Systematic review and meta-analyses on the accuracy of diagnostic tests for IgE-mediated food allergy

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July 12, 2023

Abstract

Abstract: Background: The European Academy of Allergy and Clinical Immunology's (EAACI) is updating the Guidelines on Food Allergy Diagnosis. We aimed to undertake a systematic review of the literature with meta-analyses to assess the accuracy of diagnostic tests for IgE-mediated food allergy. **Methods**: We searched three databases (Cochrane CENTRAL (Trials), MEDLINE (OVID) and Embase (OVID)) for diagnostic test accuracy studies published between 1 st October 2012 and 30 th June 2021 according to a previously published protocol (CRD42021259186). We independently screened abstracts, extracted data from full-texts, and assessed risk of bias with QUADRAS 2 tool in duplicate. Meta analyses were undertaken for food-test combination where 3 or more studies were available. **Results**: 149 studies comprising 24,489 patients met the inclusion criteria and were generally heterogeneous. 60.4% of studies were in children [?]12 years of age, 54.3% undertaken in Europe, [?]95% conducted in a specialized pediatric or allergy clinical setting and all included oral food challenge in at least a percentage of enrolled patients, in 21.5% DBPCFC. Skin prick test (SPT) with fresh cow's milk and raw egg had high sensitivity (90% and 94%) for milk and cooked egg allergies. Specific IgE to individual components had high specificity: Ara h 2 had 92%, Cor a 14 95%, Ana o 3 94%, casein 93%, ovomucoid 92/91% for the diagnosis of peanut, hazelnut, cashew, cow's milk and raw/cooked egg allergies, respectively. BAT was highly specific for the diagnosis of peanut (90%) and sesame (93%) allergies. **Conclusions:** SPT and specific IgE to extracts had high sensitivity whereas specific IgE to components and BAT had high specificity to support the diagnosis of individual food allergies. **PROSPERO registration:** CRD42021259186 **Funding:** European Academy of Allergy (EAACI).

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Conflicts of Interest

Carmen Riggioni reports research funding from the Spanish Society of Paediatric Allergy and the National University of Singapore. She is an associate editor for PAI journal and a member of the Paediatric Board for the EAACI.

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Daria Levina reports a grant from the Moscow Health Department for the standardization of oral food challenges in the Russian Federation.

Graham Roberts reports research funding from National Institute of Health and Food Standards Agency. He is president of British Society of Allergy and Clinical Immunology.

Rachel Peters reports grants from the National Health & Medical Research Council of Australia

George Du Toit reports grants and personal fees from Aimmune, grants and personal fees from DBV, personal fees from FARE, grants from NIH-NIAID, grants and personal fees from Novartis, outside the submitted work.

Isabel Skypala reports honoraria from ThermoFisher, Royal College of General Practitioners and Touch Independent Medical Education

A.F. Santos reports grants from Medical Research Council (MR/M008517/1; MC/PC/18052; MR/T032081/1), Food Allergy Research and Education (FARE), the Immune Tolerance Network/National Institute of Allergy and Infectious Diseases (NIAID, NIH), Asthma UK (AUK-BC-2015-01), BBSRC, Rosetrees Trust and the NIHR through the Biomedical Research Centre (BRC) award to Guy's and St Thomas' NHS Foundation Trust, during the conduct of the study; personal fees from Thermo Scientific, Nutricia, Infomed, Novartis, Allergy Therapeutics, Buhlmann, as well as research support from Buhlmann and Thermo Fisher Scientific through a collaboration agreement with King's College London.

Abstract:

Background: The European Academy of Allergy and Clinical Immunology's (EAACI) is updating the Guidelines on Food Allergy Diagnosis. We aimed to undertake a systematic review of the literature with meta-analyses to assess the accuracy of diagnostic tests for IgE-mediated food allergy.

Methods : We searched three databases (Cochrane CENTRAL (Trials), MEDLINE (OVID) and Embase (OVID)) for diagnostic test accuracy studies published between 1st October 2012 and 30th June 2021 according to a previously published protocol (CRD42021259186). We independently screened abstracts, extracted data from full-texts, and assessed risk of bias with QUADRAS 2 tool in duplicate. Meta analyses were undertaken for food-test combination where 3 or more studies were available.

Results : 149 studies comprising 24,489 patients met the inclusion criteria and were generally heterogeneous. 60.4% of studies were in children [?]12 years of age, 54.3% undertaken in Europe, [?]95% conducted in a specialized pediatric or allergy clinical setting and all included oral food challenge in at least a percentage of enrolled patients, in 21.5% DBPCFC. Skin prick test (SPT) with fresh cow's milk and raw egg had high sensitivity (90% and 94%) for milk and cooked egg allergies. Specific IgE to individual components had high specificity: Ara h 2 had 92%, Cor a 14 95%, Ana o 3 94%, casein 93%, ovomucoid 92/91% for the diagnosis of peanut, hazelnut, cashew, cow's milk and raw/cooked egg allergies, respectively. BAT was highly specific for the diagnosis of peanut (90%) and sesame (93%) allergies.

Conclusions: SPT and specific IgE to extracts had high sensitivity whereas specific IgE to components and BAT had high specificity to support the diagnosis of individual food allergies.

PROSPERO registration: CRD42021259186

Funding: European Academy of Allergy (EAACI).

Keywords : Food allergy, IgE-mediated, diagnosis, diagnostic tests, skin prick test, specific IgE, component-resolved diagnostics, basophil activation test, sensitivity, specificity

Abbreviations:

BAT: basophil activation test

BBEA: bead-based epitope assay

CM: cow's milk

CRD: component resolved diagnosis

DBPCFC: double-blind placebo-controlled food challenge

EAACI: European Academy of Allergy and Clinical Immunology

FA: food allergy

HE: hen's egg

MAT: mast cell activation test

OFC: oral food challenge

PPV: positive predictive value

SPT: skin prick test

SPP: skin prick to prick test

SR: systematic review

RCT: randomised control trial

Introduction

The burden of food allergy (FA) remains a significant public health concern. There is ample evidence for the negative impact that FA can have on the quality of life of patients and their families, on the breadth and quality of social interactions, on the performance at school or work and on overall psychological well-being [1-3]. This is aggravated by the financial strain that FAs impose on families and individuals through the cost of allergen-free food, direct and indirect medical expenses, and missed work or school days [4].

A recently published study documents a continued increase in the prevalence of FA in Europe. It estimates lifetime and point prevalence of self-reported FA to be 20% and 13%, respectively [5]. Considering both a clinical diagnosis of food allergy or a positive OFC, FAs have increased from 2.6% in the early 2000's to 3.5% in the next decade [5]. Currently, FA confirmed by oral food challenge (OFC) worldwide is estimated at 4%[6].

This has resulted in a growing demand for appropriate FA diagnosis, driving health care professionals to employ a wide range of allergy tests. However, not all these diagnostic tests are equally useful or appropriate to reach an accurate diagnosis of FA and while the OFC remains the reference standard, it is a costly and time-consuming procedure that may lead to life-threatening anaphylaxis [7]. For a highly sensitive test, a negative result effectively rules out the diagnosis of FA; for a highly specific test, a positive result rules in a FA diagnosis. Deeper understanding of diagnostic test accuracy could reduce the need for OFC and guide clinical practice.

Determining the optimal diagnostic cut-offs in single studies that are generalisable to other clinical settings poses a significant challenge. By combining and analysing data from multiple studies, we can overcome the limitations of individual studies and gain a more comprehensive understanding of the diagnostic performance of tests. Meta-analyses allow us to synthesize findings from various sources, enhancing the reliability and generalizability of the results. Thus, they play a crucial role in guiding clinical decision-making and improving diagnostic accuracy.

The European Academy of Allergy and Clinical Immunology (EAACI) is updating their guidelines on both the diagnosis and management of FA [8, 9]. A systematic review (SR) of index tests is the most reliable form of evidence in the diagnostic field and enables clinicians and other healthcare professionals to make well-informed decisions [10, 11]. To inform the EAACI guidelines on FA diagnosis, we undertook a SR and meta-analysis (meta-analyses) about the accuracy of index tests to support the diagnosis of IgE-mediated FA, following a previously registered and published protocol [12].

This SR addresses the question: What is the diagnostic accuracy measured by the sensitivity and specificity of any index test for IgE-mediated FA to any food compared with the reference standard OFC (in at least a subset of patients) or previous clear history of immediate reaction to the food and evidence of IgE sensitisation?

Methodology

This SR was commissioned by EAACI and undertaken by an EAACI task force comprising methodologists, patient representatives, allergists, paediatricians, primary care doctors and other clinicians, psychologists, dieticians, and other allied health representatives, from 23 countries, including Austria, Australia, Brazil, Canada, Denmark, France, Germany, Greece, Hong Kong, Italy, Ireland, Japan, the Netherlands, Poland, Russia, Romania, Spain, Singapore, South Africa, Switzerland, Turkey, UK, USA.

The methods are described in brief here, a full review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration: CRD42021259186) and previously published [12]. We report our findings herein according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[13].

Search strategy

The task force searched three databases (Cochrane CENTRAL (Trials), MEDLINE (OVID) and Embase (OVID)) for diagnostic test accuracy studies published between 1st October 2012 and 30th June 2021. Manuscripts preceding this date were evaluated previously in the EAACI SR on diagnostic tests [8]. A manual SR search was performed by the task force and additional relevant references were found following suggestions from the EAACI expert panel group. For non-English language studies, a native speaker within the task force extracted and presented the relevant data for the group to reach a consensus on inclusion and assessment.

Eligibility criteria

Studies were deemed eligible for the review if they included all the following:

* Population: Humans (irrespective of age) with suspected IgE-mediated allergy to any specific food.

* Intervention: Any index test

* Comparator: IgE-mediated FA diagnosis determined by OFC using any method including open food challenge or double-blind placebo-controlled food challenge (DBPCFC) in at least a portion of study participants.

* Outcome: Sensitivity and specificity of the index test.

We excluded conference abstracts, editorials, correspondence, narrative reviews, qualitative studies, case reports and case series of less than 20 patients, as well as animal studies and studies in which allergies are defined based on sensitization tests alone without a history following ingestion.

Data collection

The reviewers screened, titles, abstracts, and reviewed full texts of potentially eligible records using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). The data were extracted using standardized forms in duplicate by two reviewers independently. Any conflicts were resolved by a third reviewer and consensus of the task force core team (CR, IS, GdT, AFS). Where relevant information was missing from a study that was potentially eligible for the SR, the corresponding author of the respective study was contacted and inclusion of this study was contingent on completion of this information by email from the corresponding author.

Data analysis

We evaluated the diagnostic accuracy for each index test for each individual food. The data was synthetized by tabulating the index test's sensitivity, specificity, true positives, true negatives, false positives, and false negatives. For allergens with variable allergenic profiles resulting from extensive heating or cooking, separate analysis was conducted for each allergenic configuration. For hen's egg (HE) protein, the analysis was divided into baked HE, cooked (extensively heated) HE and raw HE. For cow's milk (CM), it was separated into baked milk and fresh milk.

Where three or more studies for a given combination of index test and food were available, a meta-analyses was performed with a generalized linear mixed model of the binomial family with a logit link. This approach was chosen to perform a random effect estimate of both sensitivity and specificity, accounting for their correlation, computing the pooled sensitivity and specificity and performing the summary receiver operating curves (ROC)[14]. Briefly, every study contributed with its own contingency table for its specific cut-off value (i.e. true positive, true negative, false positive and false negative) were included in the model as a count. These analyses resulted in a bivariate random effect estimation of sensitivity and specificity along with heterogeneity assessed by I-squares defined according to Zhou and Dendukuri, 2014 [15]. We defined tests with high accuracy as those which had a sensitivity or specificity of [?]90% with I-squares under 50%. Low sensitivity and specificity were considered for test performing under 75%.

We performed sensitivity and specificity analysis using the optimal cut-off reported by the individual studies using the optimal cut-off reported by the individual studies, e.g. Youden's Index or other methods. To obtain the estimated cut-offs used for each meta-analysis, we reported the median and interquartile range of all cut-offs considered optimal by the different authors. Further analyses were performed and focused on the maximum values for sensitivity and specificity as reported by the authors of included studies.

Further analyses were undertaken with the pre-established 95% positive predictive values (PPV) available in literature [16]. For skin prick tests (SPT) we used values of 8 mm for peanut [17] and CM and 7 mm for HE [18]. For sIgE, we used the following values: 15 kU_A/L for peanut [17], CM and tree nuts, 7 kU_A/L for HE and 20 kU_A/L for fish [19, 20]. We included only values which have been previously validated thus this are not available for all foods. [18, 21-23].

As the PPV is dependent on the prevalence of allergic disease in a specific population, we looked at the sensitivity and specificity of pooled data for these cut-offs and defined them as highly accurate if they reached a value [?] 90%.

In supplementary analyses, studies were stratified by test-specific threshold values, age of the participants (below 24 months, 24 months to 16 years and above 16 years) and by the country of origin. Where data

on at least three different tests on the same food were available, a comparison was performed. To this end, the relative ratio of sensitivity and specificity was computed using an intercept only model [24]. Data for differences in subgroups were considered significant if there was a change in sensitivity or specificity over 7% (CI 95%) or they reached high diagnostic accuracy (over 90% of sensitivity or specificity for any given test).

To reduce heterogeneity in the meta-analyses, only index tests using the same characteristics where combined. For SPT, results are shown for studies using commercial extracts separate from those using skin prick to prick tests (SPP) with fresh foods. For sIgE testing, results from different platforms were used individually for meta-analyses (ImmunoCAP Specific IgE, ImmunoCAP ISAC, etc). Throughout the manuscript when talking about sIgE this refers to ImmunoCAP, if other methods are used for analysis, it will be specified accordingly. The random effect bivariate meta-analysis was performed using the metadata function of the STATA software version 15.

Assessment of risk of bias and quality of evidence

Data from included studies were reviewed for risk of bias assessment and applicability using the QUADAS-2 tool. [25] All evaluations were performed independently by two different reviewers. Disagreements were resolved by a third reviewer and consensus of the task force core team (CR, IS, GdT, AS). The four key domains covering patient selection, index test, reference standard (OFC comparator), flow and timing were evaluated.

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [26, 27] approach was used to assess heterogeneity and to evaluate the certainty of the body of evidence. [28-30] The task force reviewed studies about each intervention and created evidence profiles. Authors were not involved in decisions about topics where they had a potential conflict of interest. All taskforce members decided on the conclusions by consensus.

Results

Summary of included studies

The systematic search identified 1,494 unique records. 149 studies [31-180] were included after application of our predefined eligibility criteria. **Figure 1** llustrates the PRISmeta-analyses flowchart for the study screening and selection process. This resulted in 24,489 subjects included in the analysis. The current SR includes representative data for thirty-two countries and all continents. The data principally originate from Europe (54.3%), Asia (19.9%) and America (13.9%). Only 13.4% of eligible data are derived from multicentre studies.

The studies evaluated were predominantly prospective (63.8%) including consecutive (51.0%) and randomized (6.7%) studies. Within the retrospective studies (34.2%), most were performed consecutively (30.2%). The studies included are mostly cross-sectional (59.1%) or cohort studies (35.6%). Only 5.4% are case controls. Most studies include subjects under 18 years of age (79.2%), most of which were in infants or children [?]12 years of age (60.4%). Studies exclusive on adults represent only 7.4%. The included studies where largely performed in an allergy or paediatric clinic setting (94.6%). All included studies used OFC as a reference standard in a proportion of patients, most of them in over 70% of the subjects included. Only 7.4% of studies explicitly stated OFCs were done in all subjects. Overall, 63.8% used open OFCs and 21.5% double blind placebo-controlled food challenges (DBPCFC). The full summary of characteristics of the included studies is given in **Table 1** . Further information for individual studies is compiled in **Table S1** .

Nineteen different index tests were identified, most commonly sIgE (128 studies), component resolved diagnosis (CRD) (87 studies) and SPT (79 studies). Additional identified tests were SPP (15 studies), basophil activation test (BAT) (13 studies), mast cell activation test (meta-analysesT) (2 studies) [38, 149] and bead-based epitope assay (BBEA) [159]. **Table S2** lists the identified index test studies. Note that studies may have more than one diagnostic test reported. Evaluable data was available for 21 foods: foremost peanut (34.2%) followed by HE (25.5%), CM (18.1%), tree nuts (12.1%), wheat (10.7%), sesame (6.0%), soy and

shellfish (4.7%). All foods tested in the studies are listed in **Tables S3** . The group of most frequently studied foods with three or more included publications per index test were peanut, CM, baked HE, extensively heated HE, raw HE, sesame, soy, walnut, hazelnut, cashew, almond, wheat, and shrimp.**Table 2** summarizes results for each food where meta-analyses was possible.

Risk of bias assessment

The selected studies were heterogeneous, the overall risk of bias assessment for the included studies is displayed in **Figure 2** . Within the patient selection domain, 43.6 % of studies showed high risk, 31.5% showed low risk and 24.8% were of unclear risk of bias. This originates from studies that did not randomly select, consecutively enrol participants, use a case-control design, or not report how exclusion was managed, highlighting the necessity to adhere to standardized procedures. For applicability, 96.0% of studies had low concerns that the included patients did not match the review question.

For the index test domain, 22.1% of studies showed high risk, 38.3% low risk and 36.9% unclear risk of bias. The most common reasons for assigning a high risk of bias were studies with a lack of blinding or failure to establish a threshold for the index tests before conducting the analysis. For applicability, 77.2% of studies had low concerns that the index test, its conduct, or interpretation differed from the review question.

For the reference standard domain, 18.1% of studies showed high risk of bias, 38.9% low risk and 43.0% unclear risk. An increase in the risk of bias was seen in studies which included prior information of the reference standard test while performing the index test. For applicability, 88.6% of studies had low concerns that the target condition as defined by the reference standard does not match the review question.

For the flow and timing domain, 61.1% of studies showed high risk, 23.5% low risk and 15.4% unclear risk of bias. We considered studies to be of low risk of bias if all participants received the same reference standard within six months of having received the index test.

Table 3 shows the risk of bias assessment summary for each domain question and **Table S4** shows the individual risk of bias assessment per study.

Peanut allergy

We included 51 studies [38, 54, 57, 58, 61, 80, 81, 92, 94, 103, 111, 114, 135-137, 139, 141, 148, 150, 154-156, 159, 180] on the accuracy of diagnostic tests for peanut allergy. For meta-analyses, 20 studies of SPT-peanut [38, 54, 57, 58, 80, 81, 92, 94, 103, 111, 136, 137, 139, 141, 148, 150, 155, 156, 159, 180] and 24 studies of sIgE-peanut [38, 44, 54, 61, 62, 67, 70, 75, 81, 90-92, 96, 112, 119, 136, 137, 141, 148, 150, 156, 159, 171, 180] met the inclusion criteria.

Studies for SPT showed a pooled sensitivity of 84% and specificity of 86% at a 4 mm median cut-off (**Table 2**). We could not detect differences in accuracy of SPT to peanut in younger age groups (**Table 6**). There were differences in data obtained in different geographical regions. Most notably there was a high specificity for SPT to peanut in Australian studies (97%) but not in Asian studies (**Table 7**). sIgE to peanut showed a pooled sensitivity of 81% and specificity 83% at a 4.3 kU_A/L cut-off. In children [?]2 years of age, sIgE-peanut shows an increase in accuracy with better sensitivity and high specificity of 94%. We also observed specificity of 93% for studies from Western Europe and Australia.

Twenty-seven [31, 38, 44, 57, 58, 61, 62, 66, 67, 70, 75, 81, 90-93, 96, 101, 102, 112, 119, 139, 141, 148, 150, 154, 159] included studies employed CRD. When applying optimal cut-offs, CRD tests for peanut showed high specificity, 92% for Ara h 2-sIgE [31, 38, 44, 57, 58, 61, 62, 66, 67, 70, 75, 81, 90-93, 96, 101, 102, 112, 119, 139, 141, 148, 150, 154, 159], 93% for Ara h 3-sIgE [67, 70, 90-93, 112, 159] and 94% for Ara h 6-sIgE [31, 90, 91, 141]. In studies using ISAC [80, 81, 93, 99], the performance of Ara h 2 sIgE was less heterogeneous with a specificity of 93% using the 0.3 cut-off. The specificity of Ara h 2-sIgE increased for adult subjects. Ara h 2-sIgE was highly accurate in Northern Europe and Australia with specificity of 97% in both regions. The specificity was lower for North American subjects at 89% and was lower even for Asia subjects at 75%. Data on Ara h 8-sIgE [70, 90-92, 112, 119] and Ara h 9-sIgE [31, 70, 91, 93] was highly

heterogeneous. In general, sensitivity for CRD in peanut allergy was lower than specificity. BAT to peanut was analysed in 4 studies [38, 141, 148, 150] with pooled sensitivity of 84% and high specificity of 90%. These studies were less heterogeneous and had a lower risk of bias compared to other index test studies of peanut allergy **(Figure 3A).**

The maximum sensitivity and maximum specificity were [?]90% for SPT to peanut, sIgE to peanut, Ara h 2-sIgE and BAT to peanut (**Tables S5 and S6**).

Hen's egg allergy

We included 35 studies [33, 34, 41, 43, 49, 59, 60, 68, 72, 74, 78, 82, 84, 88, 94, 97, 105, 118, 126, 128, 129, 131, 133, 137, 142, 146, 152, 156-158, 161, 166, 168, 172, 180] on the accuracy of diagnostic tests for HE allergy. For meta-analyses, tests were divided into raw, cooked and baked HE.

For raw HE, SPT to egg white [33, 34, 137, 172] had a specificity of 80% compared to specificities of 96 % for SPT to egg yolk [33, 34, 49] and 91% for SPT to ovalbumin [34, 49, 172]. Nine studies on sIgE to egg white (EW) [33, 34, 43, 60, 74, 78, 137, 142, 172], 4 on sIgE-egg yolk [33, 34, 78, 142] and 6 on CRD [34, 43, 60, 74, 78, 142, 172] met the inclusion criteria. sIgE-EW showed pooled sensitivity of 73% with a specificity of 88%. (**Table 2**) This increased to 95% for subjects [?]2 years of age (**Table 6**). sIgE-egg yolk had low sensitivity and specificity. Ovomucoid [34, 43, 60, 74, 78, 172] showed high specificity of 91% with low sensitivity of 74% at a median cut-off 0.8 kU_A/L and ovalbumin [34, 43, 60, 78, 142, 172] did not reach appropriate accuracy with sensitivity of 78% and specificity of 79%.

For cooked HE, 6 studies on SPT-EW [33, 82, 84, 118, 157, 168], 4 on SPP with raw EW [33, 82, 126, 168], 14 on sIgE-EW [33, 43, 74, 82, 88, 97, 118, 128, 131, 152, 157, 168, 172] , 7 on ovomucoid-sIgE [33, 34, 43, 74, 118, 142, 172] and 3 studies on ovalbumin [33, 43, 172] met the inclusion criteria. SPP [33, 82, 126, 168] was highly sensitive for cooked HE allergy diagnosis with pooled sensitivity of 94% and specificity of 66% at the 6 mm cut-off. SPT to EW [33, 82, 84, 118, 157, 168] showed pooled sensitivity of 68% with a specificity of 77%. The sensitivity increased to 79% for subjects [?]2 years. sIgE to EW showed pooled sensitivity of 85% with a specificity of 73%, respectively. Ovomucoid-sIgE had a sensitivity of 74% with high specificity of 91% at the 0.8 kU_A/L cut-off. sIgG4 to HE had low sensitivity and low specificity in highly heterogenous studies. Studies for cooked HE allergy were less heterogeneous than those for raw or baked HE allergies.

For baked HE allergy, sIgE to EW [41, 137, 146] showed high specificity (94%) but very low sensitivity of 40% at the 8 kU_A/L cut-off with values ranging widely from 6 to 50 kU_A/L. The accuracy for SPT to EW [41, 137, 146, 166] was low for baked HE allergy. There was insufficient data for meta-analyses on accuracy of CRD in baked HE allergy. **(Figure 2B)**

For raw HE allergy, maximum sensitivity of [?] 90% was not reached by analysed diagnostic tests. Maximum specificity was [?] 90% for sIgE to EW, ovalbumin and ovomucoid. For cooked HE allergy, maximum sensitivity of [?] 90% for SPP and maximum specificity was [?] 90% for SPP and ovomucoid. For baked HE, maximum specificity was [?] 90% for SPT and sIgE EW (**Tables S5 and S6**).

Cow's milk allergy

We included 27 studies on accuracy of tests to support the diagnosis of CM allergy. Eleven studies for SPT to CM [37, 49, 52, 73, 84, 94, 95, 106, 134, 156-158, 167, 180], 5 for SPP using fresh CM [37, 49, 157, 167, 180] and 3 for SPT to casein [37, 49, 52, 73] met the inclusion criteria for meta-analyses. SPT to CM and SPT to casein showed sensitivities of 52% and 64% and specificities of 80% and 87% respectively. SPP showed a high sensitivity of 90% with specificity of 80% at the 4 mm cut-off (**Table 2**). CM-sIgE [37, 51, 52, 73, 94, 95, 97, 106, 134, 143, 152, 156, 157, 167, 178, 180] showed pooled sensitivity of 82% with a high specificity of 92% at the 3.5 kU_A/L cut-off. CRD also showed high specificity: casein 93% [32, 37, 51, 52, 73, 127, 134, 167] and alpha-lactalbumin 92% [51, 52, 73, 167] with sensitivities of 67% and 58% at 1.8 kU_A/L and 1.7 kU_A/L cut-offs, respectively. Studies of CRD were less heterogeneous compared to SPT and sIgE to CM **(Figure 2C).** For CM, maximum sensitivity was [?] 90% for SPP and maximum specificity was [?] 90% for SPT-casein, sIgE-CM and CRD (**Tables S5 and S6**). We could not determine changes in accuracy for

index tests on CM for various age groups or geographical regions. There was insufficient data on baked CM for meta-analyses.

Tree nut allergies

We included 18 studies on accuracy of diagnostic tests for tree nut allergy. Seven studies for SPT [48, 50, 63, 70, 114, 123, 148, 156], 8 for sIgE [44, 48, 50, 63, 70, 87, 122, 123, 148, 156] and 8 for CRD met inclusion criteria for hazelnut allergy meta-analyses [44, 47, 48, 50, 63, 66, 70, 87, 122, 123, 148]. SPT to hazelnut and sIgE to hazelnut showed pooled sensitivities of 82% and 79% and pooled specificities of 78% and 62%, respectively (**Table 2**). The specificity increased to 73% in the 2–16-year age group for sIgE-to hazelnut (**Table 6**). Cor a 14-sIgE [44, 47, 48, 50, 63, 66, 70, 122, 123, 148] showed pooled sensitivity of 73% and high specificity of 95% at the 0.64 kU_A/L cut-off. For the 2–16-year age group Cor a 14 maintains high specificity of 97%.

(Figure 2D)

Four studies for SPT [53, 124, 148, 156], 5 for sIgE [53, 86, 148, 153, 156] and 3 for CRD [108, 148, 153] met inclusion criteria for cashew nut allergy meta-analyses. SPT to cashew showed high sensitivity of 93% and high specificity of 92% at the 5 mm cut-off. sIgE to cashew showed high sensitivity of 94% with a pooled specificity of 64% at the 1.1 kU_A/L cut-off. Ana o 3 showed high sensitivity of 96% and high specificity 94% at the 0.4 kU_A/L cut-off.

(Figure 2E)

Four studies for sIgE-walnut [39, 45, 69, 156, 174] met inclusion criteria for meta-analyses showing a pooled sensitivity of 87% and 82% specificity. For Jug r 1 sensitivity has higher at 90% for a median cut-off 0.2 kU_A/L[45, 66, 69] **(Figure 2F).** Four studies for sIgE-almond [89, 148, 156, 174] met inclusion criteria for meta-analyses, with a pooled sensitivity of 72% and 95% specificity at a median cut of 3.4 kU_A/L. Hazelnut and walnut studies were heterogeneous regarding co-sensitizations, comorbidities, and age of subjects. Studies for cashew and almond were less heterogeneous than those for hazelnut and walnut.

For hazelnut, the maximum sensitivity was [?] 90% using hazelnut-sIgE. The maximum specificity was [?] 90% for hazelnut SPT and Cor a 14-sIgE. For cashew, maximum sensitivity was [?] 90% and maximum specificity was [?] 90% for SPT to cashew, sIgE to cashew and Ana o 3-sIgE. For walnut-sIgE, maximum specificity was [?] 90% for Jug r 1. For almond, maximum sensitivity and specificity were [?] 90% for almond-sIgE (**Tables S5 and S6**).

Sesame seed allergy

We included 9 studies on accuracy of diagnostic tests for sesame allergy. Seven studies for SPT [35, 76, 137, 145, 147, 148, 156] , 7 for sIgE [76, 120, 137, 145, 147, 148, 156], 3 for Ses i 1 [76, 120, 145]and 3 for BAT [35, 76, 148] met inclusion criteria for sesame allergy meta-analyses. SPT to sesame and sIgE to sesame showed pooled sensitivity of 70% each with a specificity of 89% and 83%, respectively. (Figure 2G)

Sensitivity increased in the 2–16-year age group for sIgE-sesame to 94% (**Table 6**). For studies done in the Middle East, specificity of SPT to sesame decreased to 69% (**Table 7**). For CRDs, Ses i 1 had a sensitivity of 77% with a specificity of 87%. BAT to sesame showed pooled sensitivity of 89% with a high specificity of 93% (Table 2) at a 10% cut-off. Studies on SPT to sesame and sIgE to sesame were more heterogeneous than those for BAT to sesame.

The maximum sensitivity was [?] 90% for BAT to sesame and the maximum specificity was [?] 90% for sIgE to sesame, BAT to sesame, and SPT to sesame (**Tables S5 and S6**).

Soy allergy

Three studies for SPT [65, 100, 158, 180] met the inclusion criteria for soy allergy meta-analyses, with pooled sensitivity of 47% and specificity of 79% (**Table 2**). IgE to soy [100, 121, 151, 180] and Gly m 4 [64, 100,

121] had sensitivities of 73% and 61% with specificities of 75% and 69% respectively. For SPT to soy the maximum specificity was [?] 90% (**Table S5 and S6**).

(Figure 2H)

Wheat allergy

We included 16 studies on accuracy of diagnostic tests for wheat allergy. For meta-analyses there were 5 studies of SPT to wheat [36, 84, 106, 116, 138, 156, 158, 180], 10 of sIgE to wheat [32, 36, 55, 56, 79, 106, 116, 130, 132, 138, 152, 156, 160, 180] and 6 of ω-5 gliadin [32, 56, 79, 130, 132, 138] with pooled sensitivities of 53%, 72%, 79% and specificities of 72% 79% and 78%, respectively (**Table 2**) and **(Figure 2I)** . For sIgE-wheat and ω-5 gliadin, sensitivity increased for subjects [?]16 years of age (**Table 6**). The maximum sensitivity was [?] 90% for wheat-sIgE and the maximum specificity was [?] 90% for ω-5 gliadin (**Tables S5 and S6**).

Fish and shellfish allergies

We included two studies on fish and seven on shellfish allergies. Most studies focused on shrimp allergy, 3 studies of SPT to shrimp [158, 162, 165, 175], four of shrimp-sIgE [162, 165, 173, 175] and 3 of CRD to Pen m 1 [165, 173, 175] met inclusion criteria for shrimp allergy meta-analyses. SPT to shrimp had pooled sensitivity of 62% with specificity of 90% at the median 3 mm cut-off. sIgE-shrimp showed high sensitivity of 96% with a pooled specificity of 63% at a median cut of 1.2 kU_A/L. Pen m 1 had a sensitivity of 62% and specificity of 89% (**Table 2**) and **(Figure 2J)** . The maximum sensitivity was [?] 90% for shrimp-sIgE. The maximum specificity of [?] 90% was for SPT shrimp. (**Table S5**). There was insufficient data for meta-analyses on other fish or shellfish allergies.

Comparison of tests to support the diagnosis of specific food allergies

To further evaluate the different diagnostic tests, we compared them against each other for each food. Table 4 shows the statistically significant comparisons of tests by food. For the diagnosis of peanut allergy, the SPT to peanut has a higher relative sensitivity and relative specificity compared to the sIgE. Ara h 2 shows a higher relative specificity compared to sIgE to peanut. When different techniques are used to measure CRD, Ara h 2 by ImmunoCAP has a higher relative specificity than Ara h 2 using ISAC. The relative sensitivity of Ara h 2 is higher than for BAT.

For the diagnosis of cooked HE allergy, sIgE has a higher relative sensitivity that SPT to egg white, SPP to raw egg white and ovomucoid. Ovomucoid performed better than ovalbumin. For CM allergy diagnosis, SPP to fresh CM had higher relative sensitivity and specificity than SPT using commercial extracts and higher sensitivity than sIgE to CM. sIgE to Casein performed better than SPT to CM. For the diagnosis of hazelnut allergy, sIgE and SPT show higher relative sensitivity than Cor a 14 and can help in ruling out allergy to hazelnut. Cor a 14 has a higher specificity than Cor a 9 and can used to rule in allergic disease. sIgE to wheat and shrimp respectively had a higher sensitivity and so will be more useful to rule out allergy while w-5 gliadin and Pen m 1 had higher relative specificity and could be used to rule in wheat and shrimp allergy respectively.

Stratified analyses by pre-defined thresholds

We evaluated the sensitivity and specificity of the data at cut-off values commonly used as 95% PPV. For peanut SPT [?] 8mm, sIgE peanut [?] 15 kU_A /L and Ara h 2 [?] 0.35 kU_A /L are all highly specific ([?] 90 %) with results at or over those values ruling in food allergy. For HE allergy (both raw and cooked HE) an Ovomucoid [?] 0.35 kU_A/L was highly specific ([?] 90 %) and when positive rules in food allergy. For CMA, SPT [?] 8mm, was highly specific ([?] 90 %). We were unable to calculate sIgE CM [?]15 kU_A/L as the Bivariate binomial model failed to converge due to over dispersed parameter along with limited number of studies. Cor a 14 was highly specific for hazelnut allergy and with values [?] 0.35 kU_A /L can rule in food allergy. More information is available in Table 5.

Stratified analyses by age groups

We performed a sub-analysis using different age groups to assess the performance of diagnostic tests per age. Table 6 shows more details. For patients [?] 2 years old sIgE to peanut was more specific (94%) than for other age groups thus in toddlers a positive sIgE can help rule in allergic disease. Ara h 2 was specific for all age groups but especially for those [?] 16 years old where a positive result can accurately rule in allergy. sIgE to egg white was more specific in [?] 2 years olds (95%) compared to [?] 16 years olds where it only had 81% specificity for the diagnosis of raw HE allergy. For CMA, sIgE to CM and Casein had higher specificity ([?] 90 %) in the [?] 16 year olds compared to SPT.

Stratified analyses by geographical region

sIgE to peanut was highly sensitive in North America (94%) but presented lower sensitivities in Asia (75%), Australia (80%), Northern Europe (77%) and Western Europe (59%). Ara h 2 was highly specific in Australia (97%), Northern Europe (99%) and Western Europe (92%) but lower in Asian populations (79%). For the diagnosis of CMA, SPT and sIgE had a lower performance in Asian populations. SPT and sIgE had a lower specificity in Asia (74% and 89%) compared to Southern Europe (82% and 96%). For wheat allergy diagnostic accuracy of sIgE was also lower in Asia with a specificity of 73% vs 87% in Northern Europe. Overall, diagnostic tests showed variability according to geographical regions, more details can be seen in Table 7.

A summary of the diagnostic tests and its accuracy is shown in Table 8.

Discussion

Summary of the evidence

This SR of 149 diagnostic accuracy studies comprising 24,489 patients with suspected IgE-mediated FA shows that many IgE sensitization tests to suspected food triggers can support the diagnosis of IgE-mediated FA. Our findings favour the use of SPT and sIgE testing in clinical settings in the diagnosis of FA, especially for peanut, HE, CM, and tree nut allergies for which there is more evidence and their diagnostic accuracy is higher. Their high sensitivity means a negative test is useful for ruling out food allergy. Conversely, SPT and sIgE are less accurate in supporting the diagnosis of sesame, soy, wheat and shrimp allergies with moderate certainty of evidence.

High certainty of evidence for the diagnostic accuracy of CRD for ruling in food allergy (high specificity) has been demonstrated for several allergen components, namely: Ara h 2 in peanut, Cor a 14 in hazelnut and Ana o 3 in cashew. Ovomucoid can support the diagnosis of raw and cooked HE allergies whilst casein can support diagnosis of CM allergy; however, the accuracy of these allergen components is not superior to the allergen extracts. Current diagnostic tests (SPT, specific IgE to extracts or components) do not accurately reflect a subject's ability to tolerate baked foods and there is limited evidence on test accuracy for baked HE and baked CM allergies.

There is high certainty of evidence for the ability of BAT to diagnose peanut and sesame allergies, particularly in cases where the clinical history and results of other diagnostic tests are inconclusive. BAT had very good diagnostic performance, but is not widely available in clinical practice and the interpretation of BAT results can be complex and require expert knowledge.

It is important to note that the accuracy of these diagnostic tests may vary depending on the individual being tested and the specific allergen being evaluated. Diagnostic tests should always be interpreted in the context of the patient's pre-test probabilities (likelihood of having an FA before being tested) which is influenced by the medical history, co-morbidities and symptoms of presentation. There is also inherent variability in the diagnostic methods employed, particularly in the case of SPTs, the specific technique, individual performing the test, reagents and equipment used locally can potentially impact the outcomes. There can also be variability within subjects with the site of testing, time of day, temperature, exercise prior to testing, etc. To ensure comprehensive coverage in our analysis, we included studies utilizing a range of commercial extracts. It is important to consider that including studies which used different SPT reagents

or methods may have influenced the results [181]. These variations become particularly significant when dealing with allergens that lack standardization, such as fish [182] and shellfish [183].

Due to limited data available, we were unable to conduct a thorough meta-analyses on some food allergies, such as LTP-related food allergy, fish or shellfish allergies. For allergy tests not included in the SR there is insufficient evidence on the accuracy of that test for diagnosing IgE-mediated FA and no conclusions can be made on the certainty of evidence for its use in clinical practice.

Comparison with previous research

The previous SR on diagnostic test accuracy [8] included only studies where at least 50% of subjects had a DBPCFC as reference standard. While this approach may potentially increase the rigor of the studies included, it may also exclude evidence from various geographical regions and clinical settings where the logistics of a DBPCFC are not feasible or practical and may exclude a subset of patients seen in allergy clinic who do not have an indication or do not accept to undergo an OFC (e.g. highly sensitized subjects or patients with a recent history of reaction to the culprit food). As the objective of the current systematic review is to inform clinical recommendations, we chose to include index tests validated with other OFC techniques, namely open OFCs which are widely used in clinical practice and reliable in most clinical cases. We considered merging the studies included in the previous SR in this SR as an update and a way to increase the number of studies; however, we decided not to include older studies as methodologies have changed and available diagnostic tools have higher quality and diversity compared to those used prior to 2012.

Strengths and limitations

This SR was based on an ambitious, open and inclusive protocol, which aimed to include studies using any test to support the diagnosis of any food allergy. This way we captured all available evidence beyond the commonly used tests and the most common food allergies. However, we were limited by the number of studies available to do meta-analyses and by the quality of the available evidence. For instance, randomized controlled trials (RCTs) are considered the highest level of evidence for evaluating the effectiveness of diagnostic strategies; however, none of the studies found by our SR followed this methodology. It is important to note that RCTs may not always be feasible or practical for evaluating diagnostic strategies, especially if the strategy is already in widespread use as is the case for SPT, sIgE and CRD. In such instances, observational studies may be used to evaluate diagnostic tests. Evidence from our SR met these criteria and included cross-sectional and cohort study designs. Although we included 8 case control studies, this were judged as having high risk of bias and did not contribute to the certainty of evidence.

The heterogeneity of studies was a major obstacle for our SR complicating meaningful comparisons across studies. We found variability in the definition of the target condition, in the interpretation of test results and in the characteristics of the study populations. The different diagnostic thresholds implemented across the studies as well as the composition of the food extracts and commercial brands could affect the sensitivity and specificity of the tests used in the meta-analyses. Most studies on FA diagnosis have been conducted in children. Of the studies included, 60.4% were undertaken in a population [?]12 years of age. While these studies have provided important insights, they may not be fully generalizable to adults.

Our data highlights the important of having age validated cut-offs for allergy diagnostic test. Previous research has examined diagnostic test accuracy in specific age groups or ethnicities as one single population and pooled analysis of this data have thus far not been performed. While the individual raw data were not available, we were able to draw inferences of interest. For example, we found that peanut-sIgE had greater diagnostic accuracy in children under 2 years of age while Ara h 2-sIgE exhibited high specificity among adults.

Data included in the SR came mainly from Europe. Multiple geographical locations had only limited or no studies, such as Southeast Asia, Middle East, Africa and Central and South America. Only 13.4% of eligible data were derived from multicentre studies, highlighting a need for future collaboration to understand cross-population differences. The lack of representation from certain regions or populations can limit the

generalizability of the findings and may not accurately reflect the diversity of the global population.

While studies from Europe may provide valuable insights into the diagnosis in that region, it is important to recognize that test accuracy may vary in other parts of the world. We analyzed the data for different geographical regions and saw that Ara h 2-sIgE presented higher specificity in Northern Europe and Australia than in North America or Asia [184]. Furthermore, various ethnicities within a geographical region could have different diagnostic test accuracies. Most studies included in this SR made no reference to ethnicity variations within the populations studied. Only 12 studies mentioned the ethnicity of the subjects enrolled and 3 studies [80-82] analyzed the accuracy of diagnostic test between different ethnicities within the same population. Better descriptions of the study populations in future diagnostic test accuracy studies may help to establish more personalized approaches.

Another limitation of diagnostic studies is that the results are often dichotomous, meaning that a specific cut-off value is used to classify participants as allergic or tolerant, and this affects the reported diagnostic performance. For example, if a high cut-off value of 8 mm is used, sensitivity (proportion of participants with true food allergy with SPT [?]8mm) would be relatively low while the specificity (proportion of true tolerant participants with SPT <8mm) would be relatively high. This gives a misleading impression that the test has a low sensitivity when it may be good at ruling out food allergy when the SPT result is much smaller (e.g. <3mm). Ideally, a continuous model would be used linking actual results to probability of food allergy to accurately evaluate the results of allergy tests, but this approach requires additional raw data that were not available at this stage. Furthermore, we assessed the cut-offs employed in various studies; this approach using pooled estimates obtained may not accurately represent any specific cut-off point studied. Consequently, there is a need to exercise caution and rate the certainty of the findings lower due to the indirect nature of the evidence.

The sensitivity and specificity of the tests rely on the chosen threshold. Tables S5 and S6 demonstrate that when the threshold is set sufficiently high, almost every test for every food exhibit high specificity. Similarly, by setting the threshold low enough, most tests can achieve high sensitivity. Instead of solely concentrating on pooled results to determine optimal thresholds, it's important to consider that different studies may have been designed to optimize different factors. Consequently, pooling them together may not yield meaningful results. Utilizing the Youden's index to maximize sensitivity and specificity can lead to a threshold that does not perform well for either metric.

We performed meta-analyses for maximum sensitivity and specificity, whose aim was to provide insights into the specific cut-offs which could help rule in or out specific food allergies. A highly sensitive test when negative rules out allergic disease while a highly specific test when positive rules it in. The values obtained for the maximum specificity and sensitivity analysis were those provided by the authors as their maximum cut-offs; thus, this is dependent on the way the data is reported in the different studies.

Implications for practice, policy, and future research

In clinical practice, validated allergy tests can guide diagnosis and reduce the need for prolonged restrictive diets and high-risk OFC. To assist clinicians in decision-making, further research is necessary to determine the clinical impact and cost-effectiveness of allergy tests, including SPT, sIgE, CRD and BAT, and their use in various combinations to provide optimal diagnostic pathway for individual foods that is guided by patient outcomes and health economics.

The utility of diagnostic tests differs between geographical regions; stakeholders should promote studies that can correctly identify cut-offs for their specific populations considering ethnicity and age to improve the accurate diagnosis of IgE-mediated FA on a global scale. Ultimately, the goal of evaluating diagnostic strategies is to improve patient outcomes and inform clinical decision-making. The most appropriate study design should be chosen to achieve this goal, considering logistics and health economics in each geographical area.

Studies validating age-appropriate cut-offs are needed. There is lack of evidence in adult FA regarding

of allergen exposure due to dietary habits and comorbidities, including cross-sensitization to aeroallergens. More evidence is needed to assess food allergies in toddlers specifically for CM, HE and peanut. Future research should consider specific cut-offs which guide diagnosis of tolerance to baked goods (foods containing baked egg or baked milk specifically) and safety of introduction to sensitized patients with no history of prior food ingestion. Establishing these parameters for clinical practice can prevent prolonged unnecessary restrictive diets and improve quality of life for patients.

There is limited evidence on diagnostic tests for less common allergens such as fish, a wide variety of shellfish, fruits, vegetables, and legumes. Properly designed studies addressing allergy to these foods is needed.

To minimize bias and confounding, RCTs with DBPCFCs are required to evaluate accuracy of novel diagnostic strategies and their impact in patient outcomes and health economics. Such studies could provide high-quality evidence on the sensitivity, specificity and cost effectiveness of these tools compared to current tests.

Conclusions

There is strong evidence supporting the accuracy of SPT, sIgE, and CRD to support the diagnosis of peanut, CM, HE, and tree nut allergies and of BAT to support the diagnosis of peanut and sesame allergies, in patients with suggestive clinical history of IgE-mediated reactions. However, for other foods such as soy, sesame, wheat, and shrimp, the evidence is not as robust. Further research is needed to evaluate the usefulness of combining existing diagnostic tests and to assess novel diagnostic techniques to minimize the need for OFCs.

The upcoming FA diagnostic guidelines from EAACI will incorporate the findings of this review, along with expert opinions and other evidence, to provide practical recommendations for best practice to diagnose IgE-mediated food allergy.

Authors' contributions

All authors conceptualized the work, commented on the work and approved it for submission. MA, IB, AB, BB, MG, EG, SJ, HJ, DL, AMM, AP, ES, DW searched for studies, extracted data and performed risk of biased analysis. BM and CaR did dual review, cleaning and formatting data extracted and risk of biased assessment. CaR, AS, IS and GdT solved conflicts relating to studies inclusion, data summaries and risk of biased assessment. DC and RP provided methodological guidance. CrR performed the data analysis. CaR and AS and drafted the review.

Acknowledgements

The European Academy of Allergy and Clinical Immunology (EAACI) funded the systematic review to support the update of the guideline on IgE-mediated FA diagnosis. The funder had no role in the development of the protocol, conduct or write up of the review or decision to publish. The authors would like to acknowledge input in the initial stages of the SR from Drs. Jon Genuneit, Daniel Munblit and Robert Boyle.

Tables:

Table 1: Characteristics of diagnostics test accuracy studies for IgE-mediated food allergy.

Table 2: Estimates of the accuracy of diagnostic tests for IgE-mediated food allergy using optimal cut-off points.

Table 3: Risk of bias assessment per domain of diagnostic test accuracy studies in IgE-mediated food allergy.

Table 4. Comparison of tests to support the diagnosis of specific food allergies.

Table 5. Stratified analyses by pre-defined thresholds.

Table 6. Stratified analyses by age groups

Table 7. Stratified analyses by geographical region

Figures:

Supplementary Material

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