British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN

Final

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

[D] Evidence review for accuracy of skin prick test in children for the diagnosis of asthma

BTS/NICE/SIGN collaborative guideline NG245

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Final

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1. Skin prick tests in children

1.1. Review question

In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of skin prick tests 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. Skin prick testing is done by applying small drops of allergen extracts in solution to the skin (usually the anterior forearm), then using a small lancet to penetrate the superficial skin, allowing the solution to enter the epidermis and dermis. If the patient is sensitised (allergic) to any allergens then they would typically mount a rapid immune response that would lead to skin redness, itchiness and swelling within 10-15 minutes. Skin prick testing 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	Inclusion: People with suspected asthma (presenting with respiratory symptoms). • Children/young people (5-16 years old) Exclusion: • Young children (<5 years old) • Adults (≥17 years old) • People on steroid inhalers (washout period minimum of 4 weeks for inclusion)
Target condition	Asthma
Index test	Skin prick tests for the most common allergens (reported separately) • House dust mites • Cat • Dog • Grass pollen* (native UK grasses) • Tree pollen* (native UK trees) • Mixed pollens* (native UK species) • Aspergillus • Alternaria • Cladosporium Cut off values: 3mm Wheal (skin reaction) greater than the negative control in the presence of a positive control. • Specific IgE – reported separately for different allergens. Cut-off as specified in study.

	* Mainland Europe (including Denmark; excluding Norway, Sweden, Finland, Iceland, Russia, Greece), North America (USA + Canada), Australia, New Zealand (as trees/grasses/pollen similar to UK in included countries but not in other countries) Stratification: • Different cut-offs
Reference standard	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. Stratification • Different reference standards Maximum interval between initial/suspected diagnosis and confirmation of asthma: 12 months.
Statistical measures	• Sensitivity (thresholds: upper 90%, lower 10%) • Specificity (thresholds: 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

Three observational studies were included in the review;(Drkulec, et al., 2013, Gaig, et al., 1999, Miraglia Del Giudice, et al., 2002) 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 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.

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

Three studies from the previous NICE guidance on this topic were excluded from the current review due to containing a population not relevant to the current review (adult population)

See the excluded studies list in Appendix H.

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)	N=131 Children between the ages of 1 and 15 years attending a children's hospital who had been referred for further diagnosis after experiencing respiratory symptoms Croatia	Asthma	SPT testing with common allergens in the region: house dust mites (*Dermatophagoides pteronyssinus*), common ragweed (*Ambrosia artemisifoliae*), and timothy grass (*Phleum pratense*) pollen. Cut-offs (IgE): House dust mites – 0.35 kIU/L Common ragweed– 0.39 kIU/L Timothy grass pollen: 0.35 kIU/L Cut-off (SPT): not reported	At least 3 episodes of wheezing and/or a positive bronchodilator response (according to NIH GINA 2009).	Retrospective cross-sectional study ICS use: Not reported Indirectness: Downgraded by two increments due to population (average age not reported (range exceeds 5-year-old cut-off), and ICS use not reported) indirectness
Gaig 1999 (Gaig et al., 1999)	N=94 Patients who had been sharing a bunk with a	Allergic asthma	Skin prick tests with the two main species of mites in the area (*Dermatophagoides pteronyssinus* and	Clinical diagnosis based on history and current symptoms	Prospective cross-sectional study

Study	Population	Target condition	Index test	Reference standard	Comments
	sibling for >6 months, always occupying the same position on the bunk, attending an outpatient allergy clinic Mean (SD) age: 16 (6) Spain		*Dermatophagoides farinae*) were performed, using histamine chloride 10 mg/mL and saline as control. Cut-off: skin wheal diameter ≥3 mm larger than that caused by the dilutant control		ICS use: Not reported. Indirectness: Downgraded by two increments due to population (mean age within age range, standard deviation exceeded upper limit, ICS not reported) indirectness
Miraglia Del Giudice 2002 (Miraglia Del Giudice et al., 2002)	Patient records of children attending a paediatric asthma and allergy centre with physician or self-referred symptoms of atopic disease N= 1426 Mean age: not reported, range 0-12 years (586 aged 0-3 years, 524 aged 4-6 years, 316 aged 7-12 years) Italy	Asthma (alternate diagnosis of allergic rhino conjunctivitis, atopic dermatitis or food allergy)	Skin prick test using a standard battery of aeroallergens and food allergens: house dust mites *Parietaria officinalis*, grasses, moulds, dog fur, cat fur, egg albumin, and cow's milk. Cut-off: skin wheal ≥3 mm diameter in response to at least one allergen	Asthma was defined as three or more episodes of wheezing before 2 years of age, or one episode from 2 years of age, or any episode of wheezing independent of age, if combined with atopic symptoms in the family or other atopic symptoms in the child.	Retrospective cross-sectional study ICS use: Not reported. Indirectness: Downgraded by two increments due to population (includes people <5 years of age and no information on ICS use), index test (includes allergens not specified in protocol) 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/specificity =0.90 and 0.80 above which a test would be recommended and 0.10 and 0.50 below which a test is of no clinical use.

Table 3: Clinical evidence summary: diagnostic test accuracy of skin prick testing in children

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
House dust mites (*Dermatophagoides pteronyssinus*) specific IgE (cut-off: 0.35 KIU/L) vs clinician diagnosis with bronchodilator response							
1 prospective cross-sectional study	131	Very serious[1]	Not serious	Very serious[2]	Serious[3]	Sensitivity= 0.89 (0.79-0.95)	VERY LOW
		Very serious[1]	Not serious	Very serious[2]	Not serious	Specificity= 0.97 (0.88-1.00)	VERY LOW
House dust mites (*Dermatophagoides pteronyssinus* and/or *farinae*) (cut-off: ≥3mm greater than control) vs clinical diagnosis based on history and symptoms							
1 prospective cross-sectional study	67	Serious[4]	Not serious	Very serious[5]	Serious[3]	Sensitivity= 0.85 (0.71-0.94)	VERY LOW
		Serious[4]	Not serious	Very serious[5]	Serious[6]	Specificity= 0.35 (0.17-0.56)	VERY LOW
Common ragweed (*Ambrosia artemisifoliae*) specific IgE (cut-off: 0.39 KIU/L) vs clinician diagnosis with bronchodilator response							
1 prospective cross-sectional study	131	Very serious[1]	Not serious	Very serious[2]	Not serious	Sensitivity= 0.56 (0.44-0.68)	VERY LOW
		Very serious[1]	Not serious	Very serious[2]	Serious[7]	Specificity= 0.80 (0.68-0.89)	VERY LOW
Timothy grass (*Phleum pratense*) specific IgE (cut-off: 0.35 KIU/L) pollen vs clinician diagnosis with bronchodilator response							
1 prospective cross-sectional study	131	Very serious[1]	Not serious	Very serious[2]	Not serious	Sensitivity= 0.61 (0.48-0.72)	VERY LOW
		Very serious[1]	Not serious	Very serious[2]	Serious[7]	Specificity= 0.82 (0.70-0.90)	VERY LOW
House dust mites (*Dermatophagoides pteronyssinus*) skin prick test (cut-off: not specified) vs clinician diagnosis with bronchodilator response							
1 prospective cross-sectional study	131	Very serious[1]	Not serious	Very serious[2]	Serious[3]	Sensitivity= 0.83 (0.72-0.91)	VERY LOW
		Very serious[1]	Not serious	Very serious[2]	Serious[7]	Specificity= 0.72 (0.59-0.83)	VERY LOW
Common ragweed (*Ambrosia artemisifoliae*) skin prick test (cut-off: not specified) vs clinician diagnosis with bronchodilator response							
1 prospective cross-sectional study	131	Very serious[1]	Not serious	Very serious[2]	Not serious	Sensitivity= 0.66 (0.54-0.77)	VERY LOW
		Very serious[1]	Not serious	Very serious[2]	Serious[6]	Specificity= 0.48 (0.35-0.62)	VERY LOW
Timothy grass (*Phleum pratense*) skin prick test (cut-off: not specified) pollen vs clinician diagnosis with bronchodilator response							
1 prospective cross-sectional study	131	Very serious[1]	Not serious	Very serious[2]	Not serious	Sensitivity= 0.66 (0.54-0.77)	VERY LOW
		Very serious[1]	Not serious	Very serious[2]	Serious[6]	Specificity= 0.50 (0.37-0.63)	VERY LOW
Positive skin prick test to ≥1 of House dust mites (*Dermatophagoides pteronyssinus*), Common ragweed (*Ambrosia artemisifoliae*) and Timothy grass (*Phleum pratense*) (cut-off: not specified) pollen vs clinician diagnosis with bronchodilator response							

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
1 prospective cross-sectional study	131	Very serious[1]	Not serious	Very serious[2]	Not serious	Sensitivity= 0.79 (0.68-0.88)	VERY LOW
		Very serious[1]	Not serious	Very serious[2]	Not serious	Specificity= 0.92 (0.82-0.97)	VERY LOW
Standard battery of aero and food allergens (cut-off: 3mm to at least one allergen) vs clinician diagnosis based on symptoms and family and child history							
1 retrospective cross-sectional study	1426	Serious[6]	Not serious	Very serious[8]	Not serious	Sensitivity= 0.44 (0.41-0.48)	VERY LOW
		Serious[6]	Not serious	Very serious[8]	Not serious	Specificity= 0.56 (0.52-0.61)	VERY LOW

[1] *Downgraded by two increments due to concerns arising from the method of participant selection (method not reported) and from the interpretation of the index test and reference standard (unclear if blinded)*
[2] *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*
[3] *Downgraded by one increment due to the 95%CI overlapping the upper threshold corresponding to 'high sensitivity' (90%)*
[4] *Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded)*
[5] *Downgraded by two increments due to population (no information on ICS use prior to study entry) and reference standard (unclear if study was diagnosing asthma or wheeze) indirectness*
[6] *Downgraded by one increment due to the 95%CI overlapping the lower threshold corresponding to 'low specificity' (50%)*
[7] *Downgraded by one increment due to the 95%CI overlapping the upper threshold corresponding to 'high specificity' (80%)*
[8] *Downgraded by two increments due to population (included participants aged <5 years, and no information on ICS use prior to study entry) and index test (included allergens not listed on this review protocol) indirectness*

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: Unit costs

Resource	Unit costs	Source
Cost of vials (a)	£20	Cannon 2019 inflated to 2022(Cannon, et al., 2019)
No. of drops per vial (b)	80	NICE Food Allergy CG116(National Institute for Health and Care Excellence, 2011)
Lancet (200) (c)	£13.78	MedicalWorld(Medical World)
Controls x2 (d)	£15.63	NICE Food Allergy CG116(National Institute for Health and Care Excellence, 2011) inflated to 2022
Nurse time minutes (e)	40	NICE Food Allergy CG116(National Institute for Health and Care Excellence, 2011)
Nurse cost per hour (f)	£63.38	PSSRU 2022(Jones, et al.)
No of allergies tested for (g)	8	NICE Food Allergy CG116(National Institute for Health and Care Excellence, 2011)
Total [(a)]	**£45**	

Note: all prices are VAT exclusive
*(a) Calculated as following: {[(a/b) + (c/200)]*g}+(d/b)+(f/60*e)*

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 the skin prick test 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

Test and treat studies

No relevant clinical studies were identified comparing the clinical effectiveness of diagnosis of asthma based on skin prick tests for any of the allergens specified in the review protocol.

Diagnostic accuracy

Three observational studies were included in this review. Studies examined the diagnostic accuracy of skin prick test for allergens including Cladosporium, cat, dog, grass pollen, aspergillus and house dust mites to detect asthma in children and young people. One study reported values for specific IgE as well as skin prick tests in the same study sample. Data for specific IgE was included in this review, as opposed to review 1.5, as the committee considered specific IgE and skin prick tests to be more closely related than specific and general IgE measurements.

The quality of the evidence was very low across studies as it was downgraded for risk of bias, most frequently due to concerns surrounding the method of participant selection or a lack of clarity over blinding of the index test and reference standard results. Indirectness was also present in all evidence due to not reporting the ICS use of participants prior to the study. Less frequently occurring was the inclusion of participants <5 years of age, a lack of clarity over the definition of asthma, and the inclusion of allergens not specified in this review protocol, all of which led to further downgrading for indirectness.

1.2.3. Benefits and harms

Very low-quality evidence from one study showed a high sensitivity (0.89) and specificity (0.97) of house dust mites specific IgE to detect asthma in children aged for 1 to 15 years. Other specific IgE allergens tested in the same study including common ragweed and timothy grass pollen showed a lower sensitivity to detect asthma (ranging from 0.56 to 0.60 respectively) and slightly lower specificity (0.80-0.82 respectively). However, the committee

noted that specificity still met the pre-specified threshold above which a test could be recommended (0.80).

Diagnostic accuracy of skin prick test for the same allergens followed a similar pattern, showing a high sensitivity (0.84) and specificity (0.71) for house dust mites and lower diagnostic accuracy for common ragweed and timothy grass pollen (sensitivity: 0.66 for both, specificity: 0.48 and 0.50, respectively). In this case specificity did not meet the threshold for decision making. Evidence from the same study, using skin prick positivity to one or more allergens, showed moderate sensitivity of 0.79 and a high specificity of 0.91. The committee acknowledged the limitations of the evidence, namely due to very serious risk of bias resulting from an unclear method of participant recruitment and unclear blinding of test results. This evidence was also indirect due to including participants <5 years of age and not reporting ICS use prior to study entry.

Very low-quality evidence from one study reported skin prick test to house dust mite (*Dermatophagoides pteronyssinus* and/or *farinae*), showing a high sensitivity (0.85) and low specificity (0.35) to detect allergic asthma. The committee acknowledged the limitations of the evidence, namely concerns arising from risk of bias due to a lack of clarity over blinding of test results, and indirectness due to unclear pre-study ICS use and a lack of clarity over asthma definition for diagnosis.

Finally, very low-quality evidence from one study reported skin prick testing using a standard battery of aero and food allergens (house dust mites, *Parietaria officinalis*, grasses, moulds, dog fur, cat fur, egg albumin, and cow's milk) with positivity for asthma defined as being sensitisation to at least one allergen. This showed moderate sensitivity (0.44) and specificity (0.56). Although there was no imprecision in the effect estimates the committee had concerns over the relevance of these findings as the battery of tests included allergens not specified in the current review protocol and no objective tests was used to obtain the final diagnosis of asthma, both of which were reflected in the overall quality assessment. Therefore, the committee agreed these findings were of very limited usefulness.

The committee agreed that the evidence showed that testing for house dust mite sensitisation (either using a skin prick test or measuring specific IgE) gave results that were both sensitive and specific for asthma, providing they were used in the context of an appropriate clinical history. However, there are practical difficulties with both (see Other Considerations below), and they reasoned that the tests might be most useful when other tests have been performed but the diagnosis is still in doubt.

1.2.4. Cost effectiveness and resource use

No relevant published health economic analyses were identified for this review question. The unit cost of a skin prick test in children was presented to aid committee consideration of cost effectiveness.

NICE guideline on food allergy (CG116) was used to estimate unit costs and resource use. The committee were aware that a skin prick test for a child with suspected asthma would have costs resembling a skin prick test for suspected food allergy as for both tests a battery of 8 allergens is usually tested for. NICE Food Allergy guideline reported a nurse time required per test of 20 minutes. This was seen by the committee as a too optimistic assumption for a test administered to young children and therefore the duration was raised to 40 minutes. The final cost per test was estimated to be around £44.95.

The committee considered skin prick tests in children alongside or in combination with a variety of tests for asthma (see evidence review 1.11). The economic analysis showed that skin prick test or IgE is cost-effective when included in a diagnostic algorithm for children. The committee acknowledged that skin prick test may not be available in some areas due to the lack of centres and training, so they recommended either a skin prick test or IgE to allow flexibility and ensure that the recommendations are implementable.

1.2.5. Other factors the committee took into account

Skin prick testing is not currently available in primary care settings in the UK. It is also relatively time consuming because the test reagents need to be applied to the skin and it is then necessary to allow time for a reaction to occur, and then to read the results. Specific-IgE measurement requires a blood test which is simple and can be performed in primary care but may not be possible in some children.

Both skin prick tests and specific IgE measurement show sensitisation to an allergen, but this can be present in other allergic conditions and in asymptomatic people. The committee emphasised again that the results need to be interpreted in the light of a good clinical history.

1.2.6. Recommendations supported by this evidence review

Recommendation 1.2.8.

1.3. References

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Appendices

Appendix A – Review protocols

Review protocol for Accuracy and clinical and cost-effectiveness of skin prick tests in children for diagnosis of asthma

ID	Field	Content
0.	PROSPERO registration number	CRD42023437772
1.	Review title	Accuracy and clinical and cost-effectiveness of skin prick tests in children for diagnosis of asthma
2.	Review question	In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of skin prick tests in children?
3.	Objective	To evaluate the diagnostic test value of skin prick tests 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
4.	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 test accuracy 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).
5.	Condition or domain being studied	Asthma
6.	Population	Inclusion: People with suspected asthma (presenting with respiratory symptoms). • Children/young people (5-16 years old) Exclusion:

		• Young children (<5 years old) • Adults (≥17 years old) • People on steroid inhalers (washout period minimum of 4 weeks for inclusion)
7.	Test	Skin prick tests for the most common allergens (reported separately) • House dust mites • Cat • Dog • Grass pollen* (native UK grasses) • Tree pollen* (native UK trees) • Mixed pollens* (native UK species) • *Aspergillus* • *Alternaria* • *Cladosporium* Cut off values: 3mm WHEAL (skin reaction) greater than the negative control in the presence of a positive control • Specific IgE – reported separately for different allergens Cut-off as specified in study * Mainland Europe (including Denmark; excluding Norway, Sweden, Finland, Iceland, Russia, Greece), North America (USA + Canada), Australia, New Zealand (as trees/grasses/pollen similar to UK in included countries but not in other countries) Stratification: Different cut-offs

8.	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. <u>Stratification</u> • Different reference standards Maximum interval between initial/suspected diagnosis and confirmation of asthma: 12 months.

9.	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
10.	Other exclusion criteria	• 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. • Not occupational asthma /allergens • Not looking at validation studies, or studies comparing different skin prick methods • Not looking at factors which influence skin prick measurements • Studies in which we are unable to calculate sensitivity and specificity (unless sensitivity/specificity has been reported by the study).
11.	Context	Primary, secondary and community care settings
12.	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 (thresholds: upper 90%, lower 10%)

		• Specificity (thresholds: upper 80%, lower 50%) • Raw data to calculate 2X2 tables to calculated sensitivity and specificity • NPV, PPV
13.	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.

14.	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
15.	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.	
16.	Analysis of sub-groups	• People with eczema • Personal history of atopy • Family history of atopy	
17.	Type and method of review	☒	Intervention
		☒	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic

<table>
<tr><td></td><td></td><td colspan="3">☐ Service Delivery</td></tr>
<tr><td></td><td></td><td colspan="3">☐ Other (please specify)</td></tr>
<tr><td>18.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>19.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>20.</td><td>Anticipated or actual start date</td><td colspan="3"></td></tr>
<tr><td>21.</td><td>Anticipated completion date</td><td colspan="3">31 July 2024</td></tr>
<tr><td rowspan="8">22.</td><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☐</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☐</td></tr>
<tr><td>23.</td><td>Named contact</td><td colspan="3">5a. Named contact
National Guideline Centre

5b Named contact e-mail
asthmachronicmanagement@nice.org.uk</td></tr>
</table>

		5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre
24.	Review team members	From the National Guideline Centre: Bernard Higgins (Guideline lead) Sharon Swain (Guideline lead) Melina Vasileiou (Senior technical analyst) Qudsia Malik (Technical analyst) Toby Sands (Technical analyst) Alfredo Mariani (Senior health economist) Lina Gulhane (Head of information specialists) Stephen Deed (Information specialist) Amy Crisp (Senior project manager)
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	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.

27.	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	
28.	Other registration details	N/A	
29.	Reference/URL for published protocol		
30.	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.	
31.	Keywords	Asthma	
32.	Details of existing review of same topic by same authors	N/A	
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	N/A	
35.	Details of final publication	www.nice.org.uk	

Health economic review protocol

Table 5: 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 skin prick tests 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 6: 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.	Skin Tests/
25.	exp Intradermal Tests/
26.	Patch tests/
27.	Skin window technique/
28.	((skin or cutaneous or intradermal or intracutaneous or epiderma* or epicutaneous or percutaneous or prick* or puncture* or scratch* or patch or photopatch or leishmanin or brucella or Rebuck*) adj3 test*).ti,ab,kf.
29.	((skin or cutaneous or intradermal or intracutaneous or epiderma* or epicutaneous or percutaneous or prick* or puncture* or scratch* or patch or photopatch) adj3 (reaction* or response*)).ti,ab,kf.
30.	(skin window adj (technic* or technique* or procedure*)).ti,ab,kf.
31.	or/24-30
32.	23 and 31
33.	exp "sensitivity and specificity"/
34.	(sensitivity or specificity).ti,ab.
35.	((pre test or pretest or post test) adj probability).ti,ab.
36.	(predictive value* or PPV or NPV).ti,ab.
37.	likelihood ratio*.ti,ab.
38.	likelihood function/
39.	((area under adj4 curve) or AUC).ti,ab.
40.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
41.	gold standard.ab.
42.	exp Diagnostic errors/
43.	(false positiv* or false negativ*).ti,ab.
44.	Diagnosis, Differential/
45.	(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.
46.	or/33-45

47.	Epidemiologic studies/
48.	Observational study/
49.	exp Cohort studies/
50.	(cohort adj (study or studies or analys* or data)).ti,ab.
51.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
52.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
53.	Controlled Before-After Studies/
54.	Historically Controlled Study/
55.	Interrupted Time Series Analysis/
56.	(before adj2 after adj2 (study or studies or data)).ti,ab.
57.	exp case control study/
58.	case control*.ti,ab.
59.	Cross-sectional studies/
60.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
61.	or/47-60
62.	randomized controlled trial.pt.
63.	controlled clinical trial.pt.
64.	randomi#ed.ab.
65.	placebo.ab.
66.	randomly.ab.
67.	clinical trials as topic.sh.
68.	trial.ti.
69.	or/62-68
70.	Meta-Analysis/
71.	Meta-Analysis as Topic/
72.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
73.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
74.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
75.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
76.	(search* adj4 literature).ab.
77.	(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.
78.	cochrane.jw.
79.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
80.	or/70-79
81.	32 and (46 or 61 or 69 or 80)

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.	Skin Test/
24.	Prick test/
25.	Intracutaneous tests/
26.	Patch test/
27.	Skin window technique/
28.	((skin or cutaneous or intradermal or intracutaneous or epiderma* or epicutaneous or percutaneous or prick* or puncture* or scratch* or patch or photopatch or leishmanin or brucella or Rebuck*) adj3 test*).ti,ab,kf.
29.	((skin or cutaneous or intradermal or intracutaneous or epiderma* or epicutaneous or percutaneous or prick* or puncture* or scratch* or patch or photopatch) adj3 (reaction* or response*)).ti,ab,kf.
30.	(skin window adj (technic* or technique* or procedure*)).ti,ab,kf.
31.	or/23-30
32.	22 and 31
33.	exp "sensitivity and specificity"/
34.	(sensitivity or specificity).ti,ab.
35.	((pre test or pretest or post test) adj probability).ti,ab.
36.	(predictive value* or PPV or NPV).ti,ab.
37.	likelihood ratio*.ti,ab.
38.	((area under adj4 curve) or AUC).ti,ab.
39.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
40.	diagnostic accuracy/
41.	diagnostic test accuracy study/
42.	gold standard.ab.
43.	exp diagnostic error/
44.	(false positiv* or false negativ*).ti,ab.
45.	differential diagnosis/
46.	(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.

47.	or/33-46
48.	Clinical study/
49.	Observational study/
50.	Family study/
51.	Longitudinal study/
52.	Retrospective study/
53.	Prospective study/
54.	Cohort analysis/
55.	Follow-up/
56.	cohort*.ti,ab.
57.	55 and 56
58.	(cohort adj (study or studies or analys* or data)).ti,ab.
59.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
60.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
61.	(before adj2 after adj2 (study or studies or data)).ti,ab.
62.	exp case control study/
63.	case control*.ti,ab.
64.	cross-sectional study/
65.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
66.	or/48-54,57-65
67.	random*.ti,ab.
68.	factorial*.ti,ab.
69.	(crossover* or cross over*).ti,ab.
70.	((doubl* or singl*) adj blind*).ti,ab.
71.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
72.	crossover procedure/
73.	single blind procedure/
74.	randomized controlled trial/
75.	double blind procedure/
76.	or/67-75
77.	Systematic Review/
78.	Meta-Analysis/
79.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
80.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
81.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
82.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
83.	(search* adj4 literature).ab.
84.	(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.
85.	cochrane.jw.
86.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
87.	or/77-86
88.	32 and (47 or 66 or 76 or 87)

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: [Skin Tests] this term only
#7.	MeSH descriptor: [Intradermal Tests] explode all trees
#8.	MeSH descriptor: [Patch Tests] this term only
#9.	MeSH descriptor: [Skin Window Technique] this term only
#10.	((skin or cutaneous or intradermal or intracutaneous or epiderma* or epicutaneous or percutaneous or prick* or puncture* or scratch* or patch or photopatch or leishmanin or brucella or Rebuck*) near/3 test*):ti,ab
#11.	((skin or cutaneous or intradermal or intracutaneous or epiderma* or epicutaneous or percutaneous or prick* or puncture* or scratch* or patch or photopatch) near/3 (reaction* or response*)):ti,ab
#12.	skin window near (technic*or technique* or procedure*):ti,ab
#13.	(or #6-#12)
#14.	#5 and #13

Epistemonikos search terms

1.	(title:(asthma*) OR abstract:(asthma*)) AND (title:((skin OR cutaneous OR intradermal OR intracutaneous OR epiderma* OR epicutaneous OR percutaneous OR prick* OR puncture* OR scratch* OR patch OR photopatch OR leishmanin OR brucella OR Rebuck* AND test*) OR (skin OR cutaneous OR intradermal OR intracutaneous OR epiderma* OR epicutaneous OR percutaneous OR prick* OR puncture* OR scratch* OR patch OR photopatch AND respons* OR reaction*) OR (skin window AND technic OR technique* OR procedure*)) OR abstract:((skin OR cutaneous OR intradermal OR intracutaneous OR epiderma* OR epicutaneous OR percutaneous OR prick* OR puncture* OR scratch* OR patch OR photopatch OR leishmanin OR brucella OR Rebuck* AND test*) OR (skin OR cutaneous OR intradermal OR intracutaneous OR epiderma* OR epicutaneous OR percutaneous OR prick* OR puncture* OR scratch* OR patch OR photopatch AND respons* OR reaction*) OR (skin window AND technic OR technique* OR procedure*)))

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 7: 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 Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 Dec 2023	
	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

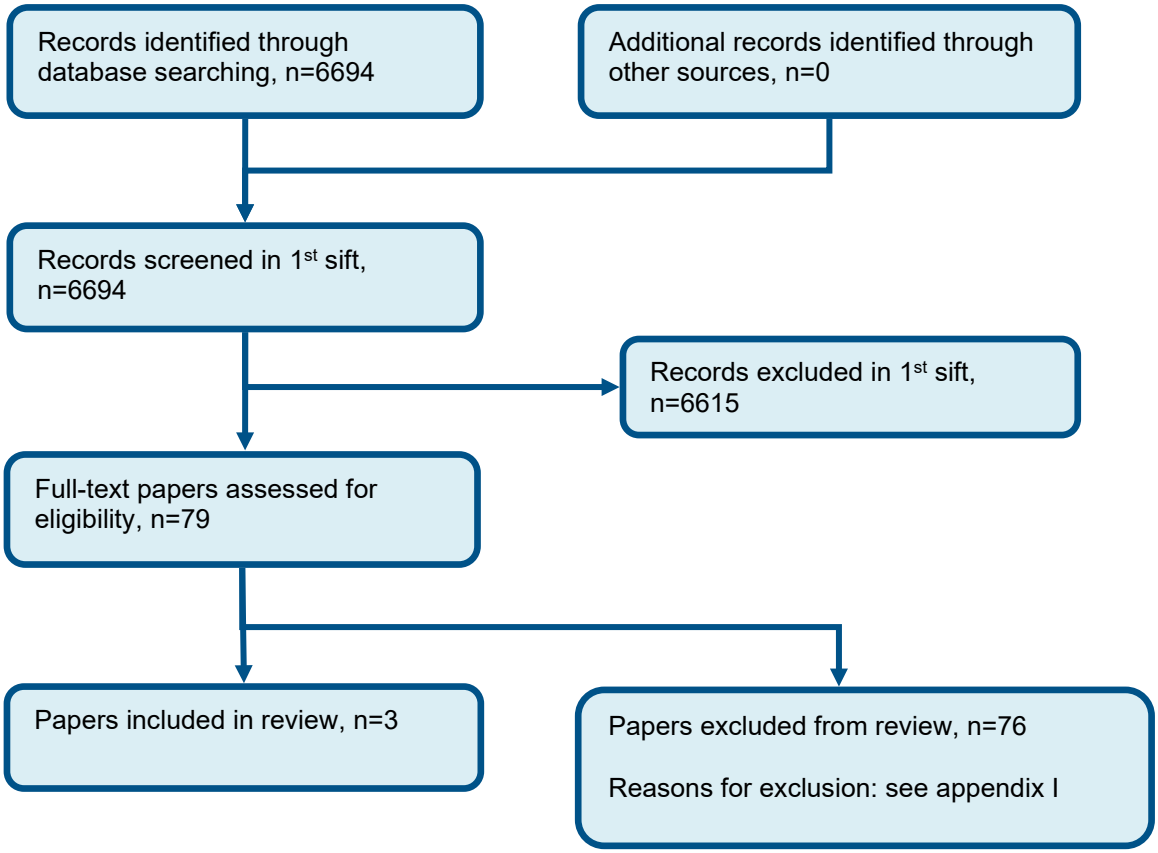
INAHTA search terms

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

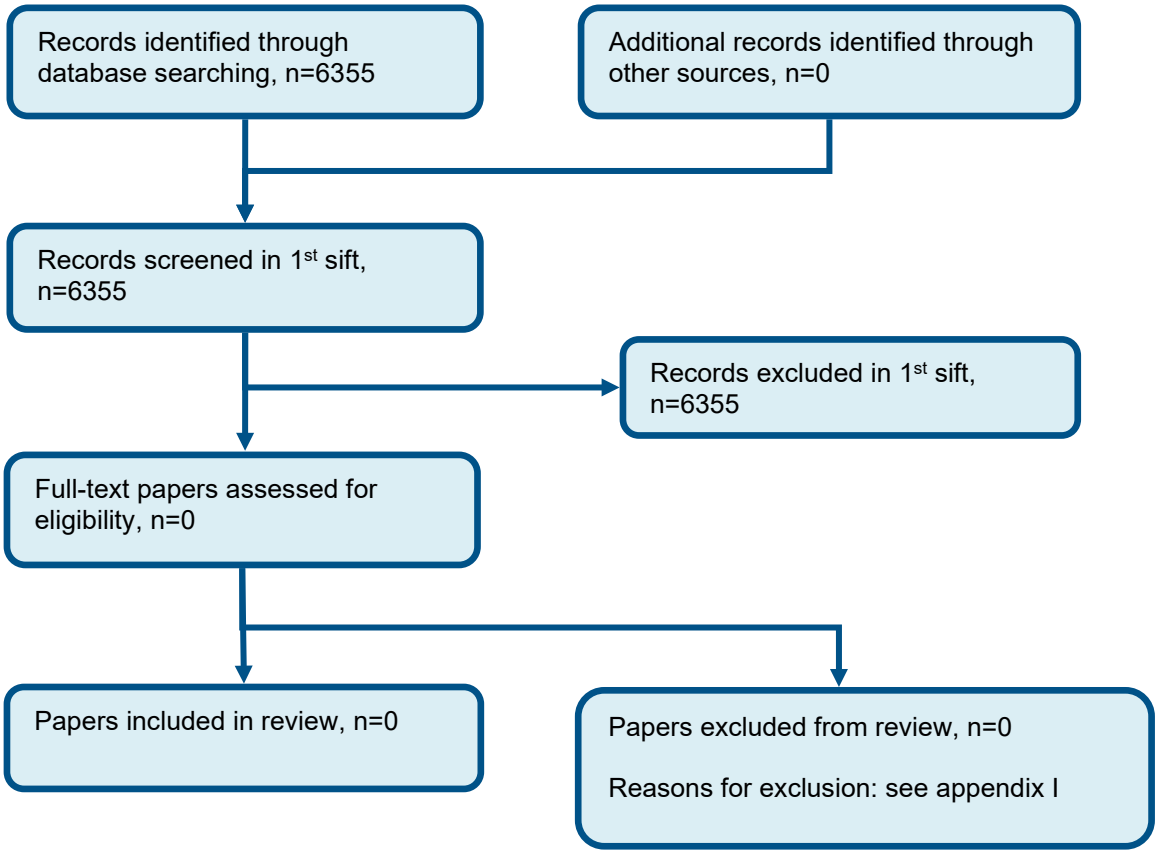
Appendix C – Study selection flow charts

Diagnostic evidence selection

Figure 1: Flow chart of clinical study selection for the review of skin prick testing in children for the diagnosis of asthma



Effectiveness evidence study selection



Appendix D – Evidence

Diagnostic evidence

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

Reference	**Drkulec 2013 (Drkulec et al., 2013)**				
Target condition(s)	Asthma				
Index test(s) and reference standard	Index test Participants underwent the standard allergological examination, including SPT to the standard set of inhalatory allergens common for the region, lung function tests, and in vitro diagnostic tests. Participants were tested for total IgE and 3 allergen specific IgE antibodies against the most prevalent aeroallergens in children in Croatia: house dust mites (*Dermatophagoides pteronyssinus*), common ragweed (*Ambrosia artemisifoliae*), and timothy grass (*Phleum pratense*) pollen The SPT was performed with standardized allergens comprising the standard set of aeroallergens common for Croatia. Cut-offs: (IgE; optimal threshold, SPT cut-off not specified (assumed to be 3mm with committee input)) House dust mites (*Dermatophagoides pteronyssinus*) – 0.35 kIU/L Common ragweed (*Ambrosia artemisifoliae*) – 0.39 kIU/L Timothy grass (*Phleum pratense*) pollen: 0.35 kIU/L Reference standard 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:				
2×2 table IgE: House dust mites (*Dermatophagoides pteronyssinus*)		Reference standard + +	Reference standard − −	Total	Prevalence= 54.1%
	Index test +	63	2	65	
	Index test −	8	58	66	
	Total	71	60	131	
2×2 table IgE: Common ragweed (*Ambrosia artemisifoliae*)		Reference standard + +	Reference standard − −	Total	
	Index test +	40	12	52	
	Index test −	31	48	79	
	Total	71	60	131	
2×2 table		Reference standard + +	Reference standard − −	Total	

Reference	**Drkulec 2013 (Drkulec et al., 2013)**				
IgE: Timothy grass (*Phleum pratense*) pollen	Index test +	43	11	54	
	Index test −	28	49	77	
	Total	71	60	131	
2×2 table SPT: House dust mites (*Dermatophagoides pteronyssinus*)		Reference standard +	Reference standard −	Total	
	Index test +	59	17	76	
	Index test −	12	43	55	
	Total	71	60	131	
2×2 table SPT: Common ragweed (*Ambrosia artemisifoliae*)		Reference standard +	Reference standard −	Total	
	Index test +	47	31	78	
	Index test −	24	29	53	
	Total	71	60	131	
2×2 table SPT: Timothy grass (*Phleum pratense*) pollen		Reference standard +	Reference standard −	Total	
	Index test +	47	30	77	
	Index test −	24	30	54	
	Total	71	60	131	
2×2 table SPT positivity to ≥1 allergen		Reference standard +	Reference standard −	Total	
	Index test +	56	5	61	
	Index test −	15	55	70	
	Total	71	60	131	
Statistical measures	Index text: IgE; House dust mites (*Dermatophagoides pteronyssinus*) Sensitivity: 0.89 (95%CI 0.79-0.95) Specificity: 0.97 (95%CI 0.88-1.00) PPV: 97% NPV: 88% Index text: IgE; Common ragweed (*Ambrosia artemisifoliae*) Sensitivity: 0.56 (95%CI 0.44-0.68)				

Reference	Drkulec 2013 (Drkulec et al., 2013)
	Specificity: 0.80 (95%CI 0.68-0.89) PPV: 77% NPV: 61% Index text: IgE; Timothy grass (*Phleum pratense*) pollen Sensitivity: 0.61 (95%CI 0.48-0.72) Specificity: 0.82 (95%CI 0.70-0.90) PPV: 79% NPV: 64% Index test: SPT; House dust mites (*Dermatophagoides pteronyssinus*) Sensitivity: 0.83 (95%CI 0.72-0.91) Specificity: 0.72 (95%CI 0.59-0.83) PPV: 78% NPV: 78% Index text: SPT; Common ragweed (*Ambrosia artemisifoliae*) Sensitivity: 0.66 (95%CI 0.54-0.77) Specificity: 0.48 (95%CI 0.35-0.62) PPV: 60% NPV: 55% Index text: SPT; Timothy grass (*Phleum pratense*) pollen Sensitivity: 0.66 (95%CI 0.54-0.77) Specificity: 0.50 (95%CI 0.37-0.63) PPV: 61% NPV: 56% Index test: SPT; positivity to ≥1 more allergen Sensitivity: 0.79 (95%CI 0.68-0.88) Specificity: 0.92 (95%CI 0.82-0.97) PPV: 91% NPV: 79%
Source of funding	None reported
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from method of patient selection (unclear recruitment method, and no exclusion criteria specified) and due to interpretation of the index test and reference standard (unclear if blinded)

Reference	**Drkulec 2013 (Drkulec et al., 2013)**
	Indirectness: Downgraded by two increments due to 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
Comments	2x2 data calculated from sensitivity, specificity and prevalence (54.1%) data reported in paper

Reference	**Gaig 1999 (Gaig et al., 1999)**
Study type	Prospective cross-sectional diagnostic study
Study methodology	Data source: Consecutive patients attending an outpatient allergy clinic Recruitment: Not reported
Number of patients	n = 94
Patient characteristics	Age, mean (SD): 16 (6) Gender (male to female ratio): 43:51 Ethnicity: Not reported Setting: Secondary care Country: Spain ICS use: Not reported <u>Subgroups</u> People with eczema: Not reported Personal history of atopy: Not reported Family history of atopy: 54 yes, 40 no Inclusion criteria: Patients who had been sharing a bunk with a sibling for more than 6 months, always occupying the same position (top or bottom) on the bunk Exclusion criteria: none reported

Reference	**Gaig 1999 (Gaig et al., 1999)**
Target condition(s)	Allergic asthma (or rhinitis as alternate diagnosis)
Index test(s) and reference standard	Index test Skin prick tests with the two main species of mites in the area (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) were performed with standardized lancets using histamine chloride 10 mg/mL and saline as control. Cut-off: skin wheal diameter ≥3 mm larger than that caused by the dilutant control Reference standard Clinical diagnosis based on history and current symptoms Time between measurement of index test and reference standard: not reported

2×2 table

	Reference standard +	Reference standard −	Total	Prevalence= 61.2%
Index test +	35	17	52	
Index test −	6	9	15	
Total	41	26	67	

Statistical measures	Index text: House dust mites (*Dermatophagoides pteronyssinus*) Sensitivity: 0.85 (95%CI 0.71-0.94) Specificity: 0.35 (95%CI 0.17-0.56) PPV: 67% NPV: 60%
Source of funding	None reported
Limitations	Risk of bias: Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if interpreted blinded to one another) Indirectness: Downgraded by two increments due to population indirectness (mean age within strata, standard deviation overlaps threshold) and no information on prior ICS use
Comments	Study not designed to assess diagnostic accuracy, sensitivity and specificity calculated from 2x2 table

Reference	**Miraglia Del Giudice 2002 (Miraglia Del Giudice et al., 2002)**
Study type	Retrospective cross-sectional diagnostic study

Reference	Miraglia Del Giudice 2002 (Miraglia Del Giudice et al., 2002)
Study methodology	Data source: Patient records of consecutive children attending a paediatric asthma and allergy centre with physician-referred or self-reported symptoms of atopic disease Recruitment: January-December 1998
Number of patients	n = 1426
Patient characteristics	Age: Not reported, range from 0-12 years (586 aged 0-3 years, 524 aged 4-6 years, 316 aged 7-12 years) Gender (male to female ratio): 814:612 Ethnicity: Not reported Setting: Secondary care Country: Italy ICS use: Not reported Subgroups People with eczema: Not reported Personal history of atopy: Not reported Family history of atopy: Not reported Inclusion criteria: Children in whom a diagnosis of asthma, allergic rhino conjunctivitis, atopic dermatitis and food allergy was confirmed by a paediatric allergologist Exclusion criteria: Children without a confirmed diagnosis
Target condition(s)	Asthma (alternate diagnosis of allergic rhino conjunctivitis, atopic dermatitis or food allergy)
Index test(s) and reference standard	Index test Atopy was identified with the skin prick test using a standard battery of aeroallergens and food allergens: house dust mites (*Dermatophagoides pteronyssinus, D. farinae*), *Parietaria officinalis*, grasses (*Dactylis glomerata, Lolium perenne, Phaleum pratense*), moulds (*Alternaria, Aspergillus, Cladosporium*), dog fur, cat fur, egg albumin, and cow's milk). Allergens were applied into a stencil

<table>
<tr><td>Reference</td><td colspan="5">Miraglia Del Giudice 2002 (Miraglia Del Giudice et al., 2002)</td></tr>
<tr><td></td><td colspan="5">stamped on the forearm with ink and pricked with a lancet. Histamine chloride 10 mg/ml was used as a positive control and the allergen diluent was the negative control. The results were read after 15 min. Atopy was diagnosed if at least one skin test was positive.

Cut-off: ≥3 mm diameter

<u>Reference standard</u>
Asthma
Bronchial asthma was defined as three or more episodes of wheezing before 2 years of age, or one episode from 2 years of age, or any episode of wheezing independent of age, if combined with atopic symptoms in the family or other atopic symptoms in the child.

Allergic rhino-conjunctivitis
Allergic rhino-conjunctivitis was diagnosed if sneezing, nasal obstruction, watery rhinorrhea, nasal itching, conjunctival hyperemia and photophobia appeared at least twice after exposure to a particular allergen and was unrelated to infection.

Food allergy
Food allergy was diagnosed as acute onset of symptoms such as skin reactions, wheezing, oral allergic symptoms, vomiting or diarrhoea on more than one occasion after ingestion of, or oral contact with, a particular type of food.

Atopic dermatitis
Atopic dermatitis was defined according to Hanifin and assessed with the Scorad index

Time between measurement of index test and reference standard: not reported</td></tr>
<tr><td>2×2 table
≥1 test</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td>Prevalence= 64.9%</td></tr>
<tr><td></td><td>Index test +</td><td>411</td><td>218</td><td>629</td><td rowspan="3"></td></tr>
<tr><td></td><td>Index test −</td><td>514</td><td>283</td><td>797</td></tr>
<tr><td></td><td>Total</td><td>925</td><td>501</td><td>1426</td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index text:</u>
Sensitivity: 0.44 (95%CI 0.41-0.48)
Specificity: 0.56 (95%CI 0.52-0.61)
PPV: 65%
NPV: 36%</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 one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if interpreted blinded to one another)</td></tr>
</table>

Reference	**Miraglia Del Giudice 2002 (Miraglia Del Giudice et al., 2002)**
	Indirectness: Downgraded by two increments due to population indirectness (study includes participants <5 years of age, no information on prior ICS use) and index test indirectness (battery included allergens not listed on protocol)
Comments	Sensitivity and specificity calculated from 2x2 tables

Effectiveness evidence

No evidence was identified for this review.

Appendix E – Forest plots

Diagnostic evidence: Forest plots

Coupled sensitivity and specificity: Forest plots

Figure 2: House dust mites (*Dermatophagoides pteronyssinus*) cut-off: IgE >0.35 kIU/L vs clinician diagnosis with bronchodilator response

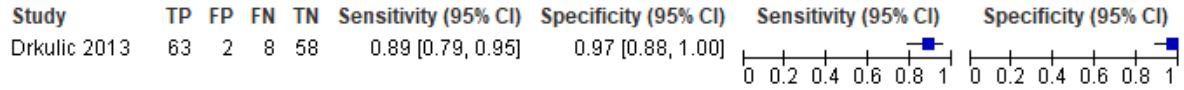


Figure 3: Common ragweed (*Ambrosia artemisifoliae*) cut-off: IgE >0.39 kIU/L vs clinician diagnosis with bronchodilator response

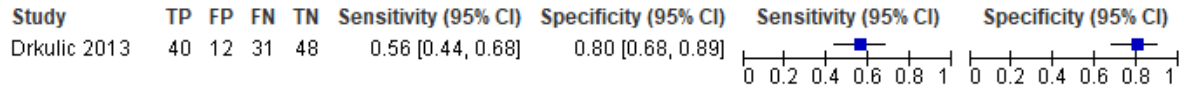


Figure 4: Timothy grass (*Phleum pratense*) pollen, cut-off: >0.35 kIU/L vs clinican diagnosis with bronchodilator response

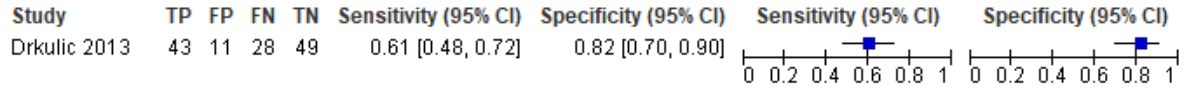


Figure 5: House dust mites (*Dermatophagoides pteronyssinus*) cut-off: SPT >3mm vs clinician diagnosis with bronchodilator response

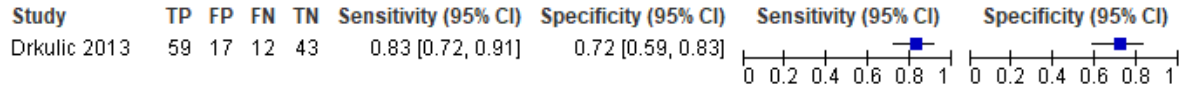


Figure 6: Common ragweed (*Ambrosia artemisifoliae*) cut-off: SPT >3mm vs clinician diagnosis with bronchodilator response

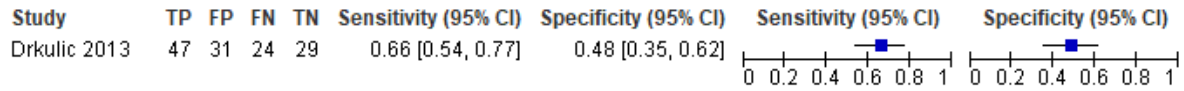


Figure 7: Timothy grass (*Phleum pratense*) pollen, cut-off: SPT >3mm vs clinican diagnosis with bronchodilator response

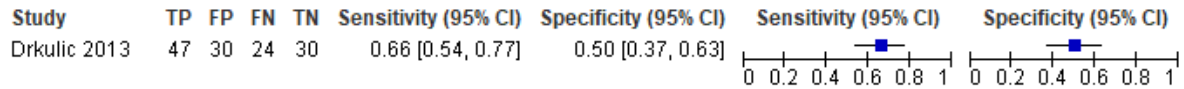


Figure 8: Positive skin prick test to ≥1 of House dust mites (*Dermatophagoides pteronyssinus*), Common ragweed (*Ambrosia artemisifoliae*) and Timothy grass (*Phleum pratense*) (cut-off: not specified) pollen vs clinician diagnosis with bronchodilator response

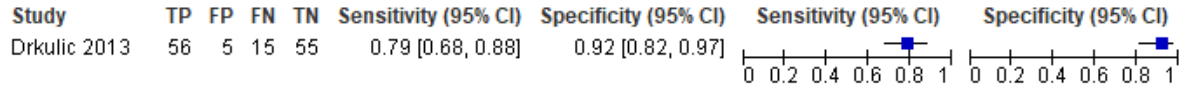


Figure 9: House dust mites (*Dermatophagoides pteronyssinus* and/or *farinae*) vs clinical diagnosis based on history and symptoms

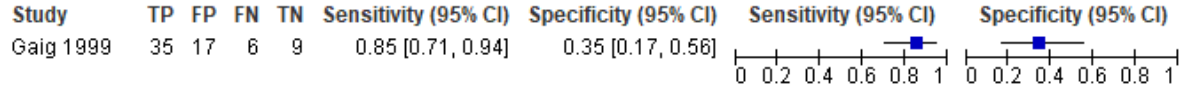
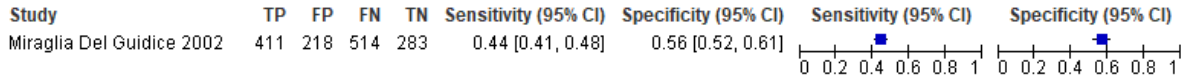


Figure 100: Standard battery of aero and food allergens (cut-off: 3mm to at least one of; house dust mites (*Dermatophagoides pteronyssinus, D. farinae*), *Parietaria officinalis*, grasses (*Dactylis glomerata, Lolium perenne, Phaleum pratense*), moulds (*Alternaria, Aspergillus, Cladosporium*), dog fur, cat fur, egg albumin, and cow's milk) vs clinician diagnosis based on symptoms and family and child history



Effectiveness evidence: Forest plots

No evidence was identified for this review.

Appendix F – Economic evidence study selection

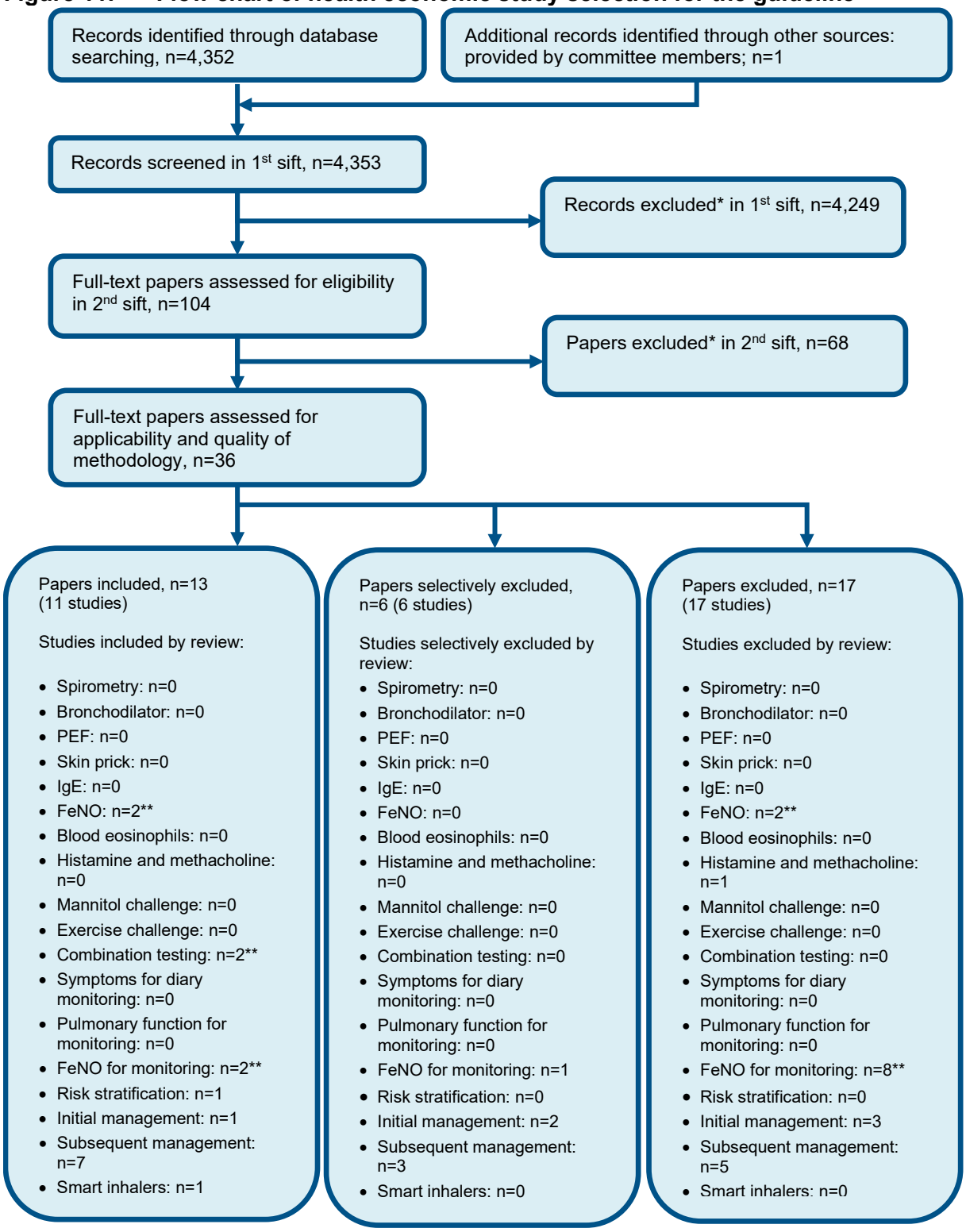
F.1 Diagnostic evidence

No evidence was identified for this review.

F.2 Effectiveness evidence

No evidence was identified for this review.

Figure 11: 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

Diagnostic evidence

No evidence was identified for this review.

Effectiveness evidence

No evidence was identified for this review.

Appendix H – Excluded studies

Diagnostic studies

Table 8: Studies excluded from the diagnostic review

Study	Code [Reason]
Agarwal, R. (2009) Allergic bronchopulmonary aspergillosis. Chest 135(3): 805-826	- Conference abstract
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
Ahmed, H., Ospina, M.B., Sideri, K. et al. (2019) Retrospective analysis of aeroallergen's sensitization patterns in Edmonton, Canada. Allergy, Asthma and Clinical Immunology 15(1): 6	- Population not relevant to this review protocol *only 9% were below the age of 18 years.*
Al-Zayadneh, E.M., Alnawaiseh, N.A., Altarawneh, A.H. et al. (2019) Sensitization to inhaled allergens in asthmatic children in southern Jordan: A cross-sectional study. Multidisciplinary Respiratory Medicine 14(1): 37	- Population not relevant to this review protocol *people aged from 6 months to 10 years (28% below the age of 5) with confirmed asthma or wheezing episodes at baseline; no relevant data: study reports frequency of sensitization to different allergens to examine factors associated with sensitisation (e.g. age); no diagnostic accuracy data*
Alimuddin, S., Rengganis, I., Rumende, C.M. et al. (2018) Comparison of Specific Immunoglobulin E with the Skin Prick Test in the Diagnosis of House Dust Mites and Cockroach Sensitization in Patients with Asthma and/or Allergic Rhinitis. Acta medica Indonesiana 50(2): 125-131	- Population not relevant to this review protocol *people aged 19-59*
Andersson, Martin, Hedman, Linnea, Nordberg, Gunnar et al. (2015) Swimming pool attendance is related to asthma among atopic school children: a population-based study. Environmental health : a global access science source 14: 37	- No relevant data *correlation data for swimming pool attendance and asthma*
Annus, T., Bjorksten, B., Mai, X.-M. et al. (2001) Wheezing in relation to atopy and environmental factors in Estonian and Swedish schoolchildren. Clinical and Experimental Allergy 31(12): 1846-1853	- No relevant data *prevalence of respiratory symptoms; not relevant setting: sensitization to pollen in Sweden*

Study	Code [Reason]
Arikoglu, T., Batmaz, S.B., Coskun, T. et al. (2016) The characteristics of indoor and outdoor fungi and their relation with allergic respiratory diseases in the southern region of Turkey. Environmental Monitoring and Assessment 188(6): 380	- Study does not contain an intervention relevant to this review protocol *Index test is aiming to diagnose fungal sensitisation to environmental allergens, not asthma*
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	- No relevant data *Rates of allergen sensitization among children with known allergic diseases including asthma and allergic rhinitis; no relevant diagnostic accuracy data*
Atay, O., Asilsoy, S., Atakul, G. et al. (2021) Allergic bronchopulmonary aspergillosis in children. Turkish Journal of Medical Sciences 51(5): 2554-2563	- No relevant data *population: people with Allergic bronchopulmonary aspergillus*
Backer, V., Klein, D.K., Bodtger, U. et al. (2020) Clinical characteristics of the BREATHE cohort-a real-life study on patients with asthma and COPD. European Clinical Respiratory Journal 7(1): 1736934	- Population not relevant to this review protocol *Adults*
Baur, X. and Czuppon, A. (1995) Diagnostic validation of specific IgE antibody concentrations, skin prick testing, and challenge tests in chemical workers with symptoms of sensitivity to different anhydrides. Journal of Allergy and Clinical Immunology 96(4): 489-494	- Population not relevant to this review protocol *chemical workers*
Bougault, V., Drouard, F., Legall, F. et al. (2017) Allergies and Exercise-Induced Bronchoconstriction in a Youth Academy and Reserve Professional Soccer Team. Clinical Journal of Sport Medicine 27(5): 450-456	- Population not relevant to this review protocol *Adults professional soccer players*
Brand, P L, Kerstjens, H A, Jansen, H M et al. (1993) Interpretation of skin tests to house dust mite and relationship to other allergy parameters in patients with asthma and chronic obstructive pulmonary disease. The Dutch CNSLD Study Group. The Journal of allergy and clinical immunology 91(2): 560-70	- Population not relevant to this review protocol *people aged 18-60*
Braun-Fahrlander, C, Wuthrich, B, Gassner, M et al. (1997) Validation of a rhinitis symptom questionnaire (ISAAC core questions) in a population of Swiss school children visiting the school health services. SCARPOL-team. Swiss Study on Childhood Allergy and Respiratory	- No relevant data *detecting atopy in children with rhinitis*

Study	Code [Reason]
Symptom with respect to Air Pollution and Climate. International Study of Asthma and Allergies in Childhood. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 8(2): 75-82	
Brunetti, Luigia, Francavilla, Ruggiero, Tesse, Riccardina et al. (2006) Exhaled breath condensate pH measurement in children with asthma, allergic rhinitis and atopic dermatitis. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 17(6): 422-7	- No relevant data *no relevant outcomes reported*
Burrows, B, Sears, M R, Flannery, E M et al. (1995) Relations of bronchial responsiveness to allergy skin test reactivity, lung function, respiratory symptoms, and diagnoses in thirteen-year-old New Zealand children. The Journal of allergy and clinical immunology 95(2): 548-56	- No relevant data *association between bronchial responsiveness and skin test reactivity in people with asthma, wheezing or hay fever. No diagnostic accuracy data*
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	- No relevant data *Incorrect setting: common aeroallergens in Korea including house dust mites, animal dander, pollen.*
Canbal, A. (2012) Evaluation of prick test results in children with allergic asthma and rhinitis in Karaman district. Duzce Medical Journal 14(1): 27-30	- Study not reported in English
Chan, E.Y., Dundas, I., Bridge, P.D. et al. (2005) Skin-prick testing as a diagnostic aid for childhood asthma. Pediatric Pulmonology 39(6): 558-562	- Population not relevant to this review protocol *Case control study with mixture of participants with suspected asthma (wheeze) and healthy controls*
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	- No relevant data *gives sensitivity and specificity of SPT to detect allergic diseases including asthma with results not given separately for asthma. Only 4.8% of the study population had asthma*
Choi, I.S., Koh, Y.I., Koh, J.-S. 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. Journal of Asthma 42(3): 197-202	- Population not relevant to this review protocol *adults 18-30 years*

Study	Code [Reason]
Dai, Lingman, Liu, Jinling, Zhao, Qi et al. (2022) Investigation of Allergic Sensitizations in Children With Allergic Rhinitis and/or Asthma. Frontiers in pediatrics 10: 842293	- No relevant data *prevalence of positive skin reaction/sensitisation to various allergens in people with asthma or allergic rhinitis; no diagnostic accuracy data*
Dey, D., Mondal, P., Laha, A. et al. (2019) Sensitization to Common Aeroallergens in the Atopic Population of West Bengal, India: An Investigation by Skin Prick Test. International Archives of Allergy and Immunology 178(1): 60-65	- No relevant data *reports % with sensitization to various allergens in people with confirmed asthma*
Dibek Misirlioglu, E and Reha Cengizlier, M (2007) Skin prick test results of child patients diagnosed with bronchial asthma. Allergologia et immunopathologia 35(1): 21-4	- No relevant data *measurement of allergen sensitization in children with known bronchial asthma; no diagnostic accuracy data; mixed population with age range from 3 months to 16 years*
Faitelson, Y.; Boaz, M.; Dalal, I. (2018) Asthma, Family History of Drug Allergy, and Age Predict Amoxicillin Allergy in Children. Journal of Allergy and Clinical Immunology: In Practice 6(4): 1363-1367	- No relevant data *predictive factors for amoxicilin allergy*
Graif, Y., Yigla, M., Tov, N. et al. (2002) Value of a negative aeroallergen skin-prick test result in the diagnosis of asthma in young adults: Correlative study with methacholine challenge testing. Chest 122(3): 821-825	- Population not relevant to this review protocol *people aged 18-24 years*
Haahtela, T., Burbach, G.J., Bachert, C. et al. (2014) Clinical relevance is associated with allergen-specific wheal size in skin prick testing. Clinical and Experimental Allergy 44(3): 407-416	- Population not relevant to this review protocol *84% adults*
Iwamoto, I., Yamazaki, H., Kimura, A. et al. (1990) Comparison of a multi-allergen dipstick IgE assay to skin-prick test and RAST. Clinical and Experimental Allergy 20(2): 175-179	- Population not relevant to this review protocol *Adults aged 18-55*
James, T.L.I. (2002) Allergy testing. American Family Physician 66(4): 621	- Review article but not a systematic review
Karakaya, G.; Ozturk, A.B.; Kalyoncu, A.F. Prediction of atopy by skin prick tests in patients with asthma and/or persistent rhinitis. Allergologia et Immunopathologia	- Population not relevant to this review protocol *Adults*

Study	Code [Reason]
Kaur, J., Kabra, S.K., Lodha, R. et al. (2013) Association of aeroallergen sensitization with asthma severity and treatment. Pediatric, Allergy, Immunology, and Pulmonology 26(4): 187-192	- Population not relevant to this review protocol *Prospective study of people with confirmed asthma; positive skin prick test result based on sensitisation to various allergens including allergens not meeting protocol (e.g. cockroach, mosquito, dust rice); no relevant data*
Klok, T.; Ottink, M.D.; Brand, P.L.P. (2021) Question 6: What is the use of allergy testing in children with asthma?. Paediatric Respiratory Reviews 37: 57-63	- Review article but not a systematic review
Konradsen, J., Nordlund, B., Winkler, A. et al. (2015) Evaluation of Microtest allergy system compared to three established diagnostic methods. Allergy: European Journal of Allergy and Clinical Immunology 70(suppl101): 173	- Conference abstract
Korhonen, Kaj, Mahonen, Saara, Hyvarinen, Anne et al. (2006) Skin test reactivity to molds in pre-school children with newly diagnosed asthma. Pediatrics international : official journal of the Japan Pediatric Society 48(6): 577-81	- Population not relevant to this review protocol *children aged 1-6 years*
Lopes, M.I.L.; Miranda, P.J.; Sarinho, E. (2006) Use of the skin prick test and specific immunoglobulin E for the diagnosis of cockroach allergy. Jornal de Pediatria 82(3): 204-209	- Study not reported in English
Lyons, T.W.; Wakefield, D.B.; Cloutier, M.M. (2011) Mold and Alternaria skin test reactivity and asthma in children in Connecticut. Annals of Allergy, Asthma and Immunology 106(4): 301-307	- Population not relevant to this review protocol *children with confirmed asthma; no relevant data: association with various allergens but no diagnostic accuracy data*
Mahmoud, H. and Elqady, M. (2013) Relationship between skin prick test, peripheral eosinophilic count, serum total and specific ige, and severity of asthma in atopic asthma. Chest 144(4meetingabstract)	- Conference abstract
Mahmoud, H.; Elqady, M.; Mohamed, H. (2011) Relationship between skin prick test, peripheral eosinophil counts, serum total & specific IgE and severity in atopic asthma. Allergy: European Journal of Allergy and Clinical Immunology 66(suppl94): 578	- Full text paper not available
Malouche, S., Boussetta, K., Hassine, L.B. et al. (2013) Skin sensitization to aeroallergens in the	- Study not reported in English

Study	Code [Reason]
child: Cross-sectional study of 200 cases. Tunisie Medicale 91(11): 627-632	
Matondang, C.S. (1991) Spectrum of asthma in children visiting the outpatient clinic of the subdivision of allergy and immunology. Paediatrica Indonesiana 31(56): 150-164	- Population not relevant to this review protocol *45% below the age of 5; no relevant diagnostic accuracy data*
Mavi, A.K., Spalgais, S., Singh, K. et al. (2021) Relevance of skin-prick test and immunoglobulin E estimation in pigeon-exposure asthma patients. Egyptian Journal of Chest Diseases and Tuberculosis 70(4): 433-440	- Population not relevant to this review protocol *adults; no relevant allergen: pigeon exposure*
May, K.L. (1990) Allergy to Artemisia vulgaris in the region of Warsaw. Allergologia et immunopathologia 18(1): 57-60	- Population not relevant to this review protocol *adults*
Menardo, J.L.; Bousquet, J.; Michel, F.B. (1982) Comparison of three prick test methods with the intradermal test and with the rast in the diagnosis of mite allergy. Annals of allergy 48(4): 235-239	- Population not relevant to this review protocol *people aged 12-66 years, majority adults; incorrect outcome: diagnosis of mite allergy*
Menz, G., Dolecek, C., Schonheit-Kenn, U. et al. (1996) Serological and skin-test diagnosis of birch pollen allergy with recombinant Bet v I, the major birch pollen allergen. Clinical and Experimental Allergy 26(1): 50-60	- Population not relevant to this review protocol *adults*
Metz-Favre, C., Linhart, B., Focke-Tejkl, M. et al. (2007) Skin test diagnosis of grass pollen allergy with a recombinant hybrid molecule. Journal of Allergy and Clinical Immunology 120(2): 315-321	- Population not relevant to this review protocol *Adults*
Mohammad, H.R., Belgrave, D., Kopec Harding, K. et al. (2016) Age, sex and the association between skin test responses and IgE titres with asthma. Pediatric Allergy and Immunology 27(3): 313-319	- No relevant data *and asthma based on symptoms and parental reporting*
Moneo, I., Alday, E., Sanchez-Agudo, L. et al. (1995) Skin-prick tests for hypersensitivity to alpha-amylase preparations. Occupational Medicine 45(3): 151-155	- Population not relevant to this review protocol *adults*
Morell, F., Codina, R., Rodrigo, M.J. et al. (1995) Diagnosis of soybean-induced asthma. Journal of Allergy and Clinical Immunology 96(3): 320-324	- Population not relevant to this review protocol *Not children*

Study	Code [Reason]
Nacaroglu, H.T., Erdem, S.B., Karaman, S. et al. (2017) Diagnostic values for egg white specific IgE levels with the skin prick test in Turkish children with egg white allergy. Allergologia et Immunopathologia 45(5): 445-451	- No relevant data *diagnosis of egg allergy*
Nielsen, J P, Ostergaard, P A, Harris, R I et al. (1992) Comparison of CLA with BPT, SPT, and RAST in children with asthma. Allergy 47(1): 30-4	- Data not reported in an extractable format or a format that can be analysed
Nogueira, J M, de Almeida, M M, Santa Marta, C et al. (1994) Quantitative skin prick tests and specific IgE (CAP System) for D. pteronissynus--correlation of results in a paediatric population. Allergie et immunologie 26(3): 102-6	- Full text paper not available
O'Brien, R.M. (2002) Skin prick testing and in vitro assays for allergic sensitivity. Australian Prescriber 25(4): 91-93	- Review article but not a systematic review *article with no relevant data*
Ortega Cisneros, M, Ramos Garcia, BC, del Rio Navarro, BE et al. (1998) Comparison of 4 skin prick tests to detect immediate hypersensitivity. Revista alergia mexico 45(2): 36-42	- Study not reported in English
Perecinsky, Slavomir, Murinova, Lenka, Jancova, Andrea et al. (2022) Allergic sensitization pattern as a marker of bronchial hyperresponsiveness in allergic rhinitis patients living in temperate continental climate zone. Wiener klinische Wochenschrift 134(2122): 766-771	- Population not relevant to this review protocol *Adult population*
Picard, M., Paradis, L., Begin, P. et al. (2014) Skin testing only with penicillin G in children with a history of penicillin allergy. Annals of Allergy, Asthma and Immunology 113(1): 75-81	- No relevant data *detecting penicillin allergy not asthma*
Piette, V., Bourret, E., Bousquet, J. et al. (2002) Prick tests to aeroallergens: Is it possible simply to wipe the device between tests?. Allergy: European Journal of Allergy and Clinical Immunology 57(10): 940-942	- Population not relevant to this review protocol *people aged 15-64 years*
Popovic-Grle, S., Mehulic, M., Pavicic, F. et al. (2002) Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. Collegium antropologicum 26suppl: 119-127	- Population not relevant to this review protocol *adults*

Study	Code [Reason]
Price, J A, Reiser, J, Longbottom, J L et al. (1989) Inhalant allergy in asthmatic children: skin prick test, radioallergosorbent test and chemiluminescent assay compared with allergen levels in their mattress dusts. International archives of allergy and applied immunology 88(12): 183-4	- Review article but not a systematic review
Rosario, N A and Vilela, M M (1997) Quantitative skin prick tests and serum IgE antibodies in atopic asthmatics. Journal of investigational allergology & clinical immunology 7(1): 40-5	- Data not reported in an extractable format or a format that can be analysed *correlation between skin reactivity and asthma severity*
Ross Pe?a, Arlenis (2009) Diagnostic effectiveness of the Prick cutaneous test with allergenic extracts of mites in asthmatic patients. Archivo m?dico de camag?ey 13(3)	- Study not reported in English
Sarpong, S.B. and Karrison, T. (1998) Skin test reactivity to indoor allergens as a marker of asthma severity in children with asthma. Annals of Allergy, Asthma and Immunology 80(4): 303-308	- No relevant data *detecting mild/moderate/severe asthma in known asthmatic cohort based on number of allergic sensitivities.*
Schoos, A.-M.M., Chawes, B.L.K., Folsgaard, N.V. et al. (2015) Disagreement between skin prick test and specific IgE in young children. Allergy: European Journal of Allergy and Clinical Immunology 70(1): 41-48	- Population not relevant to this review protocol *No steroid use for 14 hours prior to study for inclusion; no relevant data: assessment of sensitisation at various age points including at 4 and 6 years, but also 1/2 and 1 year (not meeting protocol); study measuring agreement between of skin prick test and IGE for diagnosing inhalant and food allergy, not asthma.*
Schwartz, J. and Weiss, S.T. (1995) Relationship of skin test reactivity to decrements in pulmonary function in children with asthma or frequent wheezing. American Journal of Respiratory and Critical Care Medicine 152(6i): 2176-2180	- No relevant data *examines allergen sensitivity as measured by skin test reactivity and its relationship to pulmonary function; no diagnostic accuracy data*
Shaikh, W.A. and Shaikh, S.W. (2006) Skin prick test - More reliable than estimation of specific IgE in allergy diagnosis. Journal of the Indian Medical Association 104(10): 592-595	- Population not relevant to this review protocol *Adults (mean age 29 years)*
Soriano, J.B., Anto, J.M., Sunyer, J. et al. (1999) Risk of asthma in the general Spanish population attributable to specific	- Population not relevant to this review protocol *adults*

Study	Code [Reason]
immunoresponse. International Journal of Epidemiology 28(4): 728-734	
Stafanger, G.; Kock Andersen, J.; Koch, C. (1986) Specific diagnosis of exogenous bronchial asthma in children. Allergy: European Journal of Allergy and Clinical Immunology 41(2): 110-117	- Data not reported in an extractable format or a format that can be analysed
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): 246-250	- Full text paper not available *document supply does not provide clinical trial resources*
Terzioglu, E., Sin, A., Kokuludag, A. et al. (1998) Sensitivity to Parietaria pollen in Izmir, Turkey as determined by skin prick and serum specific IgE values. Journal of Investigational Allergology and Clinical Immunology 8(3): 180-183	- Population not relevant to this review protocol *people aged 16-52 years; incorrect setting: pollen in Turkey, hence allergen not meeting protocol*
Tezcan, D., Uzuner, N., Sule Turgut, C. et al. (2003) Retrospective evaluation of epidermal skin prick tests in patients living in Aegean region. Allergologia et Immunopathologia 31(4): 226-230	- No relevant data
Thomsen, G.F., Schlunssen, V., Skadhauge, L.R. et al. (2015) Are allergen batch differences and the use of double skin prick test important?. BMC Pulmonary Medicine 15(1): 33	- Population not relevant to this review protocol *people aged 22-44 years*
Til-Perez, G., Carnevale, C., Sarria-Echegaray, P.L. et al. (2019) Sensitization profile in patients with respiratory allergic diseases: Differences between conventional and molecular diagnosis (a cross-sectional study). Clinical and Molecular Allergy 17(1): 8	- No relevant data *incorrect population: <30% were children*
Tversky, J.R., Chelladurai, Y., McGready, J. et al. (2015) Performance and Pain Tolerability of Current Diagnostic Allergy Skin Prick Test Devices. Journal of Allergy and Clinical Immunology: In Practice 3(6): 888-893	- Population not relevant to this review protocol *Adults*
Vanto, T. (1983) Efficiency of different skin prick testing methods in the diagnosis of allergy to dog. Annals of Allergy 50(5): 340-344	- No relevant data *outcome is detection of allergy to dog dander; index test cut-off/methodology not meeting protocol.*

Study	Code [Reason]
Williams, P B; Siegel, C; Portnoy, J (2001) Efficacy of a single diagnostic test for sensitization to common inhalant allergens. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 86(2): 196-202	- No relevant data *detecting individuals that are sensitive to allergens and positivity for atopy in people with rhinitis, asthma and other causes; no data to detecting asthma.*
Wittig, H J and Belloit, J D (1979) Validity of the allergy skin test. The Journal of the Louisiana State Medical Society : official organ of the Louisiana State Medical Society 131(8): 199-203	- Population not relevant to this review protocol *undefined age group (most likely adults); no relevant data*

Effectiveness studies

No evidence was 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.