

The Prevalence of Tree Nut Allergy: A Systematic Review

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Abstract Tree nuts are one of the most common foods causing acute allergic reactions and nearly all tree nuts have been associated with fatal allergic reactions. Despite their clinical importance, tree nut allergy epidemiology remains understudied and the prevalence of tree nut allergy in different regions of the world has not yet been well characterised. We aimed to systematically review the population prevalence of tree nut allergy in children and adults. We searched three electronic databases (OVID MEDLINE, EMBASE and PubMed) from January 1996 to December 2014. Eligible studies were categorised by age, region and method of assessment of tree nut allergy. Of the 36 studies identified most were in children ($n=24$) and from Europe ($n=18$), UK ($n=8$) or USA ($n=5$). Challenge-confirmed IgE-mediated tree nut allergy prevalence was less than 2 % (although only seven studies used this gold standard) while probable tree nut allergy prevalence ranged from 0.05 to 4.9 %. Prevalence estimates that included oral allergy syndrome (OAS) reactions to tree nut were significantly higher

(8–11.4 %) and were predominantly from Europe. Prevalence of individual tree nut allergies varied significantly by region with hazelnut the most common tree nut allergy in Europe, walnut and cashew in the USA and Brazil nut, almond and walnut most commonly reported in the UK. Monitoring time trends of tree nut allergy prevalence (both overall and by individual nuts) as well as the prevalence of OAS should be considered given the context of the overall recent rise in IgE-mediated food allergy prevalence in the developed world.

Keywords Tree nut allergy · Systematic review · Prevalence · Epidemiology

Abbreviations

Primary tree nut allergy	IgE-mediated allergic reaction upon exposure to tree nuts that is due to a specific immune response directed against tree nut allergens
Secondary tree nut allergy	IgE-mediated allergic reaction upon exposure to tree nuts that is due to cross-reactivity of specific IgE directed against non-tree nut allergens
Tree nut sensitisation	Presence of tree nut allergen-specific IgE measured by skin prick test (SPT) or specific IgE blood testing (sIgE)
Oral allergy syndrome (OAS)	A secondary tree nut allergy that occurs predominantly in pollen-sensitised individuals, mediated by cross-reactive IgE responses to allergens present in pollen and other plants. Presents with oral pharyngeal symptoms (itching mouth/tongue)
Pollen food syndrome (PFS)	Another term for oral allergy syndrome

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Introduction

Tree nut is the collective term used to describe nuts that grow on trees. Contrary to popular belief, peanuts are not tree nuts and are in fact a groundnut and classified as a legume. Tree nuts most likely to result in an IgE-mediated food allergy reaction are almond, brazil nut, cashew nut, hazelnut, macadamia, pecan, pistachio and walnut. Although botanically unrelated, tree nut and peanut allergies share many clinical similarities. Peanut and tree nuts are two of the most common foods reported to cause IgE-mediated food allergic reactions. IgE-mediated food allergy reactions can occur after ingestion of very small amounts of peanut and tree nut, typically within minutes of ingestion with symptoms including hives, angioedema or vomiting. Reactions can also be life threatening, with the most severe reactions termed anaphylaxis. Peanut and tree nuts together account for 70–90 % of reported food-induced anaphylaxis fatalities, with tree nuts alone accounting for around 18–40 % [1–4]. Allergies to peanut and tree nuts also commonly co-exist with around 20–30 % of people with a peanut allergy also allergic to one or more tree nuts [5, 6]. For individuals with one tree nut allergy, around 30 % will have at least one additional tree nut allergy [6]. Tree nut and peanut allergies are usually lifelong [7]. Peanut allergy has been well described and widely reported with population prevalence estimates between 1 and 6 % [8, 9]. Despite the similarities to peanut allergy, the population prevalence of tree nut allergy has been less well characterised.

Determining tree nut allergy prevalence at a population level can be complex. Firstly, the definition of a ‘tree nut’ may vary. Some studies include peanut and tree nuts together as ‘nuts’, while other studies only include one or two tree nuts. Few studies investigate allergy to all eight common individual tree nuts. Secondly, allergic reactions to tree nuts can result from primary IgE-mediated mechanisms or, alternatively, via secondary cross-reactivity mechanisms to birch pollen, in a form of food allergy known as oral allergy syndrome (OAS) or pollen food syndrome (PFS). In individuals with birch pollen sensitisation, birch pollen-specific IgE can cross-react with similar proteins found in a range of fresh fruits, vegetables and nuts (apple, apricot, carrot, celery, hazelnut, peach, peanut, pear, potato and plum) resulting in oral pharyngeal symptoms [10, 11]. Finally, the method of tree nut allergy diagnosis may vary from self-reported methods such as surveys and questionnaires (which have been found to overestimate the true prevalence of food allergy) [8, 9], IgE testing methods such as skin prick testing (SPT) or specific IgE (which are limited to IgE-mediated food allergy and are indicative of sensitisation not clinical allergy), to the most objective but time-consuming and cumbersome methods of oral food challenge (OFC) and double-blind placebo-controlled food challenges (DBPCFC).

One previous systematic review by Zuidmeer et al., of studies published between 1990 and 2006, reported the

prevalence of perceived reactions to tree nut as ranging between 0 and 7.3 %; however, most studies included in this review ($n=27$ of 36) were based in Europe where the prevalence of oral allergy syndrome is high, and few studies used objective definitions of tree nut allergy such as challenge confirmed outcomes [12]. A more recent systematic review by Nwaru et al. was confined to European studies only and did not distinguish between individual tree nuts [13]. A more up-to-date global prevalence estimate of tree nut allergy is needed since 20 new studies have been published since 2006, and understanding the regional variation in tree nut allergy is important given the overall rising burden of food allergy [14, 15] in developed countries and the importance of tree nuts as a cause of severe allergic reactions.

The aim of this paper is to provide a comprehensive, up-to-date systematic review of the population prevalence of tree nut allergy in children and adults including details of all individual tree nuts in various regions of the world.

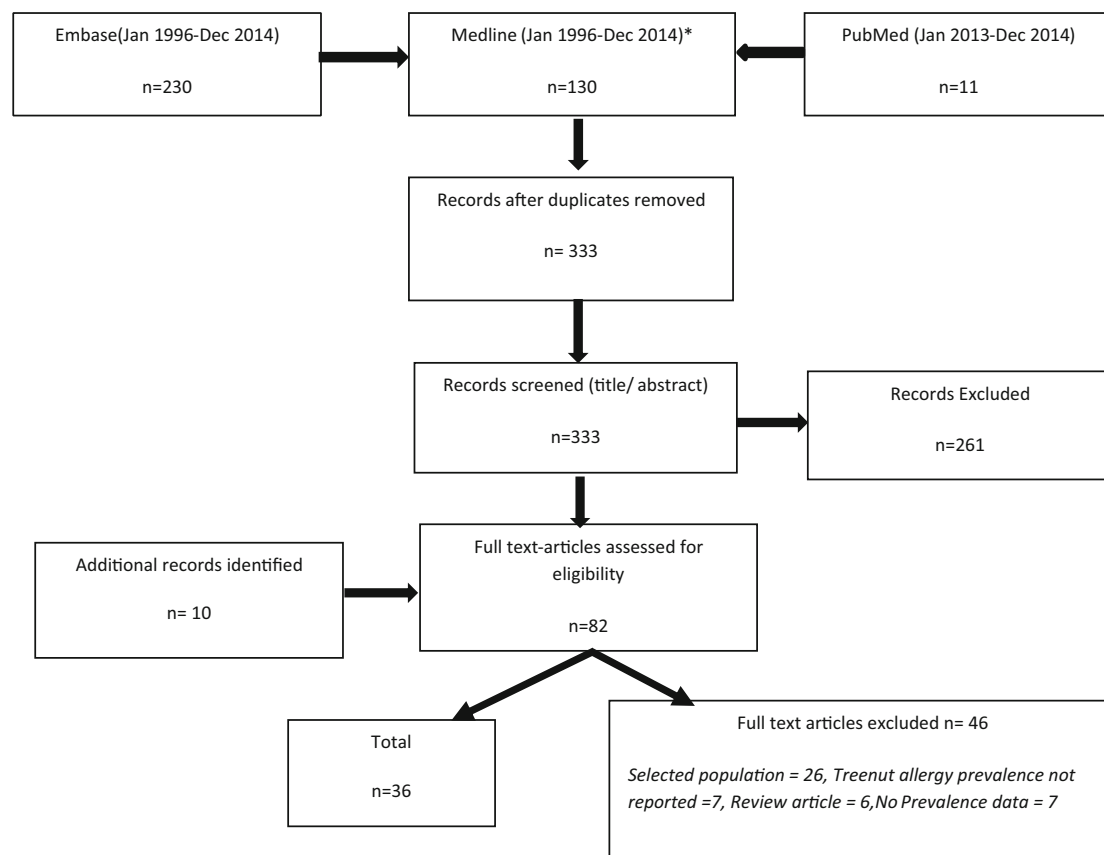
Methods

Search Strategy

Following closely the methods and procedures of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16], we systematically searched three electronic databases (OVID MEDLINE, EMBASE and PubMed) based on a search strategy formulated with the assistance of a research librarian. The search strategy was created in OVID MEDLINE and modified for EMBASE and PubMed. Figure 1 outlines the full OVID MEDLINE search strategy.

Study Selection

Tree nuts were defined as walnut, almond, pistachio, cashew, pecan, hazelnut, macadamia and Brazil nut. Studies reporting on all forms of allergic reactions (primary and secondary IgE-mediated and non-IgE-mediated reactions) were included and there were no age restrictions applied. All tree nut allergy outcomes were included for both individual and combined tree nut allergies. We included eligible studies that reported tree nut allergy based on self-report, sensitisation (sIgE or SPT), OFC/DBPCFC or convincing clinical history. The search was limited to English-language articles and, to capture more recent publications, limited to the period January 1996 to December 2014. To ensure unbiased estimates of tree nut allergy prevalence in the community, we excluded studies in selected patient groups or those performed in hospital or allergy clinic settings and included only population-based cross-sectional and cohort studies. Reviews and case reports were



* The primary search was conducted in OVID MEDLINE and modified for EMBASE and PubMed. The search involved a combination of three search groups as either MeSH terms or keywords, each of which had to be present in order for an article to be included: 1) “nut s”, “tree nuts” or an individual tree nut term; 2) “hypersensitivity” or “allergy”; and 3) “prevalence” or “epidemiology”. The search was limited to English language articles. The exact search conducted in OVID MEDLINE is shown in the box below.

1. (hazelnut* or hazel nut* or cashew* or pistachio* or almond* or treenut* or tree nut* or pecan* or brazilnut* or brazil nut* or walnut*).af. 2. Nuts/ae, im, po, to 3. prevalence 4. Epidemiology 5. food hypersensitivity/ or nut hypersensitivity 6. allerg*.af. 7. (1 or 2) and (3 or 4) and (5 or 6) 8. nut hypersensitivity/ep 9. food hypersensitivity/ep and (1 or 2) 10. 7 or 8 or 9 11. limit 10 to english language

Fig. 1 Summary of the search method

excluded along with studies of which full-text articles were not available.

Identified articles were screened via title and abstract by two independent reviewers. Any discrepancies were resolved by consensus and if necessary a third reviewer consulted. Reference lists of identified studies were reviewed for additional articles. A full-text review was then undertaken for all articles identified.

Quality assessment of the studies was performed by two reviewers based on participation rate, ability of the study design to address tree nut allergy outcomes objectively and inclusion of individual tree nut information.

Analysis

Using a standardised method, relevant study details were summarised including reference details, age, sample size and response rate, prevalence estimates and 95 % confidence intervals (CI) for all reported food allergy outcomes (self-/parent report, specific IgE testing, skin prick testing, symptoms and food challenges) for overall food allergy and tree nut allergy. If not reported, prevalence estimates were calculated as the observed proportion with 95 % CI calculated on the assumption of a binomial sampling distribution.

We subclassified the prevalence estimates and 95 % CI for age, region and method of tree nut allergy diagnosis.

For this review, the approaches used to determine tree nut allergy have been grouped as follows:

1. Confirmed tree nut allergy—defined as food challenge confirmed tree nut allergy (OFC or DBPCFC) or recent history (<2 years) of *IgE-mediated reaction* with positive allergy testing (SPT or sIgE) undertaken as part of the study in the absence of a formal food challenge.
2. Probable tree nut allergy—defined as reported history (>2 years) of *IgE-mediated reaction* with allergy or self-report of doctor diagnosis (presumed to include allergy-specific history and testing).
3. Self-reported tree nut allergy—defined as parent or self-reported tree nut allergy in the absence of data on allergy testing.
4. Sensitisation only (allergy testing via SPT or sIgE, without confirmation of clinical allergy).

We performed a random effects meta-analysis and in an attempt to address the significant heterogeneity observed across the studies stratified by age, region and method of tree nut allergy diagnosis. Statistical analyses were undertaken using STATA 13 (Stata Corp, College Station, TX, USA).

Results

Study Selection and Characteristics

Figure 1 summarises the search methodology. The systematic search of the literature resulted in 333 articles after duplicates were removed. Title and abstract review identified 261 that did not meet the inclusion criteria. The remaining 72 articles and an additional ten records identified through manually searching reference lists underwent full-text review. Forty six full-text articles were excluded (26 were in selected populations, seven did not report tree nut allergy prevalence, seven did not include prevalence data and six were review articles).

Included studies are described in Table 1 ($n=36$). Twenty six studies were designed to measure overall food allergy prevalence and reported tree nut allergy as a study outcome, seven were studies specifically aimed at investigating tree nut allergy prevalence and three studies included tree nut allergy prevalence data as part of an investigation of peanut allergy prevalence or associated factors.

Quality assessment of the studies based on participation rate, ability of the study design to address tree nut allergy outcomes objectively and inclusion of individual tree nut information resulted in 28 studies graded as moderate and eight poor. Three of the studies were assessed as poor because they were not designed to measure tree nut allergy prevalence but reported some

tree nut prevalence data, which we have included in this review. The majority ($n=28$) of the studies were population-based cross-sectional studies and the remaining eight were cohort studies. Six studies did not provide participation rate details, ten studies had a participation rate above 80 %, 13 between 50 and 80 % and seven less than 50 %. One study by Greenhawt et al. in American college students had a participation rate of only 3 % and reported a very high overall self-reported food allergy prevalence of 54 % and a self-reported tree nut allergy prevalence of 9.16 % (95% CI 6.8–11.9) [24]. This study has been included in the summary table, but the prevalence estimates not discussed as part of the review since the participation rate was extremely low and the study therefore not necessarily representative of the population from which it was sampled.

The random effects meta-analysis showed heterogeneity to be too great to report pooled results ($I^2 > 98$ %, $p=0.000$ for all analyses).

Tree Nut Allergy Prevalence by Age and Allergy Diagnosis Method

The majority ($n=24$) of studies in this review were in children and adolescents, four studies included both adults and children, six studies adults only and two studies reported an overall tree nut allergy prevalence without age breakdown; in one of these studies, participants were >15 years [23] and the second <61 years of age [25].

Prevalence estimate ranges for all allergy definitions, categorised by age, are outlined in Table 2. Seven studies used the most objective assessment of oral food challenge (or convincing recent history of allergic reaction together with positive allergen-specific IgE) with an overall prevalence range of 0–1.6 %. Nine studies combined self-reported food allergy with additional objective assessment such as specific details regarding doctor diagnosis or sensitisation details (sIgE/SPT) and were classified as probable food allergy for this review. The overall probable tree nut allergy prevalence range was 0.05–4.9 %, with only one study reporting adult data. However, the majority of prevalence estimates for tree nut allergy were based on self-reported reactions ($n=20$ studies). The self-reported tree nut allergy prevalence range was wider for adults (0.18–8.9 %) and those studies including both adults and children (0.4–11.4 %) than those studies including only children (0–3.8 %). Overall self-reported tree nut allergy prevalence ranged from 0 to 11.4 %.

Three studies based tree nut allergy prevalence on sensitisation alone (sIgE or SPT) without any clarification of presence of clinical allergy. One reported hazelnut sensitisation by SPT in Russian children of 0.8 % (95 % CI 0.4–1.1) and Finnish children of 6.3 % (95% CI 3.6–9.8) [52]. The second study reported sensitisation based on SPT of 1.0 % in 7-year-old children in the UK [40]. The third study in adults reported sensitisation prevalence to hazelnut of 9.26 % and walnut 2.98 % (overall 12.2 % (95% CI 11.7–12.7)) [20]. This was

Table 1 Summary of the characteristics of studies in review: studies published January 1, 1996–Dec 31, 2014 (alphabetical by author)

Reference	Country	Study design	Allergy outcome	Type of allergy	N	Participation rate (%)	Age	Individual tree nuts described	Prevalence measure	Overall prevalence % (95 % CI) (N)	Study grading
Ahn et al. 2012 [17]	Korea	Cross-sectional	2. Probable (self-report of Dr diagnosis and sIgE)	Primary and secondary	7882	97	6–13 years	NA	Point and lifetime	0.05 % (0.01–0.13) (4/7882)	Moderate
Bedolla-Barajas et al. 2014 [18]	Mexico	Cross-sectional	1. Self-report	Primary and secondary	1126	NA	18–50 years	Yes	Point	0.18 % (0.02–0.64) (2/1126)	Poor
Ben-Shoshan et al. 2010 [19]	Canada	Cross-sectional	1. Self-report 2. Probable (self-report of Dr diagnosis and sIgE)	Primary and secondary	9667	34.6	All ages with breakdown	NA	Point	Children 1.173 (1.16–2.3) 2.069 (0.4–0.97) Adults: 1.107 (0.84–1.30) 2.035 (0.27–0.44) Overall: 1.122 % (1.00–1.44) (118/9667) 2.068 % (0.54–0.83)	Moderate
Burney et al. 2014 [20]	Multi (Europe)	Cross-sectional	4. Sensitisation (sIgE)	Primary and secondary	17,366	54.9	20–54 years	Yes	Point	12.2 % (11.7–12.7) (2121/17326)	Moderate
Caffarelli et al. 2011 [21]	Italy	Cross-sectional	1. Self-report	Primary and secondary	625	69	5–14 years	Yes	Point	0.32 % (0.04–1.2) (2/625)	Moderate
Dufoit et al. 2008 [22]	UK Israel	Cross-sectional	1. Self-report	Primary	4148 (UK) 4672 (Israel)	80.2 (UK) 83.2 (Israel)	4–18 years	NA	Point	UK 1.85 % (1.5–2.3) (77/4148) Israel 0.13 % (0.05–0.3) (6/4672)	Moderate
Ennmett et al. 1999 [23]	UK	Cross-sectional	1. Self-report	NA	16,434	NA	All ages	NA	Point	0.40 % (0.30–0.51) (63/16,434)	Moderate
Greenhawt et al. 2009 [24]	USA	Cross-sectional	1. Self-report	NA	571	3.5	>18 years	NA	Point	9.16 % (6.8–11.9) (47/571)	Poor
Kanny et al. 2002 [25]	France	Cross-sectional	1. Self-report	Primary and secondary	16,174	52	All ages <60	NA	Point	3 % (2.7–3.20)	Moderate
Kaya et al. 2013 [26]	Turkey	Cross-sectional	1. Self-report 3. Confirmed (DBPCFC)	Primary	10,096	89.9	11–15 years	Yes	Lifetime	1.12 % (0.1–1.4) (121/10,096) 3.005 % (0.02–0.1) (6/100,096)	Moderate
Kljakovic et al. 2009 [27]	Australia	Cross-sectional	1. Self-report	NA	3851	85	4–5 years	No	Lifetime	1.79 % (1.4–2.3) (69/3851)	Poor
Kristjansson et al. 1999 [28]	Sweden Iceland	Cross-sectional	1. Self-report 3. Confirmed (OFC)	NA	324 (Iceland) 328 (Sweden)	79 (Iceland) 90 (Sweden)	18 months	No	Point	1. Sweden 0.3 % (0.0–1.6) (1/328) Iceland 0 % 3.0 % for Iceland and Sweden	Moderate

Table 1 (continued)

Reference	Country	Study design	Allergy outcome	Type of allergy	N	Participation rate (%)	Age	Individual tree nuts described	Prevalence measure	Overall prevalence % (95 % CI) (N)	Study grading
Leung et al. 2009 [29]	Hong Kong	Cross-sectional	1. Self-report 2. Probable (self-report of Dr diagnosis)	Primary and secondary	3677	83.6 %	2–7 years	NA	NA	1. 0.41 (0.2–0.7) (15/3677) 2. 0.3 % (0.2–0.5) (11/3677)	Moderate
Marklund et al. 2004 [30]	Sweden	Cross-sectional	1. Self-report	Primary and secondary	1451	97	13–21 years	NA	Point	11.37 % (9.5–12.8) (165/1451)	Moderate
Mustafayev et al. 2012 [31]	Turkey	Cross-sectional	1. Self-report 2. Probable (detailed history and SPT) 3. Confirmed (OFC)	Primary	6963	NA	10–11 years	Yes	Point	1.3.5 % (3.1,3.9) (223/6963) 2.4.9 % (4.4,5.4) (341/6963) 3.0.05 % (0.03,0.15) (4/6963)	Moderate
Nicolaou et al. 2010 [32]	UK	Cohort	1. Self-report	Primary	1029	94.9	8 years	NA	Lifetime	1.0 % (0.4,1.8) (10/1029)	Poor
Orhan et al. 2009 [33]	Turkey	Cross-sectional	1. Self-report 2. Probable (SPT) 3. Confirmed (OFC)	Primary	2739	78.2	6–9 years	Almond and walnut	Point	1.0.4 % (0.2,0.7) (11/2739) 2.0.14 % (0.03,0.4) (4/2739)	Moderate
Ostblom et al. 2008 [34]	Sweden	Cohort	1. Self-report	Primary	2563	69	4 years	NA	Point	3.0 % (0.0,1) (0/2739) 3.8 % (3.1,4.6) (98/2563)	Moderate
Osterballe et al. 2009 [35]	Denmark	Cohort	1. Self-report	Specified primary and secondary	843	77	22 years	Yes	Point	1. Primary 0 % Secondary 8.9 % (7.0,11.02) (85/843)	Moderate
Penard-Morand et al. 2005 [36]	France	Cross-sectional	1. Self-report	Primary and secondary	7781	81	9–11 years	NA	Lifetime	0.2 % (0.1,0.3) (10/6672)	Moderate
Pereira et al. 2005 [37]	UK	Cohort	1. Self-report	Primary and secondary	1532	48.7	11 and 15 years	NA	Point	1.6 % (1.1,2.4) (26/1532)	Poor
Pyrhonen et al. 2005 [38]	Finland	Cross-sectional	1. Self-report 2. Probable (self-report of Dr diagnosis)	Primary and secondary	3308	69	1–4 years	NA	Lifetime	1.1.5 % (1.1,1.9) (49/3308) 2.0.2 % (0.08,0.4) (7/3308)	Moderate
Rance et al. 2005 [39]	France	Cross-sectional	1. Self-report	Primary and secondary	2716	77.6	2–14 years	Yes	Point	0.7 % (0.4,1.1) (19/2716)	Moderate
Roberts et al. 2005 [40]	UK	Cohort	4. Sensitisation (SPT)	Sensitisation only	5848	42	7 years	Yes	Point	1.04 % (0.8,1.3) (61/5848)	Poor
Roehr et al. 2004 [41]	Germany	Cross-sectional	1. Self-report 2. Probable (SPT) 3. Confirmed (OFC)	Primary and secondary	739	31.5	0–17 years	Yes	Point	1. NA 2. 2.7 % (1.6,4.1) (20/739) 3. 1.4 % (0.7,2.5) (10/739)	Moderate

Table 1 (continued)

Reference	Country	Study design	Allergy outcome	Type of allergy	N	Participation rate (%)	Age	Individual tree nuts described	Prevalence measure	Overall prevalence % (95 % CI) (N)	Study grading
Schafer et al. 2001 [42]	Germany	Cross-sectional	1. Self-report SPT for hazelnut only	Primary and secondary	1537	60.7	25–74 years	NA	Point	1.8.5 % (7.1,9.9) (130/1537)	Moderate
Shek et al. 2010 [43]	Singapore Philippines	Cross-sectional	1. Self-report 2. Probable (self-report of Dr diagnosis)	Primary	25,692	74.2	4–6 years and 14–16 years	NA	Point	1.1.85 % (1.6,2.1) (200/10775) 2.0.28 % (0.2,0.4) (31/10,775)	Moderate
Sicherer et al. 1999 [44•]	USA	Cross-sectional	1. Self-report	Primary and secondary	4374	62	All ages with breakdown	Yes	Point	Children (<18 years) 0.2 % (0.05,0.4) (5/2998) Adults (>18 yrs) 0.7 % (0.5,0.9) (59/8049) Overall 0.5 % (0.0,0.6) (64/12032)	Moderate
Sicherer et al. 2003 [45•]	USA	Cross-sectional	1. Self-report	Primary and secondary	13,493	52	All ages with breakdown	Yes	Point	Children (<18 years) 0.2 % (0.1,0.4) (7/3127) Adults (>18 years) 0.1 % (0.4,0.6) (50/9881) Overall 0.4 % (0.3,0.5) (57/13,493)	Moderate
Sicherer et al. 2010 [46•]	USA	Cross-sectional	1. Self-report	Primary and secondary	5300	42	All ages with breakdown	Yes	Point	Children (<18 years) 1.1 % (0.05,0.4) (31/2902) Adults (>18 years) 0.5 % (0.4,0.6) (53/9845) Overall 0.6 % (0.5,0.8) (84/12,658)	Moderate
Tariq et al. 1996 [47]	UK	Cohort	1. Self-report Some participants had SPT	Primary	1218	NA	4 years	NA	Point	0.1 % (0.02,0.6) (2/1218)	Poor
Taylor-Black et al. 2014 [48]	USA	Cross-sectional	1. Self-report	Primary	368	43	4–12 years	NA	Point	1.82 % (1.06,2.9) (17/932)	Poor
Venter et al. 2006 [49]	UK	Cohort	1. Self-report 3. Confirmed (OFC)	Primary	798	55.4	6 years	Yes	Point	1. 1.37 % (0.8,2.5) (11/798) 3. 0.25 % (0.03,0.9) (2/798)	Moderate

Table 1 (continued)

Reference	Country	Study design	Allergy outcome	Type of allergy	N	Participation rate (%)	Age	Individual tree nuts described	Prevalence measure	Overall prevalence % (95 % CI) (N)	Study grading
Venter et al 2008 [50]	UK	Cohort	1. Self-report 3. Confirmed (OFC)	Primary	891	91.9	3 years	Yes	Point	3.0.93 % (0.34,2.0) (6/642)	Moderate
Vierk et al. 2007 [51]	USA	Cross-sectional	1. Self-report 2. Probable (self-report of Dr diagnosis)	Primary	4482	NA	>18 years	NA	Point	1.0.65 % (0.43,0.9) (29/4477)	Moderate
Von Hertzen et al. 2006 [52]	Finland Russia	Cross-sectional	4. Sensitisation (SPT)	Primary and secondary	Finland 367 Russia 446	NA	7–16 years	Hazelnut only	Point	2.0.5 % (0.06,0.32) (7/4477) Finland 6.3 % (3.6,9.8) (17/271) Russia 0.8 % (0.2,2.4) (3/356)	Moderate

the highest reported prevalence estimate of all four methods of tree nut allergy definition.

Tree Nut Allergy Prevalence by Region

Prevalence estimate ranges for each method of allergy definition are summarised by region in Table 3. Regional variation in self-reported tree nut allergy prevalence is illustrated in Fig. 2. Most studies were from Europe ($n=18$), the UK ($n=8$), or the USA ($n=5$). There were three studies from Asia and one each from Canada, Central America and Australia. Stratifying by region highlighted a markedly higher prevalence of tree nut allergy in some European countries with a range of 0.04–11.4 %. OAS appeared to contribute to higher tree nut allergy prevalence in some European countries since all three of the studies reporting tree nut allergy prevalence over 8 % were self-reported, all in adolescents and adults, and all from Europe. Two of these studies directly reported that all tree nut allergy found in their study was due to OAS [35, 42] and the third study did not specify the type of allergic reaction to tree nuts, but overall 33 % of all allergy, to any food, was reportedly due to OAS [30]. All other regions, regardless of allergy definition, reported tree nut allergy prevalence less than 2 %.

Individual Tree Nut Allergy Prevalence

Table 4 summarises the percentage of tree nut allergic participants allergic to each individual tree nut by region. Fourteen studies provided details of individual tree nut prevalence. The prevalence of individual tree nut allergies varied by region. Hazelnut was the most common tree nut allergy reported in six of the seven studies from Europe accounting for 17–100 % of all tree nut allergies. The two studies from the USA reported walnut and cashew as the most common tree nut allergies ranging from 20 to 30 % and 15–30 %, respectively. Brazil nut allergy was reported commonly in the UK ranging from 24 to 33 %. The one study from Mexico reported low overall tree nut allergy of 0.18 % (2/1126) with both participants allergic to walnut. None of the studies reported on the prevalence of multiple tree nut allergies.

Tree Nut Allergy Prevalence Over Time

There is limited evidence to determine if the population prevalence of tree nut allergy is increasing. Three studies in the USA utilised random-digit telephone surveys in 1997, 2002 and 2008 [44•, 45•, 46•]. Study design was consistent across each sampling period and included a large number of participants ($n=4374$; 13,493 and 5300, respectively). No significant increase in adult self-reported tree nut allergy prevalence was found over the three time points. However, the prevalence of self-reported tree nut allergy in children younger than 18 years had increased

Table 2 Summary of the range of prevalence estimates of tree nut allergy in the reviewed studies according to allergy assessment method and age

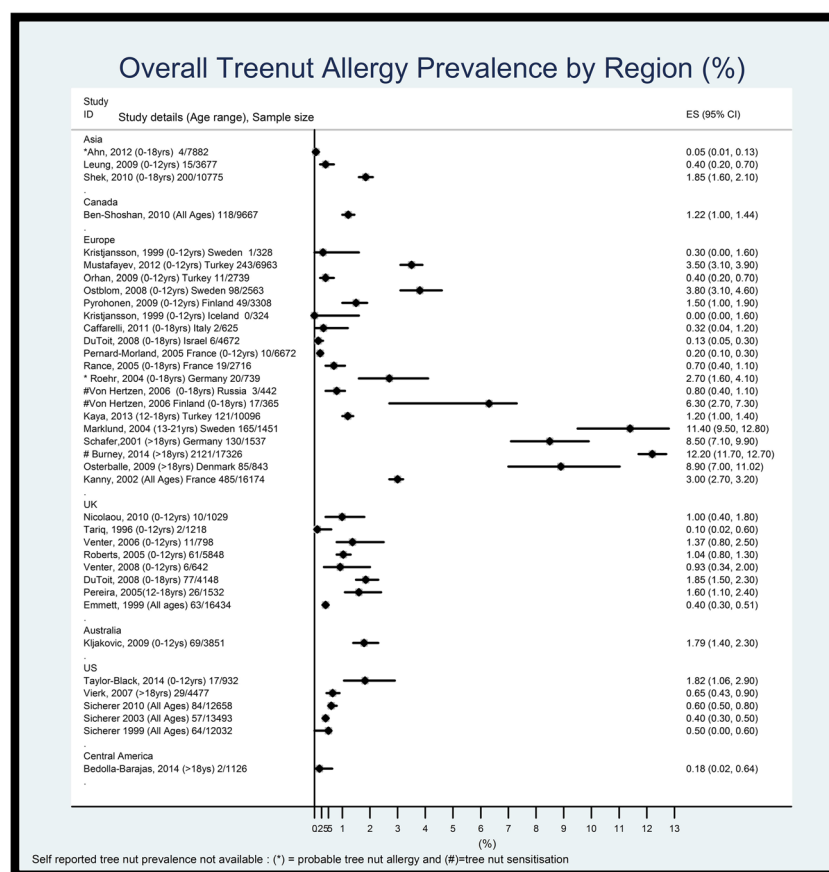
Allergy definition and age	Number of studies	Range of prevalence estimates (%)	References
Self-reported			
Children 0–18 years	22	0–3.8	[21, 22, 26–29, 31–34, 36–39, 43, 44•, 45•, 46•, 47–49, 53]
Adult	8	0.18–8.9	
All ages	3	0.4–11.4	
Overall		0–11.4	[23, 25, 30]
Probable			
Children 0–18 years	9	0.05–4.9	[17, 19, 29, 31, 33, 38, 41, 43, 51]
Adult	2	0.35–0.5	
All ages	0	NA	
Overall		0.05–4.9	
Confirmed			
Children 0–18 years	7	0–1.4	[26, 28, 31, 33, 41, 49, 50]
Adult	0	NA	
All ages	0	NA	
Overall		0–1.4	
Sensitisation			
Children 0–18 years	2	0.8–6.3	[40, 52]
Adult	1	12.2	[20]
All ages	0	NA	
Overall		0.8–12.2	

Some studies are included in more than one category as they reported prevalence estimates obtained using more than one allergy assessment method.

significantly (0.2 % in 1997, 0.5 % in 2002 and 1.1 % in 2008). Proportionally, the increase was greater than that observed for peanut over the same time periods (0.4 % in 1997, 0.8 % in 2002 and 1.4 % in 2008).

Table 3 Summary of the range of reported prevalence estimates for tree nut allergy according to allergy assessment method and region

Region		Self-report Range % (number of studies)	Probable Range % (number of studies)	Confirmed Range % (number of studies)	Sensitisation Range % (number of studies)
Asia	Children	0.3–1.85 (3)	0.05–0.3 (3)	NA	NA
	Adults	NA	NA	NA	NA
	Overall	0.3–1.85	0.05–0.3	NA	NA
Europe	Children	0.04–3.1 (10)	0.2–4.9 (4)	0–1.4 (6)	0.8 (1)
	Adults	8.5–8.9 (2)	1.6 (1)	NA	12.2 (1)
	All ages	3.0–11.7	NA	NA	NA
	Overall	0.04–11.7	0.2–4.9	0–1.4	0.8–12.2
UK	Children	0.1–1.85 (5)	NA	0.25–0.93 (2)	NA
	Adults	NA	NA	NA	NA
	Overall	0.1–1.85		0.25–0.93	
USA	Children	0.2–1.82 (4)	NA	NA	NA
	Adults	0.5–0.7 (2)	NA	NA	NA
	Overall	0.2–1.82			
Australia	Children	1.79 (1)	NA	NA	NA
	Adults	NA	NA	NA	NA
	Overall				
Canada	Children	1.73 (1)	1.59 (1)	0.69 (1)	NA
	Adults	1.07 (1)	1.0 (1)	0.35 (1)	NA
	Overall	1.07–1.73	1.0–1.59	0.35–0.69	
Central America	Children	NA	NA	NA	NA
	Adults	0.02 (1)	NA	NA	NA
	Overall				

Fig. 2 Overall tree nut allergy prevalence by region (%)**Table 4** Percentage of tree nut allergics reporting reactions to the individual tree nuts by region

Region, study details (country)	% of tree nut allergics reporting reactions to the individual tree nuts (number with specific tree nut allergy/total number with any tree nut allergy)
Europe	
Burney et al. 2014 [20] (multi-country)	Hazelnut 76 % (1605/2121), walnut 24 % (517/2121)
Caffarelli et al. 2011 [21] (Italy)	Hazelnut 100 % (2/2)
Mustafayev et al. 2012 [31] (Turkey)	Hazelnut 42 % (104/243), walnut 34 % (83/243), pistachio 22 % (55/243)
Kaya et al. 2013 [26] (Turkey)	Walnut 66 % (4/6), hazelnut 17 % (1/6), pistachio 17 % (1/6)
Osterballe et al. 2009 [35] (Denmark)	Hazelnut 75 % (56/75), Brazil nut 31 % (23/75), walnut 5 % (4/75), almond 3 % (2/75)
Rance et al. 2005 [39] (France)	Hazelnut 53 % (10/19), walnut 32 % (6/19), almond 10 % (2/19), cashew 5 % (1/19)
Roehr et al. 2004 [41] (Germany)	Hazelnut 100 % (10/10)
USA	
Sicherer et al. 1999 [44•]	Walnut 37 % (24/65), cashew 12 % (5/65), Brazil nut 12 % (8/65), almond 11 % (7/65), pecan 11 % (7/65), hazelnut 4.6 % (3/65), macadamia 3 % (2/65), unspecified 9 % (6/65)
Sicherer et al. 2010 [46•]	Walnut 48 % (41/84), cashew 34 % (29/84), pecan 30 % (26/84), almond 29 % (25/84), pistachio 22 % (19/84), Brazil nut 22 % (19/84), hazelnut 20 % (17/84), macadamia 20 % (17/84), pine nut 13 % (11/84)
UK	
Venter et al. 2008 [50]	Brazil nut 33 % (2/6), almond 33 % (2/6), hazelnut 17 % (1/6), cashew 17 % (1/6)
Venter et al. 2006 [49]	Almond 33 % (1/3), Brazil nut 33 % (1/3), hazelnut 33 % (1/3)
Roberts et al. 2005 [40]	Walnut 24 % (10/41), Brazil nut 24 % (10/41), almond 22 % (9/41), cashew 15 % (10/41), hazelnut 7 % (3/41), pecan 7 % (3/41)
Tariq et al. 1996 [47]	Hazelnut 50 % (1/2), cashew 50 % (1/2)
Mexico	
Bedolla-Barajas et al. 2014 [18]	Walnut 100 % (2/2)

Discussion

This review has confirmed that the majority of tree nut allergy prevalence studies continue to be undertaken in Europe, where there is a high prevalence of OAS, with most studies relying on self-reported prevalence, limited to children and adolescents. Using the most robust measure of tree nut prevalence (challenge confirmed or history of reaction with IgE antibodies), we estimate the overall prevalence to be <2 % in countries where OAS is not reported. Secondary tree nut allergy (OAS) estimates for older age groups including adolescents and adults is as high as 10 %, particularly in Europe. Few studies reported the population prevalence of individual tree nut allergies. However, how prevalent a particular tree nut allergy is differs significantly by region with hazelnut the most common tree nut allergy in Europe, walnut and cashew in the USA and Brazil nut, almond and walnut most commonly reported in the UK. There is limited evidence to determine if the population prevalence of tree nut allergy is increasing.

This is the first systematic review of the literature exploring tree nut allergy prevalence exclusively across the age groups and different regions of the world, utilising robust systematic review methodology, closely following PRISMA guidelines. A further strength of this review is we categorised prevalence by robustness of the study methodology employed to define tree nut allergy. We identified three studies with self-reported tree nut allergy greater than 8 %, all from Europe demonstrating that studies which do not differentiate primary and secondary tree nut allergy prevalence rates are likely to inflate prevalence estimates.

Precise estimates of true tree nut allergy were limited by the small number of studies reporting challenge confirmed tree nut allergy prevalence—the gold standard for diagnosis. As for other epidemiological studies of food allergy prevalence [8, 9], we also found higher prevalence estimates for self-report and sensitisation. Self-report is known to overestimate the true prevalence of food allergy [54] and asymptomatic sensitisation to foods is relatively common [9]; therefore, objective measures are critical. We were also unable to accurately determine whether tree nut allergy is on the rise as only one series of estimates was available. Finally, estimates of the prevalence of individual tree nut allergies could not be reliably estimated due to the paucity of data reported for individual nuts, although it is clear that there is significant regional variation in prevalence estimates [55].

We found overall tree nut allergy prevalence mirrors the global pattern of overall food allergy with countries with low prevalence of food allergy also reporting low levels of tree nut allergy. Large population-based epidemiological studies such as the ISAAC and EuroPrevall studies have demonstrated considerable regional variability of common food allergens and sensitisation patterns, but the reasons for this remain largely unexplored. It has been hypothesised that

variation in dietary patterns at the population level might lead to variations in sensitisation status and hence risk of subsequent food allergy. Du Toit et al. hypothesised that variations in peanut allergy prevalence between genetically similar populations in the UK and Israel might be due to differences in infantile peanut consumption patterns [22], whilst others have argued that boiled versus roasted peanut dietary intakes may at least partly explain the difference in allergy patterns across different regions [56, 57].

Our review found a higher self-reported tree nut allergy range (0–11.4 %) than both previous published systematic reviews. Nwaru et al. performed a meta-analysis of seven studies and reported a pooled self-reported point prevalence of 1.8 % (95% CI 1.63–1.99), although there was significant heterogeneity across the studies ($I^2=99.4$ %, $p=0.00$). Zuidmeer et al. included studies from a wider range of countries from 1990 to 2006 and reported a self-reported tree nut allergy prevalence range of 0–7.3 % based on seven studies [12]. Prevalence varied based on type of tree nut allergy, method of tree nut allergy diagnosis, age and region. Similarly to Zuidmeer et al., considering the large heterogeneity between the studies, we have not presented a pooled prevalence estimate since this would mask the differences between populations.

Nwaru et al. reported confirmed tree nut allergy pooled point prevalence of 0.45 % ($I^2=0.00$ %, $p=0.88$) while Zuidmeer et al. reported a range of 0.1–4.3, based on only three studies. We found the prevalence of tree nut sensitisation to be the highest of the four methods of allergy definition used (1.0–12.2 %). Comparison to sensitisation prevalence estimates in previous reviews is difficult as we reported sensitisation prevalence estimates based on population sensitisation. Previous reviews both reported studies where SPT or sIgE was performed only on participants that had previously self-reported tree nut allergy. Neither of these reviews differentiated between primary and secondary tree nut allergy prevalence, or reported on individual tree nut allergy prevalence nor the nature or prevalence of multiple tree nut allergies.

In conclusion, this systematic review has highlighted that there is considerable heterogeneity in tree nut allergy prevalence from studies to date and pooling individual study estimates risks masking the real differences between populations. Data is limited to largely European, US and UK studies using self-reported prevalence in children and adolescents. There is a need for further studies to determine tree nut allergy by gold standard methodologies such as food challenge, and differentiate between primary and secondary tree nut allergy. Further detailed information on individual tree nut prevalences will help inform our understanding of regional variation and repeated estimates over time will enable us to understand whether time trends in tree nut allergy mirror the general rise in IgE-mediated food allergy reported in developed countries.

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Compliance with Ethics Guidelines

Conflict of Interest Drs McWilliam, Koplin, Lodge, Tang, Dharmage and Allen declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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