British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN

Final

Asthma: diagnosis, monitoring and chronic asthma management (update)

[E] Evidence reviews for diagnostic test accuracy of IgE in children

BTS/NICE/SIGN collaborative guideline NG245

November 2024

Final

Developed by BTS, NICE and SIGN

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Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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1. Total and specific serum IgE measures in children

1.1. Review question

In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of total and specific serum IgE measures in children?

1.1.1. Introduction

Asthma can be a difficult condition to diagnose, and it is not clear which tests are most useful in supporting a diagnosis. Immunoglobulin E (IgE) is a part of the immune system involved in the response to allergens. It can be measured in the blood both as the total quality of circulating IgE or as specific IgE against any allergens of interest. Allergic sensitisation is an important cause of asthma. IgE is therefore potentially useful in establishing a diagnosis of asthma and this evidence review was carried out to determine its clinical and cost-effectiveness as a diagnostic test.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

No test-and-treat evidence was found so only the diagnostic accuracy evidence was reported.

Table 1: PICO characteristics of diagnostic accuracy review question

Population	People with suspected asthma (presenting with respiratory symptoms). • Children and young people (5-16 years old) Exclusion: • Adults (≥17 years old) • People on steroid inhalers (washout period minimum of 4 weeks for inclusion)
Target condition	Asthma
Index test	Serum IgE • Total IgE <u>Stratification</u> • Different cut-off values / thresholds
Reference standard	Reference standard: Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) • FeNO

	Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.
Statistical measures	• Sensitivity (threshold upper 90%, lower 10%) • Specificity (threshold upper 80%, lower 50%) • Raw data to calculate 2X2 tables to calculated sensitivity and specificity • NPV, PPV
Study design	• Cross sectional studies • Cohort studies

1.1.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4. Diagnostic evidence

1.1.4.1. Included studies

Two cross-sectional diagnostic accuracy studies were included in the review;(Drkulec, et al., 2013, Livnat, et al., 2015) these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below in Table 3 and references in References. The committee set clinical decision thresholds as sensitivity: upper= 90% and lower= 10%, specificity: upper= 80% and lower= 50%. Values above the upper threshold indicated a test would be recommended and values below the lower threshold indicated a test is of no clinical use.

See also the study selection flow chart in Appendix C, sensitivity and specificity forest plots in Appendix E, and study evidence tables in Appendix D.

1.1.4.2. Excluded studies

See the excluded studies list in Appendix I.

1.1.5. Summary of studies included in the diagnostic evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Target condition	Index test	Reference standard	Comments
Drkulec 2013 (Drkulec et al., 2013)	Children between the ages of 1 and 15 years attending a children's hospital who had been referred for further	Asthma	Total IgE Cut-off: >116.6 kIU/L	At least 3 episodes of wheezing and/or a positive bronchodilator response (according to NIH GINA 2009).	Cross-sectional study Indirectness: Downgraded by two increments due to population (no indication of mean age (range

Study	Population	Target condition	Index test	Reference standard	Comments
	diagnosis after experiencing respiratory symptoms N= 131 Age range: 1-15 years Croatia				exceeds 5-year-old cut-off, and no information on prior ICS use) indirectness
Livnat 2015 (Livnat et al., 2015)	Children referred for a methacholine challenge test at a pulmonary outpatient clinic N= 131 Mean age (SD) Asthma: 12.4 (3.6), non-asthma: 12.9 (3.9) years Israel	Asthma	Total IgE Cut-off: >120 IU/mL	Methacholine challenge Cut-off: PC20-FEV_1 <8 mg/mL	Prospective cross-sectional study Indirectness: Downgraded by one increment due to population (ICS use not reported) indirectness

See Appendix D for full evidence tables

1.1.6. Summary of the diagnostic evidence

The assessment of the evidence quality was conducted with emphasis on test sensitivity and specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set clinical decision thresholds as sensitivity: upper= 90% and lower= 10%, specificity: upper= 80% and lower= 50%. Values above the upper threshold indicated a test would be recommended and values below the lower threshold indicated a test is of no clinical use. Pre-specified subgroup analyses included people with eczema, personal history of atopy, and family history of atopy. No subgroup analyses were conducted which resulted from an inadequate number of studies being identified that reported the same threshold values, resulting in no pooling of data, hence no heterogeneity could be observed. Nonetheless, neither of the included studies reported eczema or family history of atopy, with one study reporting the prevalence of personal history of atopy, including participants with mixed atopic histories.

Table 3: Clinical evidence summary: diagnostic test accuracy of total IgE in children

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
IgE (cut-off: >120 IU/mL vs methacholine challenge test (cut-off: <8 mg/mL)							
1 cross-sectional study	131	Very serious [1]	Not serious	Very serious[2]	Not serious	Sensitivity = 0.75 (0.62-0.85)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
		Very serious [1]	Not serious	Very serious[2]	Serious[3]	Specificity = 0.60 (0.48-0.72)	VERY LOW
IgE (cut-off: >116.6 kIU/L) vs clinician diagnosis based on >3 wheezing episodes and/or bronchodilator response							
1 prospective cross-sectional study	131	Very serious [1]	Not serious	Very serious[4]	Not serious	Sensitivity = 0.97 (0.90-1.00)	VERY LOW
		Very serious [1]	Not serious	Very serious[4]	Serious[5]	Specificity = 0.77 (0.64-0.87)	VERY LOW

1. *Downgraded by two increments due to concerns arising from the method of participant selection (method not reported) and interpretation of the index test and reference standard (not blinded)*
2. *Downgraded by two increments due to population (no information on ICS use prior to study entry) and reference standard (no clinician decision involved in diagnosis) indirectness*
3. *Downgraded by one increment due to the confidence interval overlapping the threshold referring to 'low specificity' (50%)*
4. *Downgraded by two increments due to population (age range 1-15 years with no average or variance data, and no information on ICS use prior to study entry) indirectness*
5. *Downgraded by one increment due to the confidence interval overlapping the threshold referring to 'high specificity' (80%)*

1.1.7. Economic evidence

1.1.7.1. Included studies

No health economic studies were included.

1.1.7.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix F.

1.1.8. Summary of included economic evidence

None.

1.1.9. Economic model

A health economic model was conducted focusing on sequences and combinations of diagnostic tests. This is reported in Evidence review 1.11.

1.1.10. Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 4: Total serum IgE test

Resource	Unit cost	Resource use	Source
Allergy test	£10.92[(a)]	1 test	Lothian NHS trust / Committee source
Emla 5% cream	£0.41 per g	1g	BNF 2022(Joint Formulary Committee, 2024)

Resource	Unit cost	Resource use	Source
Phlebotomy	£4.70	1	NHS reference costs 2021/2022 DAPS08(NHS England, 2022)
Total	**£16.03**		

(a) This includes staff and consumable costs

Table 5: Specific serum IgE test (7 allergens)

Resource	Cost	Source
Allergy tests[(a)]	£98.78	Lothian NHS trust / Committee source.
Phlebotomy	£4.70	NHS reference costs 2021/2022 DAPS08(NHS England, 2022)
Emla 5% cream	£0.41	BNF 2022(Joint Formulary Committee, 2024)
Total	**£103.89**	

(b) Based on following tests: total IgE, house dust mites, tree pollen, grass pollen, cat, dog and aspergillus

1.1.11. Evidence statements

1.1.11.1. Economic

- No relevant economic evaluations were identified.

1.2. The committee's discussion and interpretation of the evidence

1.2.1. The outcomes that matter most

Clinical and cost effectiveness

The outcomes considered for this review were: severe asthma exacerbations, mortality, quality of life, asthma control, hospital admissions, reliever/rescue medication use, lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF), adverse events (linear growth, pneumonia frequency, adrenal insufficiency, bone mineral density), inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks). For purposes of decision making, all outcomes were considered equally important and were therefore rated as critical by the committee. No relevant evidence was identified for any of the outcomes.

Diagnostic accuracy

The committee considered the diagnostic measures of sensitivity and specificity of total IgE for diagnosing asthma in children and young people as well as the positive and negative predictive values where these were reported by the studies. Clinical decision thresholds were set by the committee as sensitivity/specificity 0.9 and 0.8 above which a test would be recommended and 0.1 and 0.5 below which a test is of no clinical use.

1.2.2. The quality of the evidence

Two cross-sectional studies investigated the diagnostic accuracy of total IgE to detect asthma in children and young people. The quality of the evidence was very low as it was downgraded for risk of bias due to lack of clarity over the method of participant selection and a lack of detail over blinding of the index test and reference standard results. All evidence was downgraded due to indirectness, namely due to not reporting pre-study ICS use and including participants <5 years of age, or due to the reference standard not directly matching that specified in the review protocol due to not including a clinician decision in the asthma diagnosis. In both pieces of evidence imprecision was seen in the estimates of specificity.

1.2.3. Benefits and harms

Very low-quality evidence from one study reported IgE using a cut-off of >120 IU/mL, showing a moderate sensitivity of 0.75 and a specificity of 0.60.

Very low-quality evidence from one study reported IgE using a cut-off of >116.6 kIU/L, showing high sensitivity of 0.97 and moderate specificity of 0.77.

Based on the evidence and their clinical experience the committee agreed that measuring total IgE could be useful in the diagnosis of asthma in children and young people. The test offers reasonable sensitivity and specificity although this will depend on the cut-off used to define a positive test (see Other Considerations below).

1.2.4. Cost effectiveness and resource use

No relevant published health economic analyses were identified for this review question. The unit costs of general and specific serum IgE tests were presented to aid committee consideration of cost effectiveness.

Local anaesthetic cream, Emla 5%, is routinely applied to the venepuncture site before the test to minimise children's discomfort and, therefore, its cost was added to the calculation

assuming 1 gram needed for each child as reported in the BNF. The committee were aware that, after the anaesthetic was administered by a nurse, it takes between 30 to 60 minutes for the child to be ready for blood to be taken, although the nurse would be able to carry out other work during this period. Using costs provided by the committee from Lothian NHS trust, the cost of total serum IgE was estimated to amount to £16.03 (£10.92 for the allergy test, £4.70 for phlebotomy and £0.41 for the local anaesthetic). The cost of specific serum IgE was assumed to include total IgE and six of the most commonly tested allergens (house dust mites, tree pollen, grass pollen, cat, dog and aspergillus) and was estimated to amount to £103.89 (£98.78 for the allergy tests, £4.70 for phlebotomy and £0.41 for the local anaesthetic). The committee acknowledged that, in some cases, testing all allergens may not be necessary as evidence of sensitisation to house dust mite could be sufficient to reach a diagnosis. In these circumstances, the cost of the test would be significantly lower (£18.78).

The committee considered IgE testing alongside or in combination with a variety of tests for diagnosing asthma in children (see evidence review 1.11. The economic analysis found that IgE or skin prick tests are cost-effective when included in a diagnostic algorithm for children. Therefore, a recommendation to test children with a negative FeNO and BDR with one of these two allergic tests was made.

1.2.5. Other factors the committee took into account

A disadvantage of measuring total IgE is that it requires a blood sample to be taken and this is problematic in many children.

The committee were not able to specify which IgE cut-off point should be used to support an asthma diagnosis because the normal range for IgE levels varies considerably over childhood years. After discussion they agreed that a level above the upper limit of normal for the child’s age should be used.

IgE is also raised in other common childhood conditions and the committee emphasised that it should only be used as a test for asthma when there is also a good history to support the diagnosis.

1.2.6. Recommendations supported by this evidence review

Recommendation 1.2.8.

1.3 References

Diagnostic accuracy of total and specific serum IgE measures in children

Drkulec V, Nogalo B, Perica M, et al. (2013) Sensitization profile in differential diagnosis: allergic asthma vs. chronic (nonspecific) cough syndrome *Medical Science Monitor* 19: 409-415.

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National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. . London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

NHS England. 2021/22 National Cost Collection data. 2022. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ Last accessed: 26/02/2024.

Appendices

Appendix A – Review protocols

Review protocol for diagnostic accuracy and clinical and cost-effectiveness of total IgE for the diagnosis of asthma in children and young people

Field	Content
PROSPERO registration number	CRD42023437901
Review title	Accuracy and clinical and cost-effectiveness of serum IgE measures in diagnosing asthma in children
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of total and specific serum IgE measures in children?
Objective	To evaluate the diagnostic test value of serum IgE in diagnosing asthma This evidence review will have two stages: (1) Identify the clinical and cost effectiveness of diagnosis with the test (test plus treatment) (2) If evidence on clinical effectiveness is limited, the diagnostic accuracy will instead be determined
Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR)

	• Embase • MEDLINE • Epistemonikos Searches will be restricted by: • Diagnostic accuracy will be included from 2014 onwards • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
Condition or domain being studied	Asthma
Population	Inclusion: People with suspected asthma (presenting with respiratory symptoms). • Children and young people (5-16 years old) Exclusion:

	Adults (≥17 years old) People on steroid inhalers (washout period minimum of 4 weeks for inclusion)
Test	Serum IgE • Total IgE Stratification • Different cut-off values / thresholds
Reference standard	Effectiveness (test-and-treat) • Compare to each other Diagnostic accuracy • Reference standard Reference standard: Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) • FeNO Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.

	Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis. In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing. <u>Stratification</u> • Different reference standards Maximum time interval between measurements should be 12 months.
Types of study to be included	Clinical effectiveness (test and treat): • Systematic reviews of RCTs • Parallel RCTs Published NMAs and IPDs will be considered for inclusion. Diagnostic test accuracy: • Cross sectional studies • Cohort studies
Other exclusion criteria	POPULATION: • Occupational asthma /allergens • Mixed populations of asthma with other groups such as rhinitis (unless the results for the subgroup of asthma patients have been reported separately). TESTS: • Validation studies, or studies comparing different methods of measuring IgE.

	ANALYSIS/RESULTS: • Studies that look at levels of IgE • Studies that assess factors that may influence IgE measurements (eg. smoking, age, gender) • Studies that use IgE predict the development of asthma at a later follow-up time • Studies that look at correlations or agreement between tests, but not numbers of patients who were positive and negative • Studies that look at IgE to in relation to asthma severity STUDY TYPES: • Non-English language studies • Non comparative cohort studies • Before and after studies • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	Primary, secondary and community care settings
Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making a therefore have all been rated as critical: Clinical effectiveness (test and treat) outcomes: • Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at ≥6 months) • Mortality (dichotomous outcome at ≥6 months) • Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months)

	• Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months)
	• Hospital admissions (dichotomous outcome at ≥6 months)
	• Reliever/rescue medication use (continuous outcome at ≥3 months)
	• Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months). *Note: Extract FEV1 %pred over litres if both are reported. If only litres is reported, extract and analyse separately (do not extract both). For children, only use FEV1 %pred.*
	• Adverse events
	  ○ Linear growth (continuous outcome at ≥1 year),
	  ○ Pneumonia frequency (dichotomous outcome at ≥3 months)
	  ○ Adrenal insufficiency as defined by study, including short synacthen test and morning cortisol (dichotomous outcome at ≥3 months)
	  ○ Bone mineral density (continuous outcome at ≥6 months)
	• Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks)
	
	Diagnostic accuracy: Asthma diagnosis
	• Sensitivity (threshold upper 90%, lower 10%)
	• Specificity (threshold upper 80%, lower 50%
	• Raw data to calculate 2X2 tables to calculated sensitivity and specificity
	• NPV, PPV

Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • QUADAS-2 checklist

Strategy for data synthesis	<u>Diagnostic intervention (test and treat):</u> Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. WinBUGS will be used for network meta-analysis, if possible given the data identified. <u>Diagnostic accuracy:</u>

	Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention will be placed on specificity determined by the committee to be the primary outcome for decision making. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.	
Analysis of sub-groups	Sub-grouping (splitting conditional upon heterogeneity) • People with eczema • Personal history of atopy • Family history of atopy	
Type and method of review	☒	Intervention
	☒	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	

Anticipated or actual start date			
Anticipated completion date	31 July 2024		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☐	☐
	Formal screening of search results against eligibility criteria	☐	☐
	Data extraction	☐	☐
	Risk of bias (quality) assessment	☐	☐
	Data analysis	☐	☐
Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail asthmachronicmanagement@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
Review team members			

	From the National Guideline Centre: Bernard Higgins (Guideline lead) Sharon Swain (Guideline lead) Toby Sands (Systematic reviewer) Alfredo Mariani (Senior health economist) Lina Gulhane (Head of information specialists) Stephen Deed (Information specialist) Amy Crisp (Senior project manager) Melina Vasileiou (Senior systematic reviewer)
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10186
Other registration details	N/A
Reference/URL for published protocol	

Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	N/A	
Details of existing review of same topic by same authors	N/A	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	N/A	
Details of final publication	www.nice.org.uk	

Health economic review protocol

Table 6: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).(National Institute for Health and Care Excellence) **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

	The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of total and specific serum IgE measures in children?

Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 7: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 20 Dec 2023	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 20 Dec 2023	Randomised controlled trials Systematic review studies Observational studies Diagnostic tests studies Exclusions (conference abstracts, animal studies, letters, comments, editorials, case studies/reports) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2023 Issue 12 of 12 CENTRAL to 2023 Issue 12 of 12	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 20 Dec 2023	Exclusions (Cochrane reviews) English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/

5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	exp Immunoglobulin E/
25.	(immunoglobulin* E or immuno globulin E or gamma E or gammaglobulin* E or IgE or Ig E or TIge).ti,ab,kf.
26.	Radioallergosorbent Test/
27.	(radioallergosorbent* or radio allergosorbent* or radio allergo sorbent* or RAST).ti,ab,kf.
28.	((radioimmunoassay* or immunosorbent) adj3 allerg*).ti,ab,kf.
29.	or/24-28
30.	23 and 29
31.	exp "sensitivity and specificity"/
32.	(sensitivity or specificity).ti,ab.
33.	((pre test or pretest or post test) adj probability).ti,ab.
34.	(predictive value* or PPV or NPV).ti,ab.
35.	likelihood ratio*.ti,ab.
36.	likelihood function/
37.	((area under adj4 curve) or AUC).ti,ab.
38.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
39.	gold standard.ab.
40.	exp Diagnostic errors/
41.	(false positiv* or false negativ*).ti,ab.
42.	Diagnosis, Differential/
43.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
44.	or/31-43
45.	Epidemiologic studies/
46.	Observational study/
47.	exp Cohort studies/

48.	(cohort adj (study or studies or analys* or data)).ti,ab.
49.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
50.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
51.	Controlled Before-After Studies/
52.	Historically Controlled Study/
53.	Interrupted Time Series Analysis/
54.	(before adj2 after adj2 (study or studies or data)).ti,ab.
55.	exp case control study/
56.	case control*.ti,ab.
57.	Cross-sectional studies/
58.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
59.	or/45-58
60.	randomized controlled trial.pt.
61.	controlled clinical trial.pt.
62.	randomi#ed.ab.
63.	placebo.ab.
64.	randomly.ab.
65.	clinical trials as topic.sh.
66.	trial.ti.
67.	or/60-66
68.	Meta-Analysis/
69.	Meta-Analysis as Topic/
70.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
71.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
72.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
73.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
74.	(search* adj4 literature).ab.
75.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
76.	cochrane.jw.
77.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
78.	or/68-77
79.	30 and (44 or 59 or 67 or 78)

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.

9.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	*Immunoglobulin E/
24.	(immunoglobulin* E or immuno globulin E or gamma E or gammaglobulin* E or IgE or Ig E or TIge).ti,ab,kf.
25.	*Radioallergosorbent Test/
26.	(radioallergosorbent* or radio allergosorbent* or radio allergo sorbent* or RAST).ti,ab,kf.
27.	((radioimmunoassay* or immunosorbent) adj3 allerg*).ti,ab,kf.
28.	or/23-27
29.	22 and 28
30.	exp "sensitivity and specificity"/
31.	(sensitivity or specificity).ti,ab.
32.	((pre test or pretest or post test) adj probability).ti,ab.
33.	(predictive value* or PPV or NPV).ti,ab.
34.	likelihood ratio*.ti,ab.
35.	((area under adj4 curve) or AUC).ti,ab.
36.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
37.	diagnostic accuracy/
38.	diagnostic test accuracy study/
39.	gold standard.ab.
40.	exp diagnostic error/
41.	(false positiv* or false negativ*).ti,ab.
42.	differential diagnosis/
43.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
44.	or/30-43
45.	Clinical study/
46.	Observational study/
47.	Family study/
48.	Longitudinal study/
49.	Retrospective study/
50.	Prospective study/

51.	Cohort analysis/
52.	Follow-up/
53.	cohort*.ti,ab.
54.	52 and 53
55.	(cohort adj (study or studies or analys* or data)).ti,ab.
56.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
57.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
58.	(before adj2 after adj2 (study or studies or data)).ti,ab.
59.	exp case control study/
60.	case control*.ti,ab.
61.	cross-sectional study/
62.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
63.	or/45-51,54-62
64.	random*.ti,ab.
65.	factorial*.ti,ab.
66.	(crossover* or cross over*).ti,ab.
67.	((doubl* or singl*) adj blind*).ti,ab.
68.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
69.	crossover procedure/
70.	single blind procedure/
71.	randomized controlled trial/
72.	double blind procedure/
73.	or/64-72
74.	Systematic Review/
75.	Meta-Analysis/
76.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
77.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
78.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
79.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
80.	(search* adj4 literature).ab.
81.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
82.	cochrane.jw.
83.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
84.	or/74-83
85.	29 and (44 or 63 or 73 or 84)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Asthma] explode all trees
#2.	asthma*:ti,ab
#3.	#1 or #2
#4.	conference:pt or (clinicaltrials or trialsearch):so

#5.	#3 not #4
#6.	MeSH descriptor: [Immunoglobulin E] explode all trees
#7.	(immunoglobulin* E or immuno globulin E or gamma E or gammaglobulin* E or IgE or Ig E or TIge):ti,ab
#8.	MeSH descriptor: [Radioallergosorbent Test] this term only
#9.	(radioallergosorbent* or radio allergosorbent* or radio allergo sorbent* or RAST):ti,ab
#10.	((radioimmunoassay* or immunosorbent) near/3 allerg*):ti,ab
#11.	(or #6-#10)
#12.	#5 and #11

Epistemonikos search terms

1.	(title:("immunoglobulin* E" OR "immuno globulin E" OR "gamma E" OR "gammaglobulin* E" OR "IgE" OR "Ig E" OR "TIge" OR "radioallergosorbent*" OR "radio allergosorbent*" OR "radio allergo sorbent*" OR "RAST" OR "radioimmunoassay* allerg*" OR "immunosorbent allerg*") OR abstract:("immunoglobulin* E" OR "immuno globulin E" OR "gamma E" OR "gammaglobulin* E" OR "IgE" OR "Ig E" OR "TIge" OR "radioallergosorbent*" OR "radio allergosorbent*" OR "radio allergo sorbent*" OR "RAST" OR "radioimmunoassay* allerg*" OR "immunosorbent allerg*")) AND (title:(asthma*) OR abstract:(asthma*))

Health economic literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Asthma population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies and modelling.

Table 8: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 29 Dec 2023	
	Modelling 1946 – 29 Dec 2023	
Embase (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling

Database	Dates searched	Search filters and limits applied
	Quality of Life 1974 – 29 Dec 2023	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Modelling 1974 – 29 Dec 2023	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 Dec 2023	English language

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/
7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20

22.	3 not 21
23.	limit 22 to English language
24.	quality-adjusted life years/
25.	sickness impact profile/
26.	(quality adj2 (wellbeing or well being)).ti,ab.
27.	sickness impact profile.ti,ab.
28.	disability adjusted life.ti,ab.
29.	(qal* or qtime* or qwb* or daly*).ti,ab.
30.	(euroqol* or eq5d* or eq 5*).ti,ab.
31.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
32.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
33.	(hui or hui1 or hui2 or hui3).ti,ab.
34.	(health* year* equivalent* or hye or hyes).ti,ab.
35.	discrete choice*.ti,ab.
36.	rosser.ti,ab.
37.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
38.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
39.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
40.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
41.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
42.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
43.	or/24-42
44.	exp models, economic/
45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/
48.	monte carlo method/
49.	exp Decision Theory/
50.	(markov* or monte carlo).ti,ab.
51.	econom* model*.ti,ab.
52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	Economics/
55.	Value of life/
56.	exp "Costs and Cost Analysis"/
57.	exp Economics, Hospital/
58.	exp Economics, Medical/
59.	Economics, Nursing/
60.	Economics, Pharmaceutical/
61.	exp "Fees and Charges"/

62.	exp Budgets/
63.	budget*.ti,ab.
64.	cost*.ti.
65.	(economic* or pharmaco?economic*).ti.
66.	(price* or pricing*).ti,ab.
67.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
68.	(financ* or fee or fees).ti,ab.
69.	(value adj2 (money or monetary)).ti,ab.
70.	or/54-69
71.	23 and 43
72.	23 and 53
73.	23 and 70

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract or conference paper).pt.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	quality adjusted life year/
24.	"quality of life index"/
25.	short form 12/ or short form 20/ or short form 36/ or short form 8/
26.	sickness impact profile/

27.	(quality adj2 (wellbeing or well being)).ti,ab.
28.	sickness impact profile.ti,ab.
29.	disability adjusted life.ti,ab.
30.	(qal* or qtime* or qwb* or daly*).ti,ab.
31.	(euroqol* or eq5d* or eq 5*).ti,ab.
32.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
33.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
34.	(hui or hui1 or hui2 or hui3).ti,ab.
35.	(health* year* equivalent* or hye or hyes).ti,ab.
36.	discrete choice*.ti,ab.
37.	rosser.ti,ab.
38.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
39.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
40.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
41.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
42.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
43.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
44.	or/23-43
45.	statistical model/
46.	exp economic aspect/
47.	45 and 46
48.	*theoretical model/
49.	*nonbiological model/
50.	stochastic model/
51.	decision theory/
52.	decision tree/
53.	monte carlo method/
54.	(markov* or monte carlo).ti,ab.
55.	econom* model*.ti,ab.
56.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
57.	or/47-56
58.	health economics/
59.	exp economic evaluation/
60.	exp health care cost/
61.	exp fee/
62.	budget/
63.	funding/
64.	budget*.ti,ab.
65.	cost*.ti.
66.	(economic* or pharmaco?economic*).ti.

67.	(price* or pricing*).ti,ab.
68.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
69.	(financ* or fee or fees).ti,ab.
70.	(value adj2 (money or monetary)).ti,ab.
71.	or/58-70
72.	22 and 44
73.	22 and 57
74.	22 and 71

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Asthma EXPLODE ALL TREES
#2.	(asthma*)
#3.	#1 OR #2

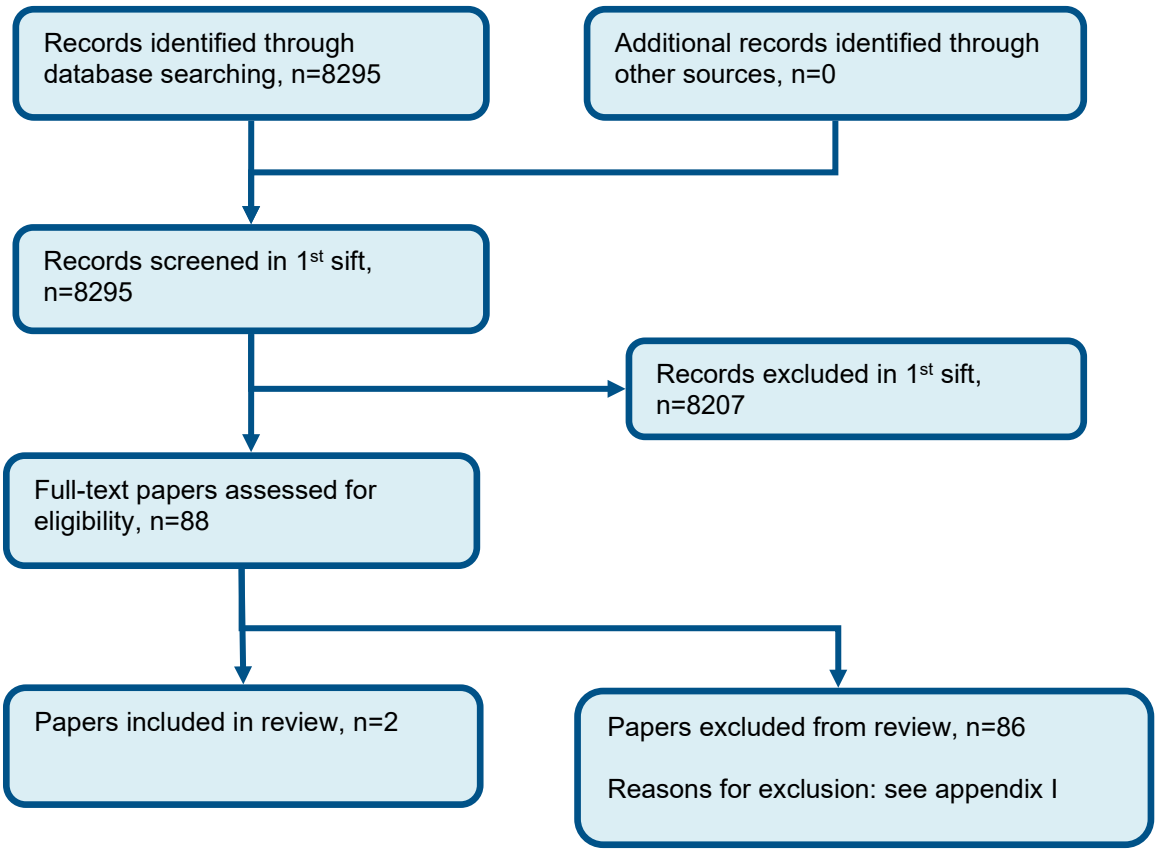
INAHTA search terms

1.	(Asthma)[mh] OR (asthma*)[Title] OR (asthma*)[abs]

Appendix C – Study selection

Diagnostic accuracy of total and specific serum IgE measures in children

Figure 1: Flow chart of clinical study selection for the review of diagnostic accuracy and clinical and cost effectiveness total IgE for the diagnosis of asthma in children and young people



Appendix D – Diagnostic evidence

Diagnostic accuracy of total and specific serum IgE measures in children

Reference	**Drkulec 2013 (Drkulec et al., 2013)**
Study type	Retrospective cross-sectional diagnostic study
Study methodology	Data source: Data collected from patients at Children's Hospital Srebrnjak, Department of Allergology and Pulmonology, Zagreb, Croatia Recruitment: Not reported
Number of patients	n = 131
Patient characteristics	Age, range: 1-15 years Gender (male to female ratio): 89:32 Ethnicity: Not reported Setting: Secondary care Country: Croatia ICS use: Not reported People with eczema: Not reported Personal history of atopy: Not reported Family history of atopy: Not reported Inclusion criteria: all patients experiencing respiratory symptoms who had been referred for further diagnosis Exclusion criteria: none reported

<table>
<tr><td>Reference</td><td colspan="5">Drkulec 2013 (Drkulec et al., 2013)</td></tr>
<tr><td></td><td colspan="5"></td></tr>
<tr><td>Target condition(s)</td><td colspan="5">Asthma</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5"><u>Index test</u>
Total serum IgE concentration was determined by fluoro immunochemical method using an automatic analyser.

Cut-off: 116.6 kIU/L (optimal threshold)

<u>Reference standard</u>
Children were defined as having clearly diagnosed allergic asthma if they had at least 3 episodes of wheezing and/or a positive bronchodilator response. The alternative diagnosis was chronic cough, defined as having less than 3 episodes of wheezing with persistent cough lasting more than 6 weeks,

Time between measurement of index test and reference standard:</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Prevalence= 54.2%</td></tr>
<tr><td></td><td>Index test +</td><td>69</td><td>14</td><td>83</td></tr>
<tr><td></td><td>Index test −</td><td>2</td><td>46</td><td>48</td></tr>
<tr><td></td><td>Total</td><td>71</td><td>60</td><td>131</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Sensitivity: 0.97 (95%CI 0.90-1.00)
Specificity: 0.77 (95%CI 0.64-0.87)
PPV: 78%
NPV: 95%</td></tr>
<tr><td>Source of funding</td><td colspan="5">None reported</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: Downgraded by two increments due to concerns arising from the selection of patients (unclear how they were selected and no exclusion criteria specified) and due to interpretation the index test and reference standard (unclear if results were interpreted blind to one another)
Indirectness: Downgraded by two increments due to very serious concerns arising from population (age range provided (1-15 years), but no indication of mean age of the study population – protocol specified children/young people 5-16 years of age, and no information on prior ICS use) indirectness</td></tr>
<tr><td>Comments</td><td colspan="5">2x2 data calculated from sensitivity, specificity and prevalence (54.2%) data reported in paper</td></tr>
</table>

Reference	**Livnat 2015 (Livnat et al., 2015)**
Study type	Prospective cross-sectional diagnostic accuracy study
Study methodology	Data source: Children referred for methacholine challenge test at a pulmonary outpatient clinic Recruitment: July 2011 – September 2012
Number of patients	n = 131
Patient characteristics	Age, mean (SD): Asthma: 12.4 (3.6), non-asthma: 12.9 (3.9) years Gender (male to female ratio): 79:52 Ethnicity: Not reported Setting: Pulmonary outpatient clinic Country: Israel People with eczema: Not reported Personal history of atopy: Asthma: 42.9%, non-asthma: 19.1% Family history of atopy: Not reported Inclusion criteria: None reported Exclusion criteria: Baseline FEV_1 <65%, presence of other systemic or lung disease, anti-inflammatory drugs, upper respiratory tract infection in the past month
Target condition(s)	Asthma
Index test(s) and reference standard	Index test Blood tests for IgE Cut-off: >120 IU/mL (optimal threshold) Reference standard

<table>
<tr><td>Reference</td><td colspan="5">Livnat 2015 (Livnat et al., 2015)</td></tr>
<tr><td></td><td colspan="5">Methacholine challenge tests were carried out using a dosimeter. Nebulized methacholine was inhaled for 2 min, with 5-min intervals between doses, until the maximal concentration or the end point was reached. PC20–FEV1 was determined by the provocative concentration that reduced FEV1 by 20 % from baseline. Patients with a positive MCT (PC20 <8 mg/ml) were considered as positive for asthma, while patients with a negative MCT (PC20 ≥8 mg/ml) were considered as negative.

Time between measurement of index test and reference standard: Immediate</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Prevalence= 48.1%</td></tr>
<tr><td></td><td>Index test +</td><td>47</td><td>27</td><td>74</td></tr>
<tr><td></td><td>Index test −</td><td>16</td><td>41</td><td>57</td></tr>
<tr><td></td><td>Total</td><td>63</td><td>68</td><td>131</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text
Sensitivity: 0.75 (95%CI 0.62-0.85)
Specificity: 0.60 (95%CI 0.48-0.72)
PPV: 64%
NPV: 71%</td></tr>
<tr><td>Source of funding</td><td colspan="5">None reported</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: Downgraded by two increments due to risk of bias arising from the selection of patients (not stated), and interpretation of the index test and reference standard (not blinded)
Indirectness: Downgraded by one increment due to population indirectness (ICS use not reported)</td></tr>
<tr><td>Comments</td><td colspan="5">2x2 data not reported, calculated from sensitivity, specificity and prevalence (48.1%) data reported in paper</td></tr>
</table>

Appendix E – Forest plots

Diagnostic Accuracy of total and specific serum IgE measures for children

Figure 1: IgE (cut-off: >120 IU/mL vs methacholine challenge test (cut-off: <8 mg/mL)

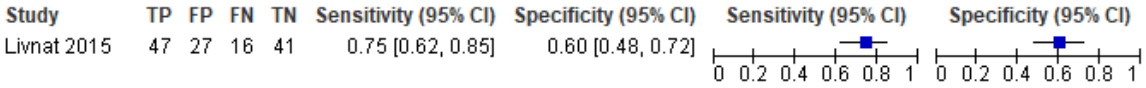
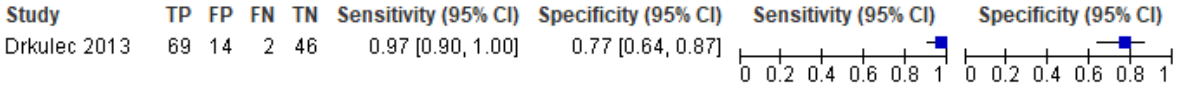


Figure 2: IgE (cut-off: >116.6 kIU/L) vs clinician diagnosis based on >3 wheezing episodes and/or bronchodilator response

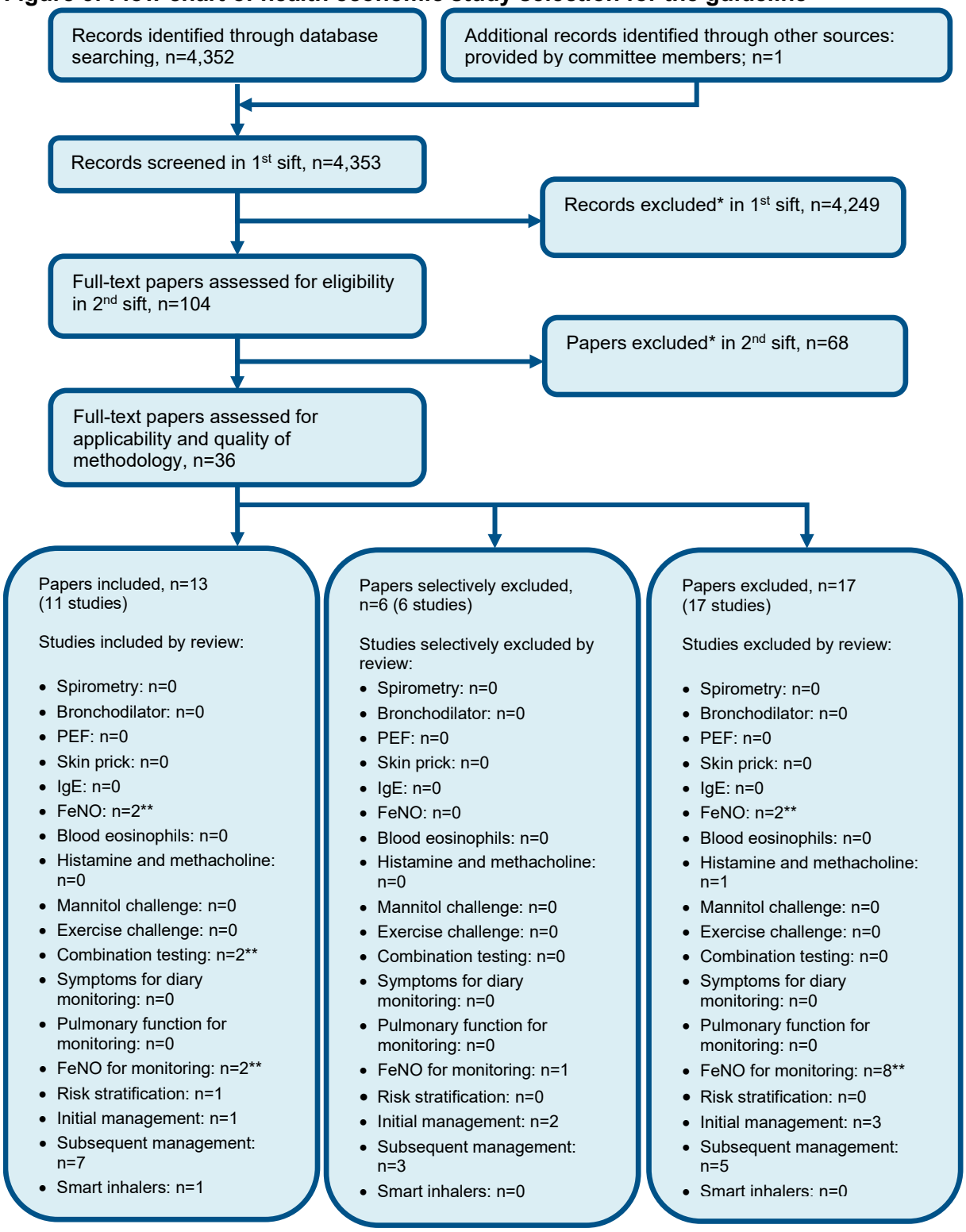


Total and specific serum IgE measures for children: test and treat

No evidence identified.

Appendix F – Economic evidence study selection

Figure 3: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

** Includes studies that are in multiple reviews

Appendix G Economic evidence tables

None.

Appendix H – Health economic model

No original economic modelling was undertaken for this review.

Appendix I – Excluded studies

Clinical studies

Diagnostic accuracy of total specific serum IgE measures in children

Table 9: Studies excluded from the clinical review

Study	Code [Reason]
Abdel-Aziz, M.I., Brinkman, P., Vijverberg, S.J.H. et al. (2020) eNose breath prints as a surrogate biomarker for classifying patients with asthma by atopy. Journal of Allergy and Clinical Immunology 146(5): 1045-1055	- Index test not relevant to this review protocol *FeNO used as index test*
Agarwal, Ritesh, Dua, Devika, Choudhary, Hansraj et al. (2017) Role of Aspergillus fumigatus-specific IgG in diagnosis and monitoring treatment response in allergic bronchopulmonary aspergillosis. Mycoses 60(1): 33-39	- Population not relevant to this review protocol *Already diagnosed with asthma*
Agodokpessi, G., Sagbo, G., Bigot, C. et al. (2019) Mite sensitization in children followed for respiratory allergy in a tropical African environment in Cotonou, Benin. Revue des Maladies Respiratoires 36(2): 135-141	- Study not reported in English
Ahlstedt, S, Eriksson, N, Lindgren, S et al. (1974) Specific IgE determination by RAST compared with skin and provocation tests in allergy diagnosis with birch pollen, timothy pollen and dog epithelium allergens. Clinical allergy 4(2): 131-40	- Population not relevant to this review protocol *Already diagnosed with asthma/allergic rhinitis*
Ahn, J.Y. and Choi, B.S. (2018) Clinical evaluation of specific immunoglobulin e in sputum in pediatric patients. Pediatric, Allergy, Immunology, and Pulmonology 31(2): 73-77	- Data not reported in an extractable format or a format that can be analysed *Data not reported for false positives and negatives*
Ahumada, V, Garcia, E, Dennis, R et al. (2015) IgE responses to Ascaris and mite tropomyosins are risk factors for asthma. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 45(7): 1189-200	- Population not relevant to this review protocol *Not presenting with respiratory symptoms*
al-Dusari, S N; Somorin, A O; Zaman, A U (1997) IgE antibodies to mites in Saudi Arabia. Allergy 52(2): 234-5	- Population not relevant to this review protocol *Average age >16 years*

Study	Code [Reason]
Arikoglu, T.; Batmaz, S.B.; Kuyucu, S. (2018) Allergen sensitization patterns in atopic children in mersin province of Turkey. Asim, Allerji, Immunoloji 16(3): 157-164	- Index test not relevant to this review protocol *IgE measured but not reported*
Armentia, A., Martin-Armentia, S., Pineda, F. et al. (2020) Allergic hypersensitivity to garlic and onion in children and adults. Allergologia et Immunopathologia 48(3): 232-236	- Population not relevant to this review protocol *Average age >16 years*
Bernardini, Roberto, Pucci, Neri, Azzari, Chiara et al. (2008) Sensitivity and specificity of different skin prick tests with latex extracts in pediatric patients with suspected natural rubber latex allergy--a cohort study. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 19(4): 315-8	- Condition not relevant to this review protocol *Study aiming to diagnose latex allergy*
Boersma, N.A., Meijneke, R.W.H., Kelder, J.C. et al. (2017) Sensitization predicts asthma development among wheezing toddlers in secondary healthcare. Pediatric Pulmonology 52(6): 729-736	- Population not relevant to this review protocol *Inclusion criteria <5 years*
Bolat, E., Arikoglu, T., Sungur, M.A. et al. (2017) Prevalence and risk factors for wheezing and allergic diseases in preschool children: A perspective from the Mediterranean coast of Turkey. Allergologia et Immunopathologia 45(4): 362-368	- Population not relevant to this review protocol *Average age <5 years*
Brand, P.L.P., Brohet, R.M., Schwantje, O. et al. (2022) Association between allergen component sensitisation and clinical allergic disease in children. Allergologia et Immunopathologia 50(2): 131-141	- Data not reported in an extractable format or a format that can be analysed
Burbach, G J, Heinzerling, L M, Edenharter, G et al. (2009) GA(2)LEN skin test study II: clinical relevance of inhalant allergen sensitizations in Europe. Allergy 64(10): 1507-1515	- Population not relevant to this review protocol *Average age >16 years*
Businco, L and Cantani, A (1990) Food allergy in children: diagnosis and treatment with sodium cromoglycate. Allergologia et immunopathologia 18(6): 339-48	- Review article but not a systematic review
Buslau, A., Voss, S., Herrmann, E. et al. (2014) Can we predict allergen-induced asthma in	- Population not relevant to this review protocol *Average age >16 years*

Study	Code [Reason]
patients with allergic rhinitis?. Clinical and Experimental Allergy 44(12): 1494-1502	
Byeon, J.H., Ri, S., Amarsaikhan, O. et al. (2017) Association between sensitization to mold and impaired pulmonary function in children with asthma. Allergy, Asthma and Immunology Research 9(6): 509-516	- Population not relevant to this review protocol *Already diagnosed with asthma*
Can, C.; Altinel, N.; Hatipoglu, S. (2021) Aeroallergen sensitisation patterns of children aged 5 years and younger with asthma and/or allergic rhinitis in Istanbul. Archives de Pediatrie 28(1): 7-11	- Population not relevant to this review protocol *Average age <5 years*
Cantani, A, Ferrara, M, Barbieri, C et al. (1990) Evaluation of new test (Phadiatop) for the screening of respiratory allergic disorders in children. Annals of allergy 64(2pt1): 158-61	- Condition not relevant to this review protocol *Study aims to diagnose atopy (rhinitis, asthma and rhino conjunctivitis) but doesn't differentiate between conditions*
Cassimos, Dimitrios C, Tsalkidis, Aggelos, Tripsianis, Gregorios A et al. (2008) Asthma, lung function and sensitization in school children with a history of bronchiolitis. Pediatrics international : official journal of the Japan Pediatric Society 50(1): 51-6	- Data not reported in an extractable format or a format that can be analysed *No information on false positives and negatives*
Caudri, Daan, Wijga, Alet H, Hoekstra, Maarten O et al. (2010) Prediction of asthma in symptomatic preschool children using exhaled nitric oxide, Rint and specific IgE. Thorax 65(9): 801-7	- Population not relevant to this review protocol *Average age <5 years*
Chang, Y.-C., Lee, T.-J., Huang, C.-C. et al. (2021) The role of phadiatop tests and total immunoglobulin E levels in screening aeroallergens: A hospital-based cohort study. Journal of Asthma and Allergy 14: 135-140	- Condition not relevant to this review protocol *Aiming to diagnose allergic rhinitis*
Chauveau, A., Dalphin, M.-L., Mauny, F. et al. (2017) Skin prick tests and specific IgE in 10-year-old children: Agreement and association with allergic diseases. Allergy: European Journal of Allergy and Clinical Immunology 72(9): 1365-1373	- Population not relevant to this review protocol *Birth cohort, not presenting with respiratory symptoms*
Chen, X.; Li, Y.; Zeng, M.Y. (2014) Diagnostic values of combination of free running asthma screening test and total serum allergen IgE level in children with asthma. Chinese Medical Journal 127(5): 873-877	- Population not relevant to this review protocol *Not presenting with respiratory symptoms*

Study	Code [Reason]
Choi, Inseon S, Koh, Youngil I, Koh, Jeom-seok et al. (2005) Sensitivity of the skin prick test and specificity of the serum-specific IgE test for airway responsiveness to house dust mites in asthma. The Journal of asthma : official journal of the Association for the Care of Asthma 42(3): 197-202	- Population not relevant to this review protocol *Average age >16 years*
Contreras, J Paola, Ly, Ngoc P, Gold, Diane R et al. (2003) Allergen-induced cytokine production, atopic disease, IgE, and wheeze in children. The Journal of allergy and clinical immunology 112(6): 1072-7	- Population not relevant to this review protocol *Birth cohort, not presenting with respiratory symptoms*
Cristina Diaz, M., Lavrut, A.J., Slullitel, P. et al. (2022) Usefulness of analytic tests for the diagnosis of cow's milk protein allergy. Archivos Argentinos de Pediatria 120(1): 21-29	- Population not relevant to this review protocol *Average age <5 years*
Cudowska, B and Kaczmarski, M (2004) Diagnostic value of birch recombinant allergens (rBet v 1, profilin rBet v 2) in children with pollen-related food allergy. Roczniki Akademii Medycznej w Bialymstoku (1995) 49: 111-5	- Data not reported in an extractable format or a format that can be analysed
Cuttitta, Giuseppina, Cibella, Fabio, La Grutta, Stefania et al. (2003) Non-specific bronchial hyper-responsiveness in children with allergic rhinitis: relationship with the atopic status. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 14(6): 458-63	- Population not relevant to this review protocol *Already diagnosed with allergic rhinitis*
Cvitanovic, Slavica, Znaor, Ljubo, Kanceljak-Macan, Bozica et al. (2007) Allergic rhinitis and asthma in southern Croatia: impact of sensitization to Ambrosia elatior. Croatian medical journal 48(1): 68-75	- Population not relevant to this review protocol *Already diagnosed with allergic rhinitis/asthma*
de Sousa, R.B., Medeiros, D., Sarinho, E. et al. (2016) Risk factors for recurrent wheezing in infants: a case-control study. Revista de saude publica 50: 15	- Population not relevant to this review protocol *Average age <5 years*
Dezfouli, S.G., Mothes-Luksch, N., Jensen, A.N. et al. (2020) Linking cross-reactivity clusters of food and respiratory allergens in PAMD@ to asthma and duration of allergy. World Allergy Organization Journal 13(12): 100483	- Population not relevant to this review protocol *Average age >17 years*

Study	Code [Reason]
Diaz-Vazquez, Carlos, Torregrosa-Bertet, Maria Jose, Carvajal-Uruena, Ignacio et al. (2009) Accuracy of ImmunoCAP Rapid in the diagnosis of allergic sensitization in children between 1 and 14 years with recurrent wheezing: the IReNE study. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 20(6): 601-9	- Reference standard not relevant to this review protocol *IgE used as reference standard for diagnosis of sensitization*
Dibek Misirlioglu, E., Gungor, S., Nacaroglu, H.T. et al. (2014) An evaluation of characteristics and concomitant allergic diseases in children with atopic dermatitis. Asim, Allerji, Immunoloji 12(2): 97-103	- Condition not relevant to this review protocol *Study aiming to diagnose atopic dermatitis*
Dogru, M. (2016) Investigation of asthma comorbidity in children with different severities of allergic rhinitis. American Journal of Rhinology and Allergy 30(3): 186-189	- Study design not relevant to this review protocol *No reference standard used*
Eidukaite, A., Gorbikova, E., Miskinyte, M. et al. (2023) Molecular sensitization patterns to cat and dog allergens in Lithuanian children population. World Allergy Organization Journal 16(10): 100827	- Reference standard not relevant to this review protocol *No reference standard*
Eigenmann, Philippe A, Kuenzli, Markus, D'Apuzzo, Vincenzo et al. (2009) The ImmunoCAP Rapid Wheeze/Rhinitis Child test is useful in the initial allergy diagnosis of children with respiratory symptoms. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 20(8): 772-9	- Population not relevant to this review protocol *Already diagnosed with asthma/allergic rhinitis*
Eysink, Petra E D, ter Riet, Gerben, Aalberse, Rob C et al. (2005) Accuracy of specific IgE in the prediction of asthma: development of a scoring formula for general practice. The British journal of general practice : the journal of the Royal College of General Practitioners 55(511): 125-31	- Population not relevant to this review protocol *Average age <5 years*
Fiocchi, A., Besana, R., Ryden, A.-C. et al. (2004) Differential diagnosis of IgE-mediated allergy in young children with wheezing or eczema symptoms using a single blood test. Annals of Allergy, Asthma and Immunology 93(4): 328-333	- Population not relevant to this review protocol *Inclusion criteria <5 years*
Freidhoff, L R and Marsh, D G (1993) Relationship among asthma, serum IgE levels	- Population not relevant to this review protocol

Study	Code [Reason]
and skin test sensitivity to inhaled allergens. International archives of allergy and immunology 100(4): 355-61	*Inclusion criteria >16 years*
Fuiano, N., Diddi, G., Delvecchio, M. et al. (2015) Diagnostic performance of the atopy patch test with inhalant allergens. Journal of Investigational Allergology and Clinical Immunology 25(1): 34-39	- Data not reported in an extractable format or a format that can be analysed *No false positive/negative data*
Gleeson, M., Cripps, A.W., Hensley, M.J. et al. (1996) A clinical evaluation in children of the Pharmacia ImmunoCAP system for inhalant allergens. Clinical and Experimental Allergy 26(6): 697-702	- Population not relevant to this review protocol *General population, not specifically people with suspected asthma*
Gonzalez-Mancebo, E., Dominguez-Ortega, J., Blanco-Bermejo, S. et al. (2017) Comparison of two diagnostic techniques, skin-prick test and component resolved diagnosis in the follow-up of a cohort of paediatric patients with pollinosis. Multicentre pilot study in a highly exposed allergenic area. Allergologia et Immunopathologia 45(2): 121-126	- Population not relevant to this review protocol *Already diagnosed with asthma*
Hoffmann-Petersen, B., Host, A., Toksvig Larsen, K. et al. (2013) Prevalence of IgE sensitization in Danish children with suspected asthma. Pediatric Allergy and Immunology 24(8): 727-733	- Population not relevant to this review protocol *30% of participants using ICS with no washout prior to testing*
Hofman, J.; Tobolczyk, J.; Puchnarewicz, A. (1997) Specific IgE against bacterial antigens in children with bronchospastic symptoms. International Review of Allergology and Clinical Immunology 3(3): 149-152	- Data not reported in an extractable format or a format that can be analysed *No data on negative test results*
Hou, Xiangqing, Luo, Wenting, Gan, Hui et al. (2022) Childhood blood eosinophils and symptoms of allergic disorders: a cross-sectional study in Southern China. Annals of medicine 54(1): 2929-2940	- Data not reported in an extractable format or a format that can be analysed *No diagnostic accuracy data reported*
Jang, Yoon Young and Ahn, Ji Young (2020) Evaluation of Fractional Exhaled Nitric Oxide in Pediatric Asthma and Allergic Rhinitis. Children (Basel, Switzerland) 8(1)	- Index test not relevant to this review protocol *FeNO used as index test*
Khakzad, M.R., Mirsadraee, M., Sankian, M. et al. (2009) Is serum or sputum eosinophil cationic protein level adequate for diagnosis of	- Population not relevant to this review protocol *Average age >17 years*

Study	Code [Reason]
mild asthma?. Iranian Journal of Allergy, Asthma and Immunology 8(3): 155-160	
Khan, M.R., Ali, F., Batool, S. et al. (2022) Association between Raised Serum IgE Levels and Bronchial Asthma in Children. Pakistan Journal of Medical and Health Sciences 16(4): 594-595	- Study design not relevant to this review protocol *No reference standard used*
Korevaar, D.A., Westerhof, G.A., Wang, J. et al. (2015) Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: A systematic review and meta-analysis. The Lancet Respiratory Medicine 3(4): 290-300	- Systematic review used as source of primary studies
Korppi, Matti, Hyvarinen, Mari, Kotaniemi-Syrjanen, Anne et al. (2008) Early exposure and sensitization to cat and dog: different effects on asthma risk after wheezing in infancy. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 19(8): 696-701	- Population not relevant to this review protocol *Average age <5 years*
Kovac, Kornelija, Dodig, Slavica, Tjesic-Drinkovic, Dorijan et al. (2007) Correlation between asthma severity and serum IgE in asthmatic children sensitized to Dermatophagoides pteronyssinus. Archives of medical research 38(1): 99-105	- Population not relevant to this review protocol *Already diagnosed with asthma*
Lee, Youn Kyung, Yang, Sohyoung, Park, Joohyun et al. (2015) House dust mite-specific immunoglobulin E and longitudinal exhaled nitric oxide measurements in children with atopic asthma. Korean journal of pediatrics 58(3): 89-95	- Population not relevant to this review protocol *Already diagnosed with asthma*
Maloney, Jennifer M, Rudengren, Magnus, Ahlstedt, Staffan et al. (2008) The use of serum-specific IgE measurements for the diagnosis of peanut, tree nut, and seed allergy. The Journal of allergy and clinical immunology 122(1): 145-51	- Condition not relevant to this review protocol *Study aiming to diagnose allergy to nuts*
Moverare, Robert, Persson, Eilif, Malinovschi, Andrei et al. (2023) Reference values of serum total IgE in Uppsala - comparison over four decades. Upsala journal of medical sciences 128	- Population not relevant to this review protocol *Retrospective analyses of biobank samples in people that did not necessarily have symptoms of asthma*

Study	Code [Reason]
Muthu, V., Singh, P., Choudhary, H. et al. (2020) Diagnostic Cutoffs and Clinical Utility of Recombinant Aspergillus fumigatus Antigens in the Diagnosis of Allergic Bronchopulmonary Aspergillosis. Journal of Allergy and Clinical Immunology: In Practice 8(2): 579-587	- Population not relevant to this review protocol *Already diagnosed with respiratory condition*
Ott, H., Stanzel, S., Ocklenburg, C. et al. (2009) Total serum IgE as a parameter to differentiate between intrinsic and extrinsic atopic dermatitis in children. Acta Dermato-Venereologica 89(3): 257-261	- Population not relevant to this review protocol *Average age <5 years*
Paganelli, R, Ansotegui, I J, Sastre, J et al. (1998) Specific IgE antibodies in the diagnosis of atopic disease. Clinical evaluation of a new in vitro test system, UniCAP, in six European allergy clinics. Allergy 53(8): 763-8	- Population not relevant to this review protocol *Inclusion criteria 8-81 years, average not reported*
Passalacqua, G, Melioli, G, Bonifazi, F et al. (2013) The additional values of microarray allergen assay in the management of polysensitized patients with respiratory allergy. Allergy 68(8): 1029-33	- Population not relevant to this review protocol *Average age >16 years*
Perzanowski, Matthew S, Ng'ang'a, Lucy W, Carter, Melody C et al. (2002) Atopy, asthma, and antibodies to Ascaris among rural and urban children in Kenya. The Journal of pediatrics 140(5): 582-8	- Population not relevant to this review protocol *Not presenting with respiratory symptoms*
Pescollderungg, L., Peroni, D., Locatelli, F. et al. (2000) Determination of serum eosinophil cationic protein, eosinophil count, and total IgE in children with different severities of atopic diseases. Pediatric Asthma, Allergy and Immunology 14(2): 109-118	- Study design not relevant to this review protocol *Assessing correlations between diagnostic tests*
Peveri, S, Pattini, S, Costantino, M T et al. (2019) Molecular diagnostics improves diagnosis and treatment of respiratory allergy and food allergy with economic optimization and cost saving. Allergologia et immunopathologia 47(1): 64-72	- Study design not relevant to this review protocol *No reference standard in study*
Pourpak, Z, Mozaffari, H, Gharagozlou, M et al. (2008) Asthma in patients with atopic dermatitis. Indian journal of pediatrics 75(2): 139-41	- Population not relevant to this review protocol *Not presenting with respiratory symptoms*
Redding, Gregory J, Singleton, Rosalyn J, DeMain, Jeffrey et al. (2006) Relationship	- Population not relevant to this review protocol *Not presenting with respiratory symptoms*

Study	Code [Reason]
between IgE and specific aeroallergen sensitivity in Alaskan native children. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 97(2): 209-15	
Saf, S., Sifers, T.M., Baker, M.G. et al. (2020) Diagnosis of Sesame Allergy: Analysis of Current Practice and Exploration of Sesame Component Ses i 1. Journal of Allergy and Clinical Immunology: In Practice 8(5): 1681-1688e3	- Full text paper not available
Saito, Junpei, Inoue, Keiichi, Sugawara, Aya et al. (2004) Exhaled nitric oxide as a marker of airway inflammation for an epidemiologic study in schoolchildren. The Journal of allergy and clinical immunology 114(3): 512-6	- Population not relevant to this review protocol *Not presenting with respiratory symptoms*
Salehi, Tahmineh, Pourpak, Zahra, Karkon, Shahnaz et al. (2009) The study of egg allergy in children with atopic dermatitis. The World Allergy Organization journal 2(7): 123-7	- Population not relevant to this review protocol *Average age <5 years*
Samolinski, B., Namyslowski, A., Raciborski, F. et al. (2016) The importance of specific IgE in epidemiology of allergic rhinitis and asthma - survey Epidemiology of Allergic Diseases in Poland (ECAP). Alergologia Polska - Polish Journal of Allergology 3(3): 102-107	- Study not reported in English
Santoso, H (1998) The value of a single skin prick testing for specific IgE Dermatophagoides pteronyssinus to distinguish atopy from non-atopic asthmatic children in the tropics. Asian Pacific journal of allergy and immunology 16(23): 69-74	- Population not relevant to this review protocol *Participants were already diagnosed with asthma prior to study entry - study aimed to distinguish between atopic and non-atopic asthma*
Schulze, J., Reinmuller, W., Herrmann, E. et al. (2013) Bronchial allergen challenges in children - safety and predictors. Pediatric Allergy and Immunology 24(1): 19-27	- Population not relevant to this review protocol *Already diagnosed with asthma*
Severcan, E.U., Bal, C.M., Gulen, F. et al. (2022) Identifying wheezing phenotypes in a pediatric Turkish cohort. Journal of Asthma 59(7): 1298-1304	- Study design not relevant to this review protocol *Longitudinal study examining prognostic factors for wheezing*
Shaikh, W.A. and Shaikh, S.W. (2006) Skin prick test - More reliable than estimation of	- Population not relevant to this review protocol *Average age >16 years*

Study	Code [Reason]
specific IgE in allergy diagnosis. Journal of the Indian Medical Association 104(10): 592-595	
Shibata, R., Fujiogi, M., Nanishi, M. et al. (2022) Total immunoglobulin E in infant bronchiolitis and risk of developing asthma. Journal of Allergy and Clinical Immunology: In Practice 10(10): 2761-2763e2	- Study design not relevant to this review protocol *Prospective study of factors predicting development of asthma*
Soriano, J.B., Anto, J.M., Sunyer, J. et al. (1999) Risk of asthma in the general Spanish population attributable to specific immunoresponse. International Journal of Epidemiology 28(4): 728-734	- Population not relevant to this review protocol *Not presenting with respiratory symptoms*
Tang, R B; Wu, K G; Hwang, B (1994) Comparison between skin testing and in vitro testing for diagnosis of allergen in asthmatic children. Zhonghua yi xue za zhi = Chinese medical journal; Free China ed 54(4): 246-50	- Full text paper not available
Tee, R D, Cullinan, P, Welch, J et al. (1998) Specific IgE to isocyanates: a useful diagnostic role in occupational asthma. The Journal of allergy and clinical immunology 101(5): 709-15	- Population not relevant to this review protocol *Average age >16 years*
Valovirta, E, Jacobsen, L, Ljorring, C et al. (2006) Clinical efficacy and safety of sublingual immunotherapy with tree pollen extract in children. Allergy 61(10): 1177-83	- Study design not relevant to this review protocol *Intervention study*
Vermani, M.; Vijayan, V.K.; Agarwal, M.K. (2015) Identification of Aspergillus (A flavus and A niger) allergens and heterogeneity of allergic patients' IgE response. Iranian Journal of Allergy, Asthma and Immunology 14(4): 361-369	- Population not relevant to this review protocol *Already diagnosed with respiratory condition*
Visitsunthorn, N., Sripramong, C., Bunnag, C. et al. (2017) Comparison between specific IgE levels and skin prick test results of local and imported American cockroach, dog, cat, dust mites and mold allergen extracts. Asian Pacific Journal of Allergy and Immunology 35(1): 60-65	- Population not relevant to this review protocol *Average age >17 years*
Weinmayr, G, Genuneit, J, Nagel, G et al. (2010) International variations in associations of allergic markers and diseases in children: ISAAC Phase Two. Allergy 65(6): 766-75	- Population not relevant to this review protocol *Not presenting with respiratory symptoms*

Study	Code [Reason]
Welsh, Kathryn G, Holden, Karl A, Wardlaw, Andrew J et al. (2021) Fungal sensitization and positive fungal culture from sputum in children with asthma are associated with reduced lung function and acute asthma attacks respectively. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology 51(6): 790-800	- Population not relevant to this review protocol *Already diagnosed with asthma*
Wenting, L., Baoqing, S., Nili, W. et al. (2014) Distribution and component analysis of 51 allergens among patients with allergic diseases in Guangzhou, Southern China. Allergy: European Journal of Allergy and Clinical Immunology 69(suppl99): 303	- Conference abstract
Yalcin, A.D., Bisgin, A., Kargi, A. et al. (2012) Serum-soluble TRAIL levels in patients with severe persistent allergic asthma: Its relation to omalizumab treatment. Medical Science Monitor 18(3): pl11-pl15	- Population not relevant to this review protocol *Average age >17 years*
Yan, Junmei, Chen, Jing, Li, Haiqi et al. (2018) The comparison of skin prick test, serological specific IgE test and solid phase immunoassay in the diagnosis of infantile allergic diseases. Minerva pediatrica	- Full text paper not available
Zahoor, F., ur Rehman, F., Shahnawaz, K. et al. (2019) Role of serum CRP, IgE, and complement levels in pediatric population. Medical Forum Monthly 30(8): 27-30	- Population not relevant to this review protocol *Already diagnosed with asthma*
Zhang, L; Prietsch, SOM; Ducharme, FM (2014) Inhaled corticosteroids in children with persistent asthma: effects on growth. Cochrane Database of Systematic Reviews	- Study design not relevant to this review protocol *Not a diagnostic accuracy study*

Total and specific serum IgE measures in children: Test and treat

No studies were identified for this review.

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.