Brazil nut, cashew nut, pistachio, pecan nut, chestnut, pine nut, and macadamia nut.[6,7] Although the systematic review aimed to provide up-to-date data on the incidence, prevalence, and time trends for TNA, data on incidence and time trends were scarce and not sufficiently homogenous to perform meta-analysis. Therefore, only data on lifetime and point prevalence were included in the meta-analysis. We did not differentiate between IgE-mediated and non-IgE-mediated FA, as this was not usually differentiated in the extant literature. Furthermore, although IgE-mediated allergy to tree nuts includes varying syndromes, including pollen-food syndrome, lipid transfer protein syndrome, and allergy to storage proteins, each with distinct clinical presentations and severity, it was not possible to differentiate these syndromes, thus the prevalence estimates reported in the manuscript constitute the entirety of manifestations and not only primary FA.

The following prevalence outcomes were investigated: (1) lifetime prevalence (i.e., prevalence of subject reporting ever having a reaction or hypersensitivity to respective foods) and point prevalence (i.e., prevalence of subjects reporting having a reaction or hypersensitivity to respective foods currently or during the past 12 months) of self-reported TNA; (2) lifetime prevalence and point prevalence of self-reported physician-diagnosed TNA (i.e., physician-diagnosed FA reported by subjects); (3) point prevalence of specific immunoglobulin E (sIgE) positivity to tree nuts; (4) point prevalence of SPT (skin prick test) positivity to tree nuts; (5) point prevalence of symptoms plus sIgE positivity to tree nuts; (6) point prevalence of symptoms plus SPT positivity to tree nuts; (7) point prevalence of FC (oral food challenge [OFC] or double-blind placebo-controlled food challenge [DBPCFC]) positivity; and (8) point prevalence of FC positivity (OFC

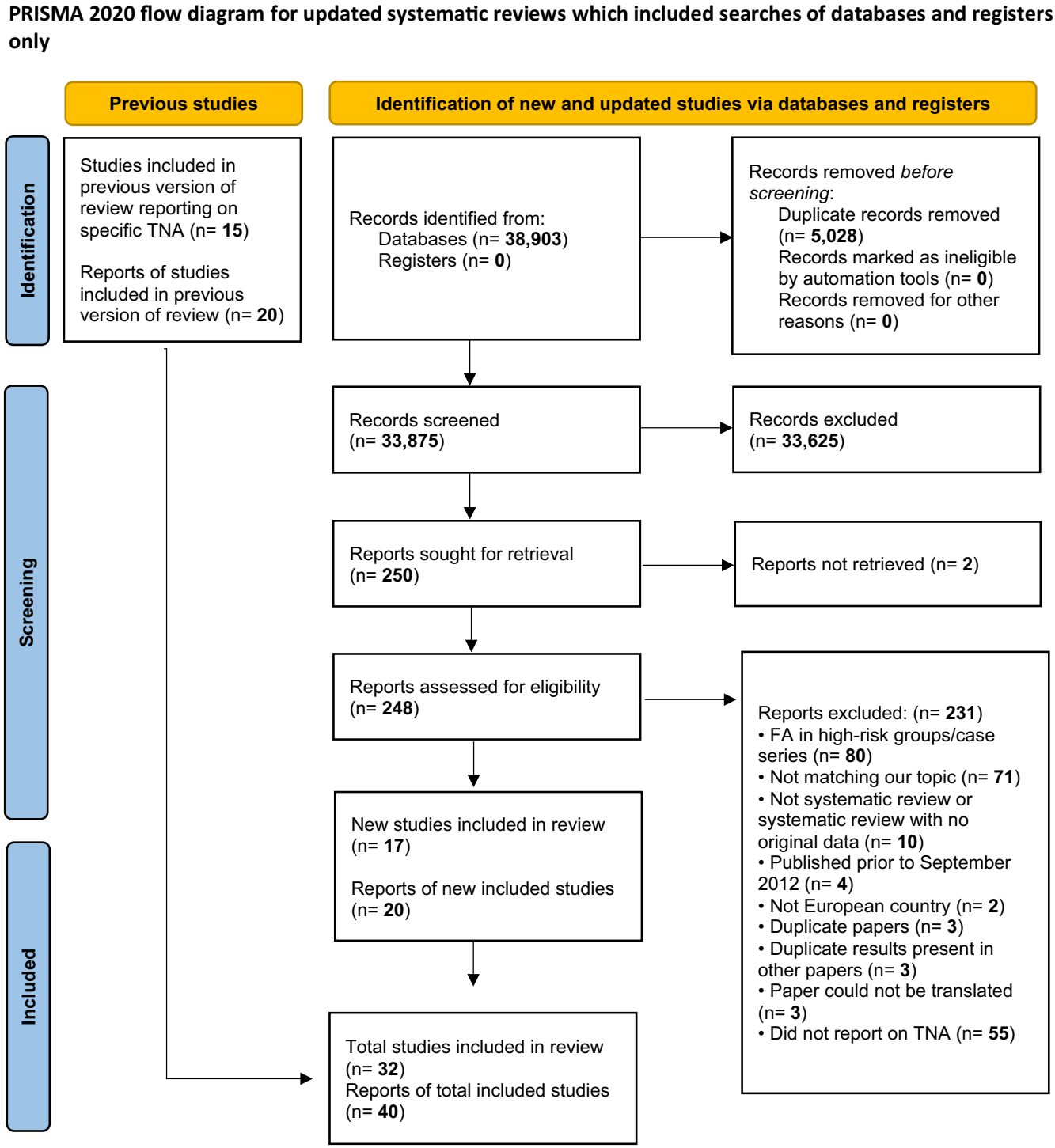

FIGURE 1 PRISMA flow diagram for updated systematic review on prevalence of food allergy to the eight common foods in Europe, 2000–2021.

TABLE 1 Summary of the characteristics and main results of the studies published 1 January 2000–30 June 2021 included in the review.

Reference, country	Study design	Study population *N* (children/adults; source of study population)		Age of subjects	Outcome studied and assessment method	
		Number approached	Number participated		Outcome(s) studied	Method of outcome assessment
Baricic et al., Croatia[9]	Cross-sectional study	Not indicated	702	6–48 months old	Hazelnut	Self-reported, SPT, sIgE
Burney et al.; Woods et al., Europe, United States of America, Australia, New Zealand[10,11]	Cross-sectional study	Not indicated	17,280	18–27 years old	Hazelnut, walnut	sIgE
Burney et al.; Lyons et al., Le et al., Switzerland, Spain, Greece, Poland, Bulgaria, Lithuania, Iceland, The Netherlands[12–14]	Cross-sectional study	All countries 30,420	All countries 17,366 Switzerland 2250 Spain 943 The Netherlands 3865 Poland 1499 Bulgaria 2118 Greece 1979 Lithuania 2598 Iceland 2114	20–54 years old	Hazelnut, walnut	Self-reported, sIgE, sIgE + symptoms, DBPCFC
Caffarelli et al., Italy[15]	Cross-sectional study	900	625	5–14 years old	Hazelnut	Self-reported
Clausen et al., Sweden[16]	Cohort study	5654	3637	0–12 years old	Hazelnut, almond	Self-reported
De Jong et al., The Netherlands[17]	Cohort study	7393	5471	10 years old	Hazelnut, cashew nut	SPT, SR-physician diagnosis
Depner et al., Austria, Finland, France, Germany, and Switzerland[18]	Cohort study	1133	793	0–12 months old	Hazelnut	sIgE
Dereci et al., Turkey[19]	Cross-sectional study	20,800	15,783	6–18 years old	Hazelnut	Self-reported, SPT/PTP, DBPCFC, OFC
Eller et al., Kjaer et al., Johnke et al., Denmark[20–22]	Cohort study	1095	562	6 years old	Hazelnut, Brazil nut	Self-reported, SPT, sIgE, OFC, DBPCFC
Fedorova et al., Russia[23]	Cross-sectional study	Not indicated	13,010	7–10 years old	Hazelnut	Self-reported, SPT, sIgE

Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Comments	Overall risk of bias assessment
Point prevalence	Data not available	Not considered in meta-analysis. Hazelnut allergy was investigated by authors, but data were not shared	Moderate
Point prevalence	sIgE point prevalence for all countries at 18–27 years: Hazelnut 3.1% Walnut 1.8% Confidence intervals not available.	Not considered in meta-analysis. Estimate of sensitization is a weighted average over all countries in the study excluding birth positivity. No weighting factor or baseline data was given, so we were unable to calculate the confidence intervals form meta-analysis.	Moderate
Point prevalence	sIgE point prevalence in adults (20–54 years) - Hazelnut: Al centers: 9.3% Switzerland: 17.8%; Spain: 6.0%; The Netherlands: 11.9%; Poland: 6.5%; Bulgaria: 6.3%; Iceland: 1.3% - Walnuts: All centers: 3.0%; Switzerland: 5.6%; Spain: 7.6%; The Netherlands: 1.9%; Poland: 3.6%; Bulgaria: 2.7%; Iceland: 0.1% sIgE + symptoms point prevalence for hazelnut and allergy see Figures 8 and 9 Data on self-reported and DBPCFC positive allergy were reported by Le et al. only for Netherlands: SR point prevalence: Hazelnut: 0.6% (0.4–0.9) Walnut: 0.6% (0.4–0.9) DBPCFC point prevalence Hazelnut: 0.2 (0.1–0.4)	For Burney et al. 2014 sIgE point prevalence was estimated as the prevalence of those with a specific IgE response to a particular food among 'cases' and 'controls' weighted back to the general population according to the sampling fraction by which these had been selected for further study. Since the sampling factor was not mentioned by the authors, it was not possible to define precise confidence intervals for meta-analysis. Therefore, data for sIgE positivity have not been included in meta-analysis. For Lyons et al. 2019 data on population prevalence estimation were obtained by the authors using a weighting procedure fully explained in the paper online repository. DBPCFC was employed to assess FA to hazelnut, A summary of the DBPCFC is presented by the authors in Table 3. Participation rate to DBPCFC was low, preventing the calculation of a meaningful population-based prevalence estimate. Data on DBPCFC were therefore not reported in meta-analysis.	Strong
Lifetime prevalence	SR lifetime prevalence of hazelnut allergy at 5–14 years: 0.3% (0.1–1.2)		Moderate
Point prevalence	SR physician diagnosed point prevalence in 12 years children: Hazelnut: 1.6% (1.2–2.0) Almonds: 0.8% (0.5–1.1)	Data on point prevalence of SR physician diagnosed allergy were not considered for meta-analysis as there were not sufficient records from other studies to allow data synthesis	Moderate
Point prevalence	SPT point prevalence at 10 years: Hazelnut: 4.1% (3.5–4.7) Cashew nut: 1.3% (1–1.7) SR physician diagnosed: Cashew nut: 1.4% (1.1–1.8)	Data on point prevalence of SR physician diagnosed allergy were not considered for meta-analysis as there were not sufficient records from other studies to allow data synthesis	Moderate
Point prevalence	Data on sIgE positivity to hazelnut are presented in a bar graph for children aged 0–12 months	Not considered in meta-analysis as it was not possible to calculate confidence intervals.	Weak
Lifetime and point prevalence	SR lifetime prevalence hazelnut allergy: 0.2% (0.2–0.3) Point prevalence SPT hazelnut allergy: 0.1% (0.1–0.16); Point prevalence of DBPCFC confirmed hazelnut allergy in 6–18 years old children: 0.0% (0.0–0.1)		Strong
Point prevalence, cumulative incidence	Not available	Not considered in meta-analysis. Hazelnut and Brazil nut allergy investigated by authors, but data not shared	Moderate
Point prevalence	Point prevalence hazelnut allergy at 7–10 years was 0.1%. The method of assessment was not specified in the main text.	Not considered in meta-analysis. In Fedorova et al. 2014a, the authors claim to have investigated SR, sIgE and SPT positive allergy to hazelnut and peanuts. Contextually, the authors report that point prevalence allergy to peanut and to hazelnut is 0.1% and 0.1%, respectively, but do not specify if the record regards SR, sIgE or SPT positivity, or a combination of all.	Moderate

(Continues)

TABLE 1 (Continued)

Reference, country	Study design	Study population *N* (children/adults; source of study population)		Age of subjects	Outcome studied and assessment method	
		Number approached	Number participated		Outcome(s) studied	Method of outcome assessment
Gelincik et al., Turkey[24]	Cross-sectional study	17,064	11,816	≥18 years old	Hazelnut, walnut	DBPCFC
Grabenhenrich et al., Erhard et al., Iceland, United Kingdom, The Netherlands, Germany, Poland, Lithuania, Spain and Greece[25,26]	Cohort study	6150	All countries 6069 Iceland 945 United Kingdom 454 The Netherlands 652 Germany 1001 Poland 819 Greece 561 Spain 688 Lithuania 2598	6–10 years old	Hazelnut, cashew nut, pine nut, walnut	Self-reported, SR-physician diagnosis, sIgE, SPT, DBPCFC
Haftenberger et al.[27]	Cross-sectional study	8152	7988	18–79 years old	Hazelnut, almond	SR- sIgE
Johansson et al., Sweden and Norway[28]	Cross-sectional study	Not indicated	Sweden 1002; Norway 500	Adults	Hazelnut	sIgE
Kaya et al., Turkey[29]	Cross-sectional study	11,233	10,096	11–15 years old	Hazelnut, walnuts, pistachio	Self-reported, physician diagnosis, SPT, sIgE, OFC; DBPCFC
Kristinsdottir et al., Iceland[30]	Cohort study	No information	1341	1 year old	Almond	Self-reported, History + SPT
Kvenshagen et al., Norway[31]	Cohort study	Not indicated	609	2 years old	Hazelnut	Self-reported, SPT, sIgE, OFC, DBPCFC
Lyons et al., Switzerland, Spain, Greece, Poland, Bulgaria, Lithuania, Iceland, and The Netherlands[32]	Cross-sectional study	28,589	16,935	7–10 years old	Hazelnut, walnut	sIgE, sIgE + symptoms
Marklund et al., Sweden[33]	Cross-sectional study	2064	1488	13–21 years old	Almond	Self-reported

Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Comments	Overall risk of bias assessment
Point prevalence	Point prevalence in adults: History + SPT (hazelnut) 0.0% (0.0–0.0) History + sIgE (hazelnut) 0.0% (0.0–0.0) Point prevalence of DBPCFC confirmed allergy in adults: Hazelnut: 0.0% (0.0–0.0) Walnut: 0.0% (0.0–0.0)	Data on history of allergy and SPT/sIgE positivity were not considered from meta-analysis as there were not sufficient records from other studies to allow data synthesis.	Moderate
Lifetime and point prevalence	Lifetime prevalence of SR hazelnut allergy for each centre: see Figure 2. Lifetime prevalence of SR physician diagnosed hazelnut allergy for each centre: see Figure 4 Point prevalence of SPT positive hazelnut allergy (all centres): 5.2% (4.4–6.2) DBPCFC positivity: Hazelnut 0.3% (0.1–0.7) (all centres); 0.4% (0.1–2.1) in Germany Cashew nut: 0.1% (0.03–0.35) Pine nut: 0.1% (0.03–0.35) Walnut 0.05% (0.01–0.27)		Moderate
Point prevalence	sIgE point prevalence at age 18–79 years: Hazelnut 15.7% (14.6–16.8) Almond 4.0% (3.5–4.6)		Moderate
Point prevalence	Point prevalence of sIgE positive sensitization in adults (Sweden + Norway): 2.5% (1.9–3.5) Sweden 3.5% (2.5–4.8) Norway 0.6% (0.2–1.8)		Moderate
Point prevalence	Point prevalence of hazelnut sensitization/allergy: sIgE: 0.0% (0–0.1); OFC: 0.0% (0.0–0.1); DBPCFC: 0.0% (0–0.1) Point prevalence of walnut sensitization/allergy: SPT: 3% (2.1–4.2); sIgE: 0.0% (0.0–0.1); OFC: 0.0% (0–0.1); DBPCFC: 0.0% (0.0–0.1) Point prevalence of pistachio sensitization: SPT: 0.0% (0–0.1); sIgE: 0.0% (0–0.1)		Moderate
Point prevalence	Point prevalence SR almond allergy: 0.1% (0.0–0.4) Point prevalence of History + SPT positive almond allergy: 0.1% (0.0–0.4)	Not considered in meta-analysis due to unclear data	Moderate
Point prevalence	Not available	Not considered in meta-analysis. Hazelnut allergy investigated by authors, but data not shared	Moderate
Point prevalence	Point prevalence of sIgE positivity to hazelnut and to walnut for each centre: see Figure 5 Symptoms + sIgE positivity point prevalence: Hazelnut: Switzerland: 0.8% (0.1–2.3), Spain: 0.5% (0.0–1.8), Greece: 0.3% (0.1–1.9), The Netherlands: 0.7% (0.1–1.9), Lithuania: 2.1% (0.4–5.3), Poland: 0.8% (0.16–1.9), Iceland: 0.1% (0.0–0.6) Walnut: Switzerland: 0.3% (0.0–1.3), Spain: 0.5% (0.0–1.8), Greece: 0.6% (0.0–2.5), The Netherlands: 0.5% (0.1–1.5), Lithuania: 0.0% (0.0–0.9), Poland: 0.5% (0.0–1.4), Iceland: 0.0% (0.0–0.3)		Strong
Point prevalence	SR point prevalence at 13–21 years: Almond 4.1% (3.2–5.3)		Moderate

(Continues)

TABLE 1 (Continued)

Reference, country	Study design	Study population *N* (children/adults; source of study population)		Age of subjects	Outcome studied and assessment method	
		Number approached	Number participated		Outcome(s) studied	Method of outcome assessment
Mortz, et al., Denmark[34]	Cross-sectional study	Not indicated	460	Not indicated	Hazelnut	SPT and sIgE
Mustafayev et al., Turkey[35]	Cross-sectional study	7653	6963	6–7 and 10–11 years old	Hazelnut, walnut, pistachio	Self-reported, SPT (positive test reported by parents), SPT (measured), sIgE, OFC
Orhan et al., Turkey[36]	Cross-sectional study	3500	2739	6–9 years old	Hazelnut, walnut	Self-reported, SPT + history, OFC, DBPCFC
Osterballe et al., Denmark[37]	Cross-sectional study	1094	843	Mean age 22 years	Hazelnut, walnut, almond, brazil nut	Self-reported, SPT, OFC, DBPCFC
Rentzos et al., Sweden[38]	Cross-sectional study	30,000 (1172 for stage 2)	18,083 (1042 for stage 2)	16–75 years old	Hazelnut, almond, brazil nut, chestnut	Self -reported, sIgE, sIgE + symptoms
Roberts et al. and Lack et al., United Kingdom[39,40]	Cohort study	13,971	12,090	0–7 years old	Hazelnut, walnut, cashew, almond, brazil nut, pecan nut	SPT
Schäfer et al., Germany[41]	Nested case–control study	2539	1537	25–74 years old	Hazelnut	SPT

Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Comments	Overall risk of bias assessment
Point prevalence	Not available.	Not considered in meta-analysis. Only data on concomitant sesame plus hazelnut allergy were available	Moderate
Point and life-time prevalence	Hazelnut: SR point prevalence at 10–11 years: 1.5% (1.2–1.8); SPT positivity point prevalence at 10–11 years: 0.4% (0.3–0.6) OFC point prevalence at 10–11 years: 0.0% (0–0.1) Walnut: SR point prevalence at 10–11 years: 1.2% (1.0–1.5); SPT point prevalence at 10–11 years: 4.5% (4.0–5.0) OFC point prevalence at 10–11 years: 0.0% (0.0–0.16 Pistachio: SR point prevalence at 10–11 years: 0.8% (0.6–1.0)		Moderate
Lifetime and point prevalence	Point prevalence of DBPCFC at 6–9 years: Hazelnut 0% (0.01–0.1) Walnut 0% (0.01–0.1) SR lifetime prevalence at 6–9 years: Hazelnut 0.3% (0.1–0.6) Walnut 0.1% (0.0–0.3) History and SPT point prevalence at 6–9 years: Hazelnut 0.1% (0.0–0.3) Walnut 0.1% (0.0–0.3)		Moderate
Point prevalence	SR point prevalence at mean age 22 years: Almond 0.2% (0.1–0.9) Brazil nut 2.7% (1.8–4.1) Hazelnut 6.6% (5.2–8.5) Walnut 0.5% (0.2–1.2)		Moderate
Point prevalence	Point prevalence at age 17–78 years: Hazelnut: - SR: 8.9% (7.1–10.6); – sIgE positivity: 13.3% (11.2–15.4); – Symptoms + sIgE positivity: Chestnut: - SR: 0.5% (0.1–0.9) Almond: - SR 3.7% (2.5–4.8); – sIgE positivity: 3.0% (1.9–4.0); – Symptoms + sIgE positivity: 0.8% (0.2–1.3) Brazil nuts: - SR 4.2% (3.0–5.4); – sIgE positivity: 0.9% (0.3–1.5); – Symptoms + sIgE positivity: 0.4% (0.0–0.8)		Strong
Point Prevalence	SPT point prevalence at 0–7 years: Almond 0.5% (0.2–0.9) Brazil nut 0.5% (0.3–0.9) Cashew nut 0.4% (0.2–0.8) Hazel nut 0.1% (0.0–0.4) Pecan nut 0.2% (0.1–0.4) Walnut 0.5% (0.3–0.9)		Moderate
Point prevalence	SR lifetime prevalence in adults 5.3% SPT point prevalence in adults (hazelnut) 11.3%	Not considered in meta-analysis. Number of included studies unclear.	Moderate

TABLE 1 (Continued)

Reference, country	Study design	Study population *N* (children/adults; source of study population)		Age of subjects	Outcome studied and assessment method	
		Number approached	Number participated		Outcome(s) studied	Method of outcome assessment
Soost et al. and Zuberbier et al., Roehr et al., Germany[42–44]	Cross-sectional study	13,300	All: 4093 Age 0–17 years: 739 Age 18–79 years: 3227	0–79 years old	Hazelnut, walnut	Self-reported, SPT + history, DBPCFC
Sterner et al., Sweden[45]	Cohort study	2568	1333	13–14 years old	Hazelnut	Component-resolved diagnostic
Strinnholm et al.; Winberg et al, Sweden[46,47]	Cohort study	2612	2585	7–12 years old	Almond	Self -reported
Venter al 2008; Dean et al.; Venter et al., United Kingdom[48–51]	Cohort study	1063	827	1–11 years old	Hazelnut, cashew nut	History or OFC
von Hertzen et al. Finland and Russia[52]	Cross-sectional study	Finland: 546 child–mother pairs	Finland: 413 children, 409 mothers	7–16 years children	Hazelnut	SPT
Westerlaken-van Ginkel et al. The Netherlands[53]	Cohort study	167,729	78,890	Adults	Almond, cashew nut, pistachio, walnut, hazelnut	Self-reported

Note: (a) Fedorova et al 2014 was extracted from conference abstracts. Clausen et al. data were extracted from a university thesis. (b) Data recorded were reported as "studies"; therefore, one row may combine data extracted from more than one paper reporting on the same study.

Abbreviations: CI, confidence interval; DBPCFC, double blind placebo-controlled food challenge; OFC, oral food challenge; sIgE, specific immunoglobulin E; SPT, skin prick test; SR, self-reported.

or DBPCFC) and/or clinical history of FA (i.e., FA confirmed by judgment of a physician, based on convincing clinical history, without food challenge).

Meta-analysis was considered meaningful for all outcomes with three or more records available.

2.3 | Data extraction, analysis, and synthesis

Data extraction was carried out by the same pairs of reviewers who participated in the study screening and selection process. Any disagreement was resolved by consensus or by consulting the project PI. All newly extracted data were recorded in a customized data extraction form. In case of unclear data, a request for clarification was sent to the corresponding author of the study. When possible, we recalculated the prevalence and/or incidence of TNA based on the available data using minimally measured events, rather than extrapolated ones. The Wilson score without continuity correction was employed to obtain the 95% confidence intervals (95% CI).[8] The extracted data were then combined with the ones already obtained in the 2014 review. All European countries defined according to the Unite Nations definition (see Appendix 1) were included in the systematic review. However, meta-analysis was performed only on countries included in the Organization for Economic Cooperation and Development (OECD), Russia, and Lithuania, as was done in the 2014 EAACI review.[1,2] Random effects meta-analysis was performed to derive pooled prevalence estimates for TNA using the Stata 16 software (StataCorp LLC, College Station). We assessed heterogeneity using

Occurrence measure(s)	Main results of the frequency of FA (FA) Percentage (95% CI)	Comments	Overall risk of bias assessment
Point and lifetime prevalence	History and SPT point prevalence: Hazelnut 0–17 years 2.0% (1.2–3.3) Children and adults 23.0% (20.2–26.0) Walnut 0–17 years 0.7% (0.3–1.6) Children and adults 7.1% (5.5–9.1) DBPCFC point prevalence of Hazelnut: 0–14 years 0.7% (0.3–1.7) 15–17 years 4.3% (2.0–9.0) All children 1.4% (0.7–2.5)		Moderate
Point prevalence	Only data on component-resolved diagnostic were available.	Not considered in meta-analysis. Hazelnut was investigated only by component-resolved diagnostic test and not with traditional tests	Moderate
Point prevalence	SR point prevalence at age 7–8 years: Almonds 2.0% (1.5–2.6)		Moderate
Point, lifetime and period prevalence, cumulative incidence	History or OFC point prevalence At 1 year: Cashew nut 0.0% (0.0–0.4) Hazelnut 0.0% (0.0–0.4) At 2 years: Cashew nut 0.0% (0.0–0.4) Hazelnut 0.0% (0.0–0.4) At 3 years: Cashew nut 0.1% (0.0–0.6) Hazelnut 0.1% (0.0–0.6)	Data on history of allergy or OFC positivity were not considered for meta-analysis as there were not sufficient records from other studies to allow data synthesis	Moderate
Point prevalence	SPT point prevalence in Finland Children (7–16 years): 6.3% (4.0–9.8) Mothers 11.3% (8.1–15.6)		Moderate
Point prevalence	SR point prevalence at mean age 47.5 years: Almond 1.0% (0.9–1.1) Cashew 0.7% (0.6–0.8) Pistachio 0.5% (0.4–0.5) Walnut: 1.8 (1.7–1.9) Hazelnut: 2.1 (2.0–2.2)		Moderate

the I^2 statistic. All studies which provided adequate and clinically and methodologically comparable numerical data were included in the meta-analysis. Meta-analysis was also performed stratifying by age groups (children [0–17 years] and adults [≥18 years]) and by European regions (Northern, Eastern, Southern, and Western Europe) following the classification by the United Nations (see Appendix 1). As an exception, United Kingdom, was assigned to Western instead of Northern Europe, as was done in the 2014 EAACI review.[1,2]

2.4 | Risk of bias assessment

The risk of bias assessment for individual studies was appraised with an adapted version of the Critical Appraisal Skills Programme (CASP; http://www.casp-uk.net) quality assessment tool, as employed in the 2014 review. Assessment was performed by the same pairs of reviewers who performed the literature screening and data extraction. Discrepancies were resolved by consensus or after consultation with the project PI.

3 | RESULTS

The study selection and screening process are summarized in the PRISMA flow chart (Figure 1). We identified 38,903 new records published between 2012 and 2021. After de-duplication, and upon completing the screening process, we included 17 new studies published during 2012–2021, which were added to the 15 studies

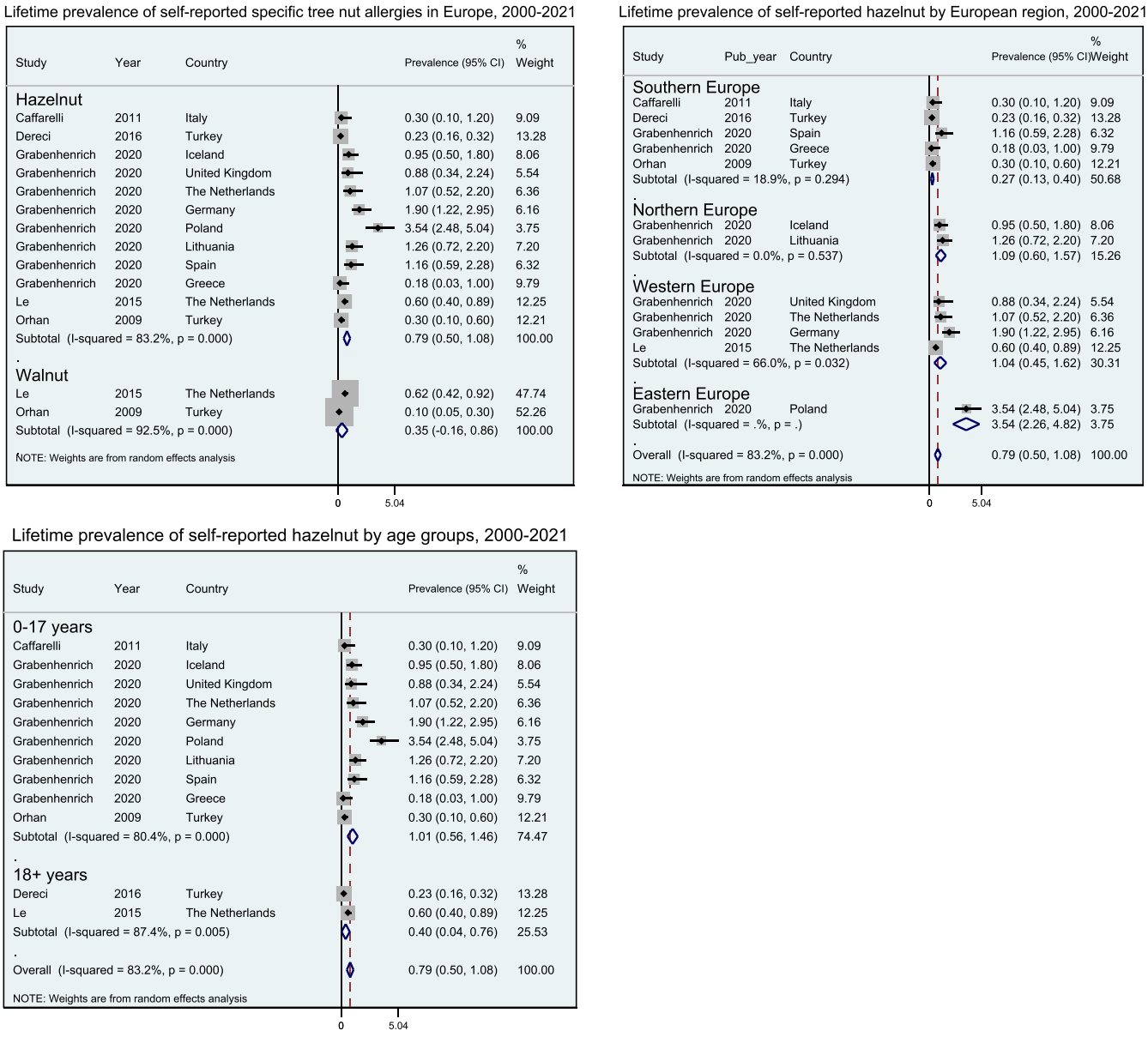

FIGURE 2 Lifetime prevalence of self-reported specific tree nut allergy (hazelnut and walnut) and lifetime prevalence of hazelnut allergy stratified by age and by European region.

already available from the EAACI 2014 review, giving a total of 32 studies included in the current systematic review, and meta-analysis.[8–52] Table 1 presents a summary of the studies involved, including the main characteristics and results of each study. Data recorded were reported as "studies"; therefore, one row may combine data extracted from more than one paper reporting from the same study. Nineteen out of the 32 included studies were cross-sectional studies,[9–15,19,23,24,27–29,32–38,42–44,52] 12 were cohort studies,[16–18,20–22,25,26,30,31,39,40,45–51,53] and one study was a nested case–control study.[41] Only estimates of point and lifetime prevalence were available across the studies. Most studies were graded at a moderate risk of bias. Figure S1 summarizes the grading of the main CASP quality assessment features for all studies.

The pooled lifetime and point prevalence estimates for specific TNA according to the different outcomes investigated (i.e., self-reported TNA, FC positive TNA) are presented in Figures 2–9. Overall, the heterogeneity between pooled studies was significant ($I^2 \geq 80$ in each case). The meta-analysis-derived estimates for TNA/sensitization prevalence are synthesized below.

3.1 | Hazelnut allergy

Hazelnut allergy or sensitization was investigated in 29 studies[9–29,31,32,34–44,48–53] of which 20 were included in meta-analysis. The overall lifetime and point prevalence of self-reported hazelnut allergy were 0.8% (95% CI 0.5–1.1) and 4.0% (CI 2.9–5.2), respectively (Figures 2 and 3). Lifetime prevalence of self-reported physician-diagnosed hazelnut allergy was 0.8% (CI 0.4–1.2) (Figure 4). Point prevalence of sensitization to hazelnut was 8.1% (4.6–11.6) for

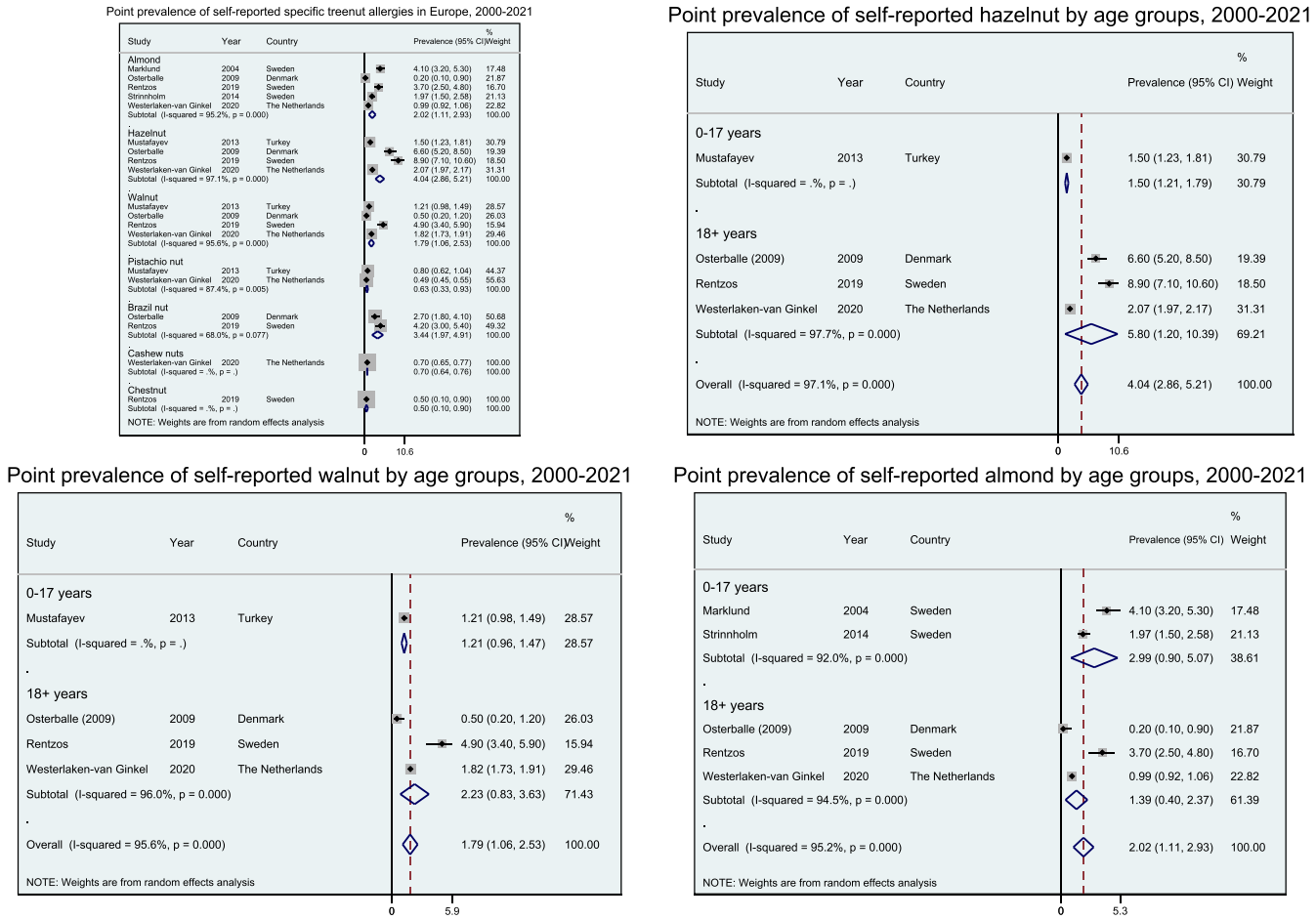

FIGURE 3 Point prevalence of self-reported specific tree nut allergy (almond, hazelnut, walnut, pistachio, Brazil nut, and cashew nut) and point prevalence of hazelnut, walnut, and almond allergy stratified by age.

sIgE positivity (Figure 5), 2.2% (1.5–2.9) for SPT positivity (Figure 6), 1.0% (0.5–1.4) for sIgE positivity plus symptoms (Figures 7 and 8), and 0.04% (0.0–0.1) for FC positivity (Figure 9). Point prevalence of hazelnut allergy or sensitization was higher in adults than in children for most outcomes investigated, while lifetime prevalence of self-reported hazelnut allergy was higher in children. Estimates on lifetime prevalence of self-reported physician-diagnosed hazelnut allergy, and on point prevalence of SPT sensitization to hazelnut were only available in children (Figures 2–9). No consistent pattern was seen in prevalence of hazelnut allergy or sensitization across European regions (Figures 2–9).

3.2 | Walnut allergy

Walnut allergy or sensitization was investigated in 12 studies[10–14,24–26,29,32,35–27,39–40,42–44,53] of which 11 were included in meta-analysis. The overall lifetime and point prevalence of self-reported walnut allergy were 0.3% (0.2–0.9) and 1.8% (1.1–2.5), respectively (Figures 2 and 3), although for lifetime prevalence only two studies were available. Point prevalence of sensitization to walnut was 4.1% (2.2–5.9) for sIgE positivity (Figure 5), 2.7% (0.3–5.6) for SPT positivity (Figure 6), 0.1% (0.0–0.2) for sIgE positivity plus symptoms (Figures 7 and 8), and 0.02% (0.0–0.1) for FC positivity (Figure 9). The point prevalence of self-reported walnut allergy was higher in adults than in children (Figure 3). Point prevalence of sIgE sensitization plus symptoms was 0.1% both in children and in adults (Figure 8). For all the other outcomes investigated differentiation by age group was not possible. Differentiation by European region was only possible for point prevalence of sIgE and of sIgE plus symptoms, but no consistent pattern was seen across European regions (Figures 5 and 8).

3.3 | Almond allergy

Almond allergy or sensitization was investigated in nine studies,[16,27,30,33,37–40,46,47,53] of which seven were included in meta-analysis. The overall point prevalence of self-reported almond allergy was 2.0% (1.1–2.9) (Figures 3). Point prevalence of sIgE positivity to almond was 3.6% (2.6–4.6) (Figure 5), based on only two studies, while for both SPT positivity and IgE positivity plus symptoms only one study was available (Figures 6 and 7). No studies were available for the other outcomes investigated. The point prevalence of self-reported almond allergy was higher in children than in adults (3.0%

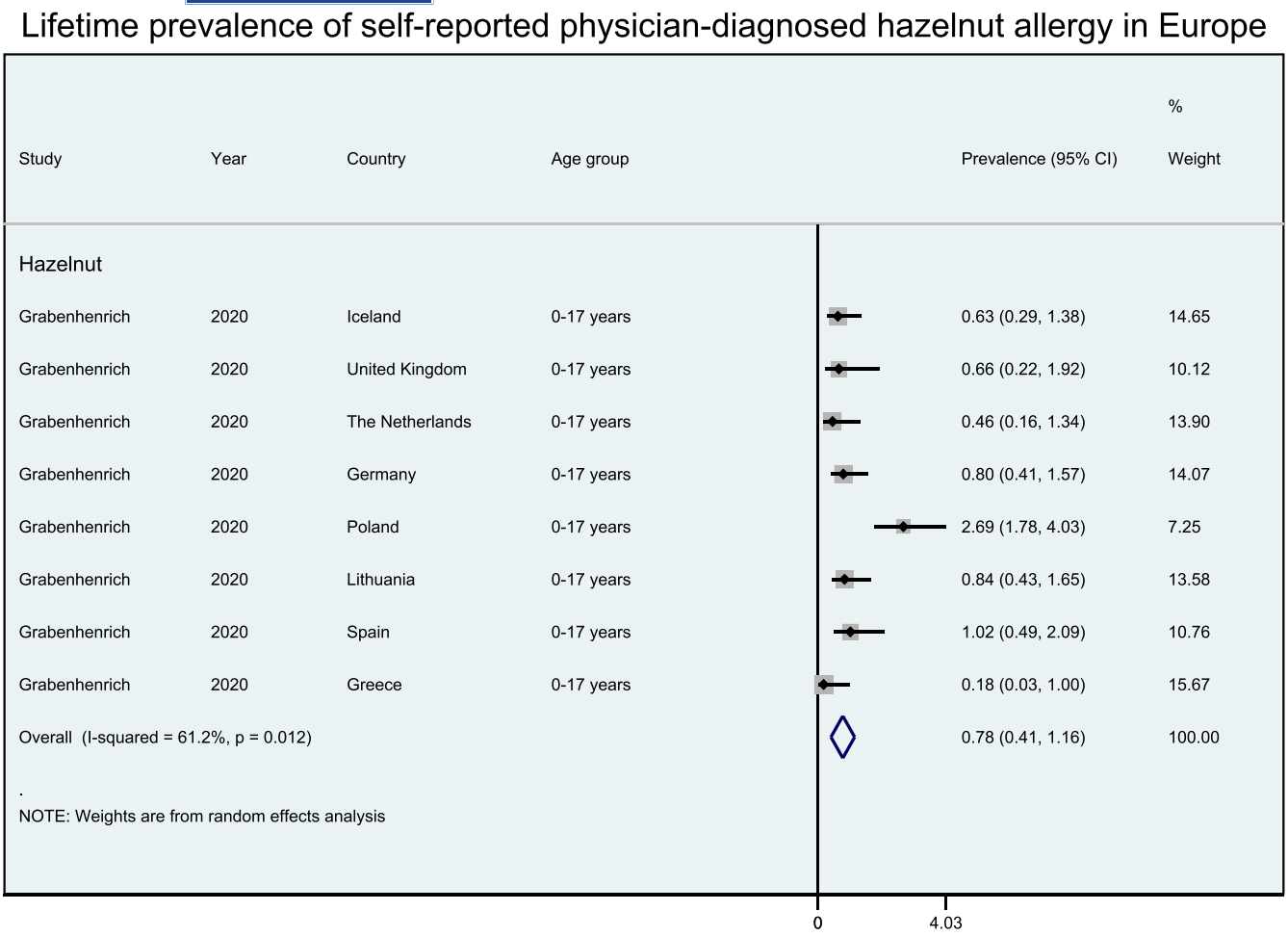

FIGURE 4 Lifetime prevalence of self-reported physician diagnosed hazelnut allergy.

vs. 2.0%) (Figure 3). However, there were no age-stratified estimates for the other outcomes, nor by European region.

3.4 | Cashew nut allergy

Cashew nut allergy or sensitization was investigated in five studies[17,25,26,39,40,48–51,53] of which four were included in meta-analysis. Point prevalence of self-reported and FC positivity to cashew nut allergy were reported by only one study (Figures 3 and 9). The overall point prevalence for SPT positive cashew nut allergy was 0.8% (0.0–1.7), based on only two studies (Figure 6). For all the other outcomes, no estimates were available. There were no age-stratified estimates, nor were there estimates by European region.

3.5 | Brazil nut allergy

Brazil nut allergy or sensitization was investigated in four studies[20–22,37–41] of which three were included in meta-analysis. The overall point prevalence of self-reported Brazil nut allergy was 3.4% (2.0–4.9), based on two studies (Figure 3). For sIgE positivity, SPT positivity and sIgE positivity plus symptoms only one study was available (Figures 5–7). There were no age-stratified estimates, nor were there estimates by European region.

3.6 | Pistachio allergy

Pistachio allergy or sensitization was investigated in three studies.[29–35,53] All three studies were included in meta-analysis. The overall point prevalence of self-reported pistachio allergy was 0.6% (0.3–0.9) based on only two studies (Figure 3). For sIgE positivity and SPT positivity only one study was available (Figures 5 and 6), while no estimates were available for all the outcomes investigated. There were no age-stratified estimates, nor were there estimates by European region.

3.7 | Chestnut, pecan nut, pine nut, and macadamia nut allergy

The data on pecan nut, chestnut, pine nut, and macadamia nut allergy or sensitization were scarce. The only study available on chestnut reported

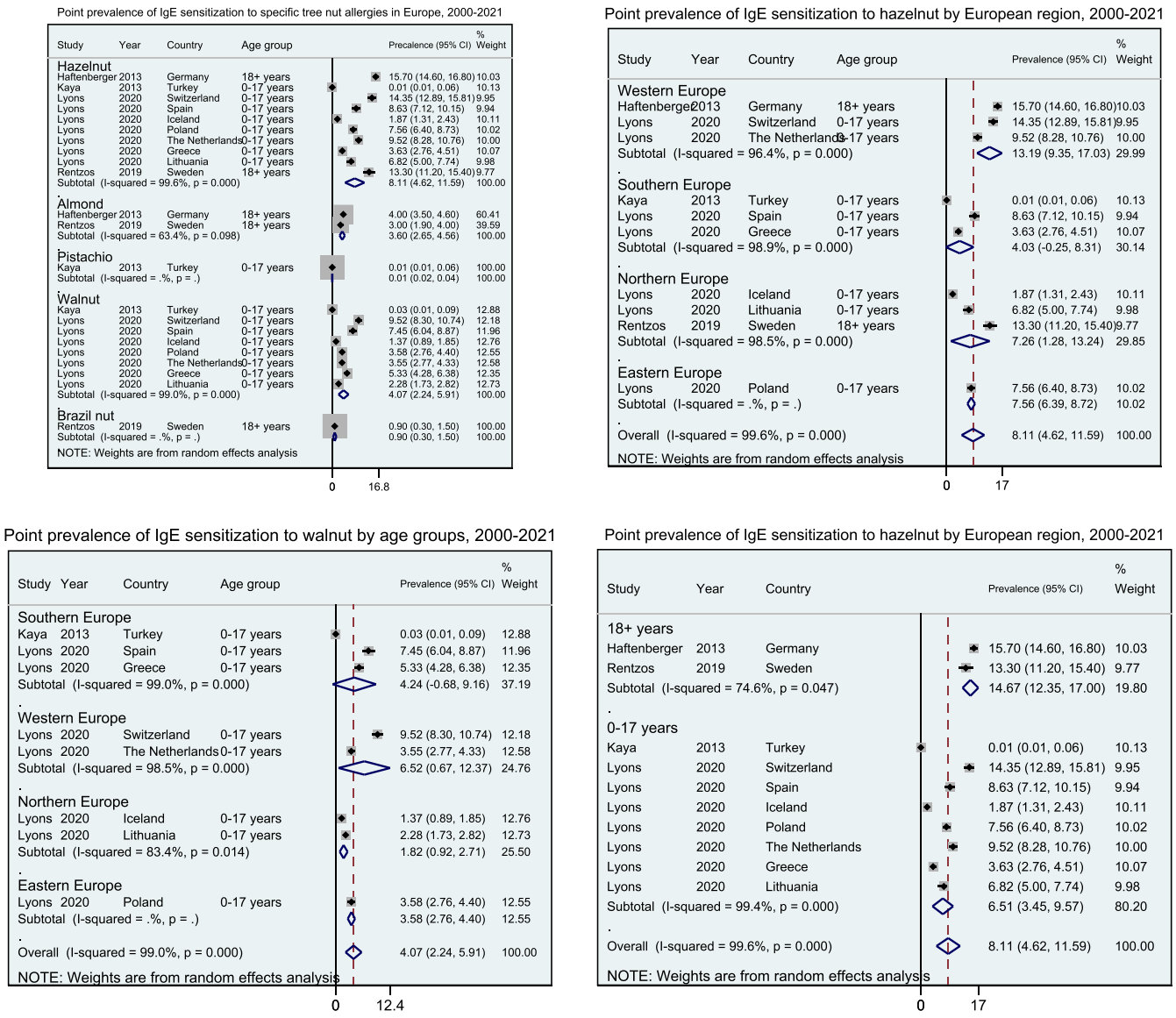

FIGURE 5 Point prevalence of sIgE positive specific tree nut sensitization (hazelnut, almond, pistachio, and walnut), point prevalence of sIgE positive hazelnut sensitization stratified by age and by European region, and point prevalence walnut sensitization stratified by European region.

on self-reported allergy (Figure 3).[38] The only study available on pecan nut reported on SPT sensitization (Figure 6).[39,40] The only study available for pine nut reported on DBPCFC positivity (Figure 9).[25,26] No study was available for macadamia nut. Therefore, it was not possible to perform meta-analysis for any of the outcomes of interest.

4 | DISCUSSION

4.1 | Statement of principal findings

This systematic review and meta-analysis, for the first time, provides estimates on the prevalence of specific TNA and sensitization in Europe, including hazelnut, walnut, almond, Brazil nut, cashew nut, pistachio, pecan nut. Although we investigated all tree nut allergies, no data were available for macadamia nut allergy. Most of the studies were rated as a "moderate" risk of bias and reported estimates on children, while fewer studies were conducted on adults. Hazelnut was the most investigated TNA/sensitization, followed by walnut, almond, Brazil nut, cashew nut, chestnut, pecan nut, and pine nut. For lifetime prevalence of self-reported specific TNA, estimates were only available for hazelnut and walnut, and pooled prevalence was higher for hazelnut (0.8%) than walnut (0.3%). The overall pooled point prevalence of self-reported specific TNA was highest for hazelnut (4.0%) and lowest for pistachio (0.6%). For IgE sensitization, the highest prevalence was for hazelnut (8.1%), and lowest for pistachio nut sensitization (0.01%), although the estimate for pistachio was based on only one study. For SPT sensitization, the highest prevalence was for walnut (2.7%) and lowest pistachio nut sensitization (0.01%), although the estimate for pistachio was based on only one study.

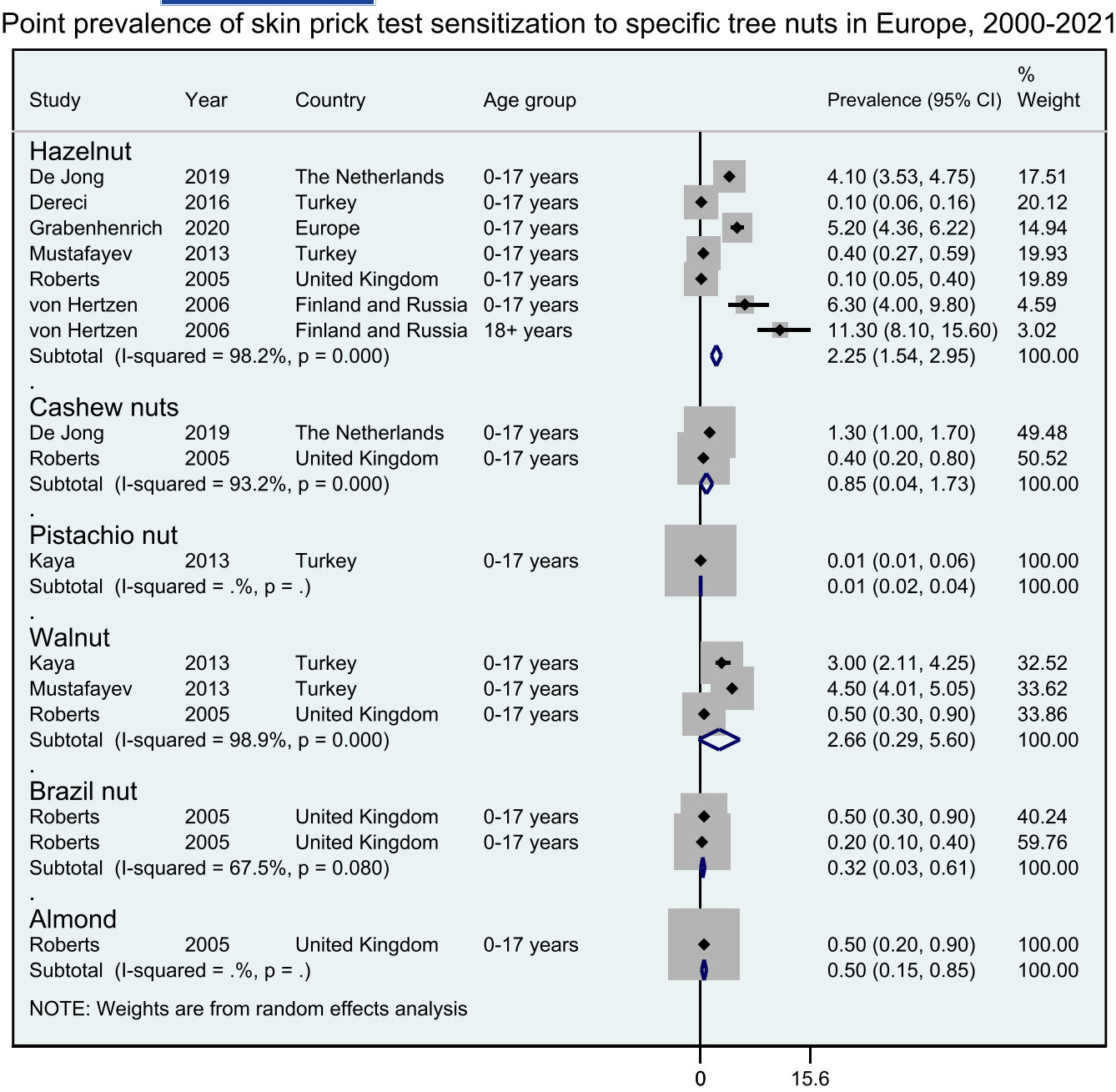

FIGURE 6 Point prevalence of SPT positive specific tree nut sensitization (hazelnut, cashew nut, pistachio, walnut, Brazil nut, and almond).

The pooled point prevalence of specific IgE sensitization plus symptoms to specific tree nuts was highest for hazelnut allergy (1.0%), followed by almond (0.8%) Brazil nut (0.4%), and walnut (0.1%). Almond and Brazil nut were reported by only one study, with prevalence of 0.8% and 0.4%, respectively. Finally, FC-confirmed specific TNA meta-analysis estimates were only available for hazelnut (0.04%) and walnut (0.02%). The highest reported FC-confirmed point prevalence was 0.1% for cashew nut, but only one study was available and meta-analysis could not be performed. There were some inconsistencies across the results obtained. For example, for hazelnut and walnut, point prevalence self-reported allergy was higher than lifetime prevalence, which seems illogical. However, the estimates for lifetime and point prevalence were not pooled from the same studies, which may explain the discrepancy. Additionally, the number or records available for the analysis was three times higher for lifetime prevalence of self-reported hazelnut allergy than for self-reported point prevalence hazelnut allergy. For walnut allergy, the available studies on lifetime prevalence self-reported allergy were only two, limiting our ability to perform a meta-analysis. The number of records available for point prevalence self-reported meta-analysis was twice the records available for lifetime prevalence. For most types of TNAs investigated, it was not possible to derive estimates stratified by age or by European region due to lack of data.

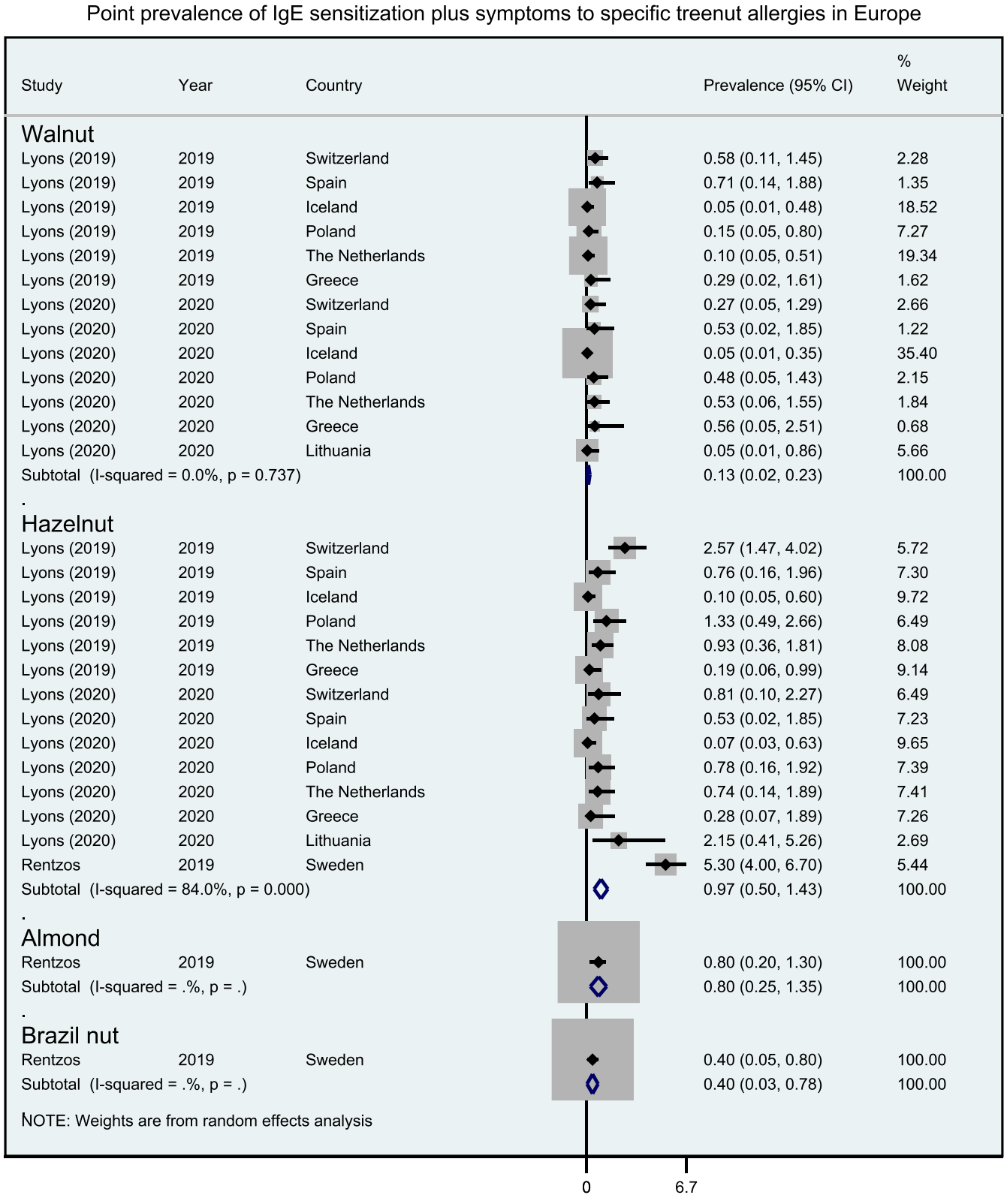

FIGURE 7 Point prevalence of sIgE positive specific tree nut (walnut, hazelnut, almond, and Brazil nut) sensitization plus symptoms.

4.2 | Strengths and limitations of the current update

We followed a rigorous methodology in implementing this systematic review, including a priori developed and registered protocol; a comprehensive search of the literature in major electronic databases, and a systematic approach at every step of the review. Compared to the 2014 review, we added two more databases to the ones already considered in 2014 and included more keywords in the database search. Through this, we minimized the risk of missing any

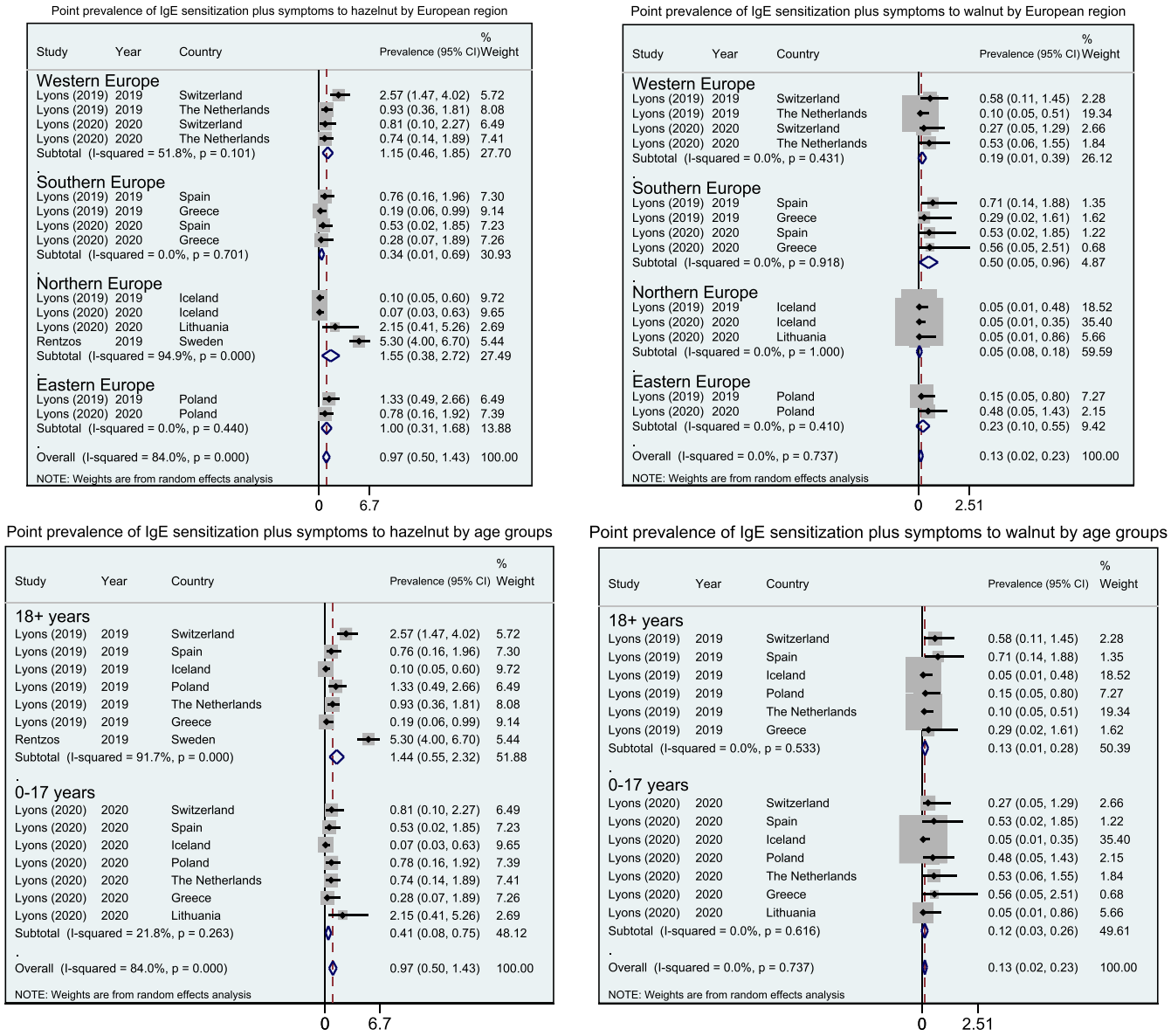

FIGURE 8 Point prevalence of sIgE positive specific tree nut (walnut and hazelnut) sensitization plus symptoms by age and by European region.

relevant studies published after the publication of the 2014 review. The inclusion of additional databases and keywords also considered developments that have been made since the publication of the previous EAACI systematic review. All methods of assessment of FA or frequency occurrence measures were included. Moreover, there was no language restriction in the database searches. To our knowledge, this is the first systematic review presenting prevalence estimates of specific TNA or sensitization in Europe, which offers a comprehensive and updated insight into the burden of specific TNA and sensitization in Europe.

The current work is however limited by the lack of data for some of the investigated outcomes, especially for the less commonly consumed tree nuts, such as chestnut, pecan nut, pine nut, and macadamia nut. In addition, most of the included studies did not distinguish between IgE and non-IgE allergy, which did not allow us to differentiate specific TNA outcomes by IgE-mediated or non-IgE-mediated phenotypes. It is also important to note that IgE-mediated allergy to tree nuts includes different syndrome such as storage protein syndrome, lipid transfer protein syndrome, and pollen-food syndrome (also known as oral allergy syndrome), each with distinct clinical presentations and severity. Our manuscript however presents the entirety of manifestation, not only primary FA. In the meta-analyses, there was high heterogeneity between the studies included, an indication of potential methodological differences between the studies (e.g., different definition of specific TNA/sensitization). A better harmonization of the methodological aspects of studies and on FA definition may produce more comparable estimates in future studies. On the other hand, the high heterogeneity may also reflect clear variations in the prevalence of specific TNA/sensitization across Europe. The fact that most of

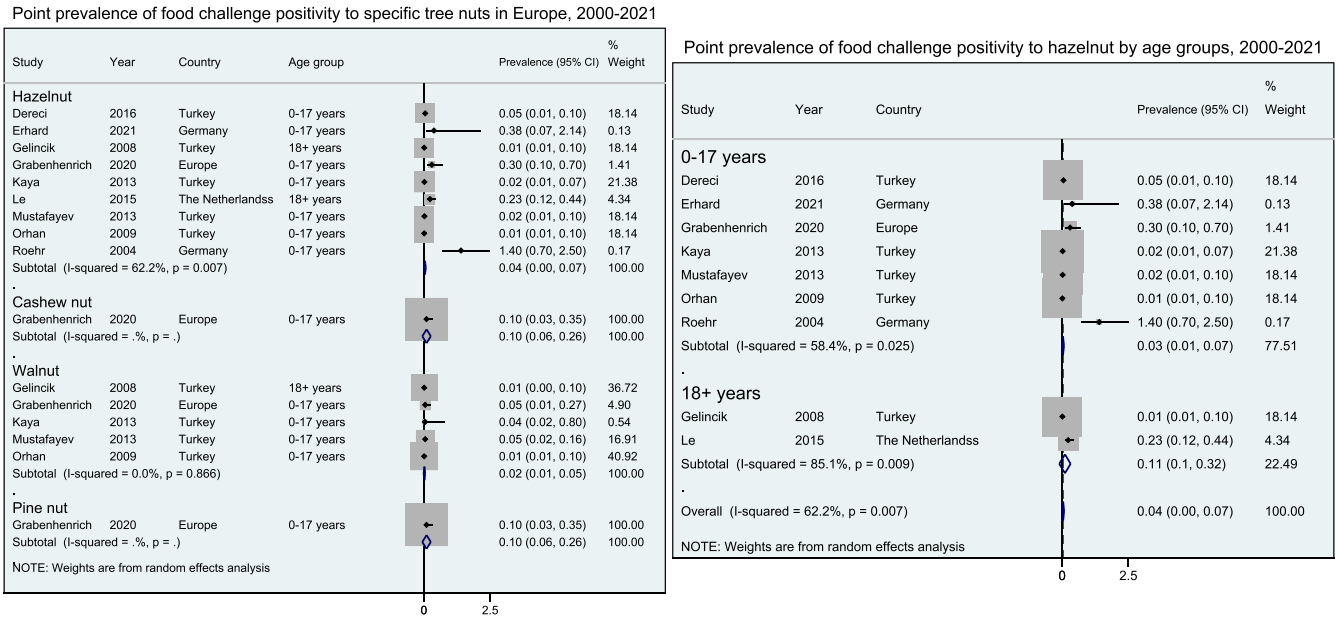

FIGURE 9 Point prevalence of FC positive specific tree nut allergy (hazelnut, cashew nut, and walnut), and point prevalence of FC positive hazelnut allergy stratified by age.

the studies included in the analysis were graded as at moderate risk of bias by the CASP quality assessment tool further uphold that the methodological quality of studies still warrants improvement and possibly standardization in Europe.

4.3 | Comparison of findings to previous studies

Only a few systematic reviews have investigated the epidemiology of TNA. The study by Van der Valk et al. (2015) synthesized evidence on the global prevalence of cashew nut allergy, but only a few studies were available.[54] The only available prevalence estimate for Europe reported by the authors was limited to the findings of one study, which reported 0.08% prevalence for SPT positivity to cashew nut in a population of UK children aged 0–4 years.[54] Zuidmeer et al. published a systematic review on the worldwide distribution of TNA. Available prevalence ranges for specific tree nuts were: 0%–4.1% for self-reported almond allergy; 0.1%–4.5%, 0.1%–1.4%, 0.07%–0.6%, 0.04%–0.4%, and 0.1%–0.5% for SPT sensitization to hazelnut, walnut, almond, cashew nut, and Brazil nut, respectively; and 0.7%–4.3% for OFC positive hazelnut. Notably, all the prevalence ranges available were based only on studies performed in Europe.[55] Finally, McWilliam et al. published a systematic review on the worldwide prevalence of TNA, but the authors reported estimates on individual TNA only as "percentage of tree nut allergics reporting reactions to the individual tree nuts" and identified hazelnut as the most common TNA in Europe, which is line with what we observed in the current review.[56]

To our knowledge, the current review is the first to provide prevalence estimates of allergy to specific tree nuts. This limits the possibility to compare the current review with the above-cited previous systematic reviews. However, all the studies agree on the overall lack of available data on TNA. The paucity of data on specific tree nuts may partly be explained by the fact that in many studies, TNA is commonly reported as "nut" allergy, which may include allergy to both tree nuts and peanut.[56] In addition, even in the instances where TNA is specifically investigated, individual tree nuts are rarely explored. Commonly, studies report the prevalence of individual TNA in terms of ratio of allergic subjects within a test-population of food allergic individuals.[57]

4.4 | Interpretation and implication of findings

The results obtained from this review should be carefully interpreted. Indeed, the majority of the studies were at "moderate" risk of bias, which limits our opportunity to provide an unequivocal and firm conclusion of the study findings. It is not clear whether the observed higher prevalence of hazelnut allergy, compared to other types of TNA, is real or because hazelnut was by far the most investigated type of tree nut. For some of the outcomes investigated, only one or two estimates were available for several of the tree nuts, less than the estimates available for hazelnut. This limited the possibility of performing meaningful meta-analyses for all types of tree nuts. More definitive and reliable results on the prevalence of TNA may be derived in the future by standardizing specific TNA definitions, as well as by employing similar methodologies across studies in investigating TNA. Nevertheless, the current study has provided the most comprehensive and up-to-date survey of the prevalence of specific TNAs in Europe and highlighted the research gaps on this topic, which should be taken into account in designing future studies.

5 | CONCLUSIONS

Of the specific tree nut allergies analyzed, hazelnut allergy/sensitization was the most common in Europe, while chestnut, pecan nut, and pine nut allergy/sensitization were the least common. Overall, there is still a paucity of data for most tree nut allergies to allow assessment of a comprehensive and definitive picture of the prevalence in Europe. The paucity of data also hindered comparison by age and region in the burden of TNA in Europe. More studies are required on this topic, and given the observed methodological heterogeneity of included studies, implementing more standardized approaches to definition and assessment of TNA across Europe will further advance the field.

AUTHOR CONTRIBUTIONS

Bright I. Nwaru and Graham Roberts defined the research question and the search strategies with assistance from Daniil Lisik. Daniil Lisik with the assistance from Bright I. Nwaru developed the data extraction form. Screening, data extraction, narrative synthesis was done by Giulia C. I. Spolidoro, Mohamed Mustafa Ali, Sungkutu Nyassi, Yohannes Tesfaye Amera, and Bright I. Nwaru. Manuscript writing was done by Bright I. Nwaru and Giulia C. I. Spolidoro. Antonella Muraro, Aziz Sheikh, Berber Vlieg-Boerstra, Carina Venter, Ekaterina Khaleva, Graciela Rovner, Margitta Worm, and Ronald van Ree were consulted concerning methodology and synthesis of the findings. All authors (Athina Ioannidou, Antonella Muraro, Aziz Sheikh, Bright I. Nwaru, Berber Vlieg-Boerstra, Carina Venter, Daniil Lisik, Ekaterina Khaleva, Graciela Rovner, Giulia C. I. Spolidoro, Mohamed Mustafa Ali, Margitta Worm, Ronald van Ree, Sungkutu Nyassi, Yohannes Tesfaye Amera) critically commented on drafts of the manuscript.

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CONFLICT OF INTEREST STATEMENT

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 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.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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