British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN Makes sense of evidence

Draft for Consultation

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

Evidence review for diagnostic test accuracy for bronchodilator reversibility in people suspected of asthma

BTS/NICE/SIGN collaborative guideline <number>

Evidence reviews underpinning recommendations 1.2.2 and 1.2.5 in the BTS/NICE/SIGN guideline

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1 Bronchilator response (using PEF or FEV1)

1.1 Review question

In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of bronchodilator response (using PEF or FEV1)?

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. A bronchodilator reversibility test involves measurement of the response to an inhaled bronchodilator, usually salbutamol, on lung function, typically using spirometry. Bronchodilators act by relaxing airway smooth muscle and therefore would be expected to relieve (improve) airflow obstruction that is caused by increased muscle tension. Bronchodilator response 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 review question

Population	Inclusion: People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: • Children and young people (5-16 years old) • Adults (≥17 years) <u>Stratified on smoking status:</u> • Smokers • Non-smokers • Mixed populations Exclusion: • Children under 5 years old • People on steroid inhalers (washout period minimum of 4 weeks for inclusion)
Target condition	Asthma
Index test	Bronchodilator response, measured using the following: ○ PEF ○ L/min ○ Change in PEF (as % of initial PEF) ○ FEV1 ○ Change in FEV1 % initial and/or change in FEV1 litres

	○ Change in FEV1 % predicted (ΔFEV1 %pred)
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); • 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
Statistical measures	• Sensitivity (thresholds: upper 90%, lower 10%) • Specificity (thresholds: upper 80%, lower 50%) • Raw data to calculate 2x2 tables to calculate sensitivity and specificity • Positive predictive value (PPV) and negative predictive value (NPV)
Study design	Cross sectional studies and cohort studies

1.1.3 Methods and process

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

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

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

Two prospective and two retrospective diagnostic test accuracy studies were included in the review;(Fortuna, et al., 2007, Kim, et al., 2012, Louis, et al., 2020, Simpson, 2024) 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 1.3 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.

Studies included in this review were in adults. No relevant diagnostic test accuracy studies of bronchodilator reversibility in children/young people under investigation for asthma were identified. No evidence was identified for the strata of smokers and non-smokers, with all included studies including participants with a mixed smoking status.

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 guideline on this topic were excluded from the present review. All three of these were excluded due to containing populations that were not relevant to the current review protocol, namely because of inadequate inhaled corticosteroid washout periods prior to study entry.

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
Fortuna 2007 (Fortuna et al., 2007)	Adults referred to hospital-based respiratory medicine outpatient clinic for diagnosis with a clinical history suggestive of asthma (dry cough, wheezing, and shortness of breath) N=50; mean age (range): 37.56 (18-68) years Spain	Asthma	Bronchodilator response to 400µg salbutamol Cut-off: Increase in FEV_1 ≥15% and/or ≥200 mL from baseline	Clinical history suggestive of asthma and a positive methacholine challenge test (cut-off: PD20 ≤16 mg/mL	Prospective cross-sectional study Strata: Adults ICS use: 4-week washout Smoking status: Mixed (19% current smokers) Indirectness: Downgraded by one increment due to population (mixed/not reported smoking status) indirectness
Kim 2012 (Kim et al., 2012)	Adults with chronic obstructive airways disorders included in an asthma cohort or a COPD cohort; all had at least one chronic persistent respiratory symptom (dyspnoea, cough, sputum production or wheeze) for >3 months or repetition of the symptom for >3 months N=514; mean age (SD) 51.38 (16.24 years (characteristics of 790 recruited participants diagnosed with asthma/COPD)	Asthma	Bronchodilator response to 400µg salbutamol Cut-off: Increase in FEV1 >200mL and >12% above baseline	Clinical decision by specialists in allergy or pulmonary departments.	Retrospective cross-sectional study Strata: Adults ICS use: Not reported Smoking status: Mixed (16.6 and 30.1% current smokers in asthma and COPD cohorts, respectively) Indirectness: Downgraded by two

Study	Population	Target condition	Index test	Reference standard	Comments
	Republic of Korea				increments due to population (unclear pre-study ICS treatment status and mixed/not reported smoking status) indirectness
Louis 2020 (Louis et al., 2020)	Patients with intermittent or chronic respiratory symptoms referred by two asthma physicians for diagnosis (FEV_1 ≥70% predicted for inclusion) N=194; mean age (SD): 49 (16) years Belgium	Asthma	Bronchodilator response to 400µg salbutamol Cut-offs: ≥12% and ≥200 mL change from baseline FEV1 increase ≥9% predicted	Methacholine challenge PC20 ≤8 mg/mL	Retrospective cross-sectional study Strata: Adults ICS use: not previously treated for asthma Smoking status: Mixed (22% current smokers) Indirectness: Downgraded by two increments due to population (mixed/not reported smoking status) and reference standard (unclear if clinician diagnosis is involved) indirectness
Simpson 2024 (Simpson, et al., 2024)	Patients referred by general practitioners with symptoms suggestive of asthma N=118; mean age (SD): 26 (12) years	Asthma	Bronchodilator response to 400 µg salbutamol FEV_1 increase ≥12% and 200 mL	Diagnosis by an expert panel, including at least three asthma clinicians with access to history, physical	Prospective cross-sectional study Strata: Adults ICS use: 4-week washout

Study	Population	Target condition	Index test	Reference standard	Comments
	UK		FEV_1 >10% of predicted	examination, ACQ, and all test results before and after ICS	Smoking status: Mixed (40 (35%) current or ex-smokers) Indirectness: Downgraded by one increment due to population (mixed smoking status of participants) indirectness

See Appendix D for full evidence tables

1.1.6 Summary of the diagnostic evidence

The assessment of the evidence quality was conducted with emphasis on test sensitivity and specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set clinical decision thresholds as sensitivity: upper= 90% and lower= 10%, specificity: upper= 80% and lower= 50%. Values above the upper threshold indicated a test would be recommended and values below the lower threshold indicated a test is of no clinical use.

Table 3: Clinical evidence summary: diagnostic test accuracy for bronchodilator response in adults with mixed smoking status

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Bronchodilator reversibility with 400 µg salbutamol (cut-off FEV_1 increase of both ≥200 mL and 12% above the pre-bronchodilator value) vs expert panel diagnosis with multiple diagnostic tests or methacholine challenge test with/without clinician decision (smoking status; 26% current/ex-smokers, atopy; 38%)							
3 cross-sectional studies	826	Very serious[1]	Serious[2]	Very serious[3]	Serious[4]	Sensitivity: 0.25 (0.08-0.59)	VERY LOW
		Very serious[1]	Serious[2]	Very serious[3]	Very serious[5]	Specificity: 0.87 (0.36-0.99)	VERY LOW
Bronchodilator reversibility with 400 µg salbutamol (cut-off FEV_1 increase >10% of predicted) vs expert panel diagnosis with multiple diagnostic tests (smoking status; 35% current/ex-smokers, atopy; 65%)							
1 cross-sectional study	118	Very serious[1]	Not serious	Serious[6]	Not serious	Sensitivity: 0.43 (0.31-0.55)	VERY LOW
		Very serious[1]	Not serious	Serious[6]	Not serious	Specificity: 0.96 (0.85-0.99)	VERY LOW
Bronchodilator reversibility with 400 µg salbutamol (cut-off: ≥9% predicted FEV_1) (smoking status: 22% current, 21% past smokers, 56% non-smokers; atopy: 44% atopic)							
1 retrospective cross-	194	Very serious[7]	Not serious	Very serious[8]	Not serious	Sensitivity= 0.30 (0.23-0.39)	VERY LOW
		Very serious[7]	Not serious	Very serious[8]	Serious[9]	Specificity= 0.79 (0.67-0.88)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
sectional study							
Bronchodilator reversibility with 400 µg salbutamol (cut-off: increase in FEV_1 ≥15% and/or ≥200 mL from baseline) (smoking status: 14% current smokers, 14% past-smokers; atopy: mean induced sputum eosinophil count: 3.16%)							
1 prospective cross-sectional study	50	Serious[10]	Not serious	Not serious	Not serious	Sensitivity= 0.41 (0.21-0.64)	MODERATE
		Serious[10]	Not serious	Not serious	Serious[9]	Specificity= 0.86 (0.67-0.96)	LOW

1. *Downgraded by two increments due to concerns arising from the method of patient selection (method not reported), interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of patients through the study*
2. *Downgraded by one increment due to considerable differences between the point estimate and 95%CI of studies reporting the same diagnostic threshold*
3. *Downgraded by two increments due to population (ICS use not reported and mixed smoking status) and reference standard (unclear if clinician decision was involved in diagnosis) indirectness*
4. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'low sensitivity' (10%)*
5. *Downgraded by two increments due to the 95%CI overlapping the thresholds corresponding to both 'low and high specificity' (50% and 80%)*
6. *Downgraded by one increment due to population (mixed smoking status) indirectness*
7. *Downgraded by two increments due to concerns arising from the method of patient selection (method not reported) and interpretation of the index test and reference standard (unclear if blinded/unblinded)*
8. *Downgraded by two increments due to population (mixed/not reported smoking status) and reference standard (unclear if clinician diagnosis was involved) indirectness*
9. *Downgraded by one increment due to the confidence interval crossing the threshold for 'high specificity' (80%)*
10. *Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded)*

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 as 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: Bronchodilator reversibility per-test cost

Resource	Quantity	Unit costs	Total cost	Source
Spirometry	2	£1.8 per spirometry	£3.60	Supply Chain Catalogues(NHS Supply Chain Catalogue., 2022)
Salbutamol reusable inhaler	400 mcg	£0.0001 per mg	£0.04	BNF(Joint Formulary Committee, 2024) PCA(NHS Business Services Authority, 2021)
Salbutamol whole inhaler	1	£1.89 per MDI	£1.89	BNF(Joint Formulary Committee, 2024) PCA(NHS Business Services Authority, 2021)
Spacer device for use with MDI without mask	1	£3.83 per spacer	£3.83	Supply Chain Catalogues(NHS Supply Chain Catalogue., 2022)
Time of practice nurse	30 minutes	£63.38 per hour	£31.69	PSSRU 2022 (Jones, et al.)
Total cost (with reusable inhaler)			£39.16	
Total cost (with whole inhaler)			£41.01	

Note: all prices are VAT-exclusive

a) See Evidence Review 1.1 for calculation.

Two spirometry measurements are needed for a bronchodilator reversibility test: one for the initial readings and one after the medication is given. If the test is given in a sequence after a standard spirometry, then the cost of the first spirometry should be removed from the final estimation.

1.1.11 Evidence statements

Economic

- No relevant economic evaluations were identified.

1.2 The committee's discussion and interpretation of the evidence

1.2.1. The outcomes that matter most

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 FEV_1 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 purposed 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 index test for diagnosing asthma 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. The committee were interested in establishing whether there was an optimal cut-off value of bronchodilator reversibility with sufficiently high sensitivity and specificity to be useful in making a diagnosis of asthma, but also in whether there are separate cut-off values which could usefully help either rule in or rule out an asthma diagnosis.

1.2.2 The quality of the evidence

Test and Treat studies

No relevant clinical studies were identified comparing the clinical effectiveness of bronchodilator response measured using PEF (L/min; change in PEF as % of initial PEF) or FEV_1 (change in FEV_1 % initial and/or change in FEV_1 litres; change in FEV_1 % predicted).

Diagnostic accuracy

Four observational studies (two prospective, two retrospective) were included in the evidence for the diagnostic accuracy of bronchodilator response. All studies were in an adult population. Three studies looked at bronchodilator reversibility to 400 µg salbutamol using a cut-off of an FEV_1 increase of both ≥200 mL and 12% above the pre-bronchodilator value to diagnose asthma. One study looked at bronchodilator reversibility to 400 µg salbutamol with cut-off ≥9% predicted FEV_1, one study used a cut-off of >10%, and one study investigated bronchodilator reversibility with 400 µg salbutamol with a cut-off of FEV_1 ≥15% and/or ≥200 mL from baseline. The quality of the evidence ranged from very low to moderate, with the vast majority being rated as very low. Evidence was mostly downgraded for risk of bias due to concerns arising from a lack of sufficient detail on the blinding of the index test and reference standard results, and/or the patient recruitment method. Additionally, indirectness was common due to ICS use prior to/during the study not being reported, or because the cut-off value used for diagnosis was different to that specified in the review protocol. Finally, imprecision of the estimate for specificity was seen in the majority of the evidence due to the 95%CI crossing the upper threshold for decision making.

No evidence was identified for children and young people.

1.2.3 Benefits and harms

Very low-quality evidence from three studies reported bronchodilator reversibility to 400 µg salbutamol using a cut-off value of an FEV_1 increase of both ≥200 mL and 12% above the pre-bronchodilator value. Meta-analysis of these studies showed a low sensitivity of 0.25 and a high specificity of 0.87. This evidence was downgraded by two increments due to very serious risk of bias arising from an unclear method of participant recruitment and unclear blinding of the index test and reference standard in the majority of the evidence. Furthermore, this evidence was downgraded for indirectness due to all included studies containing populations with mixed smoking status', one study failing to report ICS status and the other lacking clarity over the involvement of a clinician decision in the diagnosis. This evidence was downgraded by a further increment due to inconsistency in both the sensitivity and specificity estimates due to the individual studies reporting considerably different values. Finally, imprecision was seen in both estimates, with the sensitivity estimate being downgraded by one increment due to overlapping the lower threshold for decision making and the specificity estimate being downgraded by two increments due to overlapping both the upper and lower thresholds.

Very low-quality evidence from one study reported the bronchodilator response measured using a cut-off of >10% predicted FEV_1, showing a moderate sensitivity of 0.43 and a high specificity of 0.96. This evidence was from one of the studies that reported FEV_1 increase of both ≥200 mL and 12% above the pre-bronchodilator values, showing improved sensitivity, but reduced specificity.

Very low-quality evidence from one study reported the bronchodilator response measured using a cut-off of ≥9% predicted FEV_1, showing a low sensitivity of 0.30 and moderate specificity 0.79. This evidence was from one of the studies that reported FEV_1 increase of both ≥200 mL and 12% above the pre-bronchodilator values, showing an improved sensitivity but poorer specificity using a ≥9% cut-off.

Moderate-low-quality evidence reported bronchodilator reversibility to 400 µg salbutamol using as the cut-off an increase in FEV_1 ≥15% and/or ≥200 mL from baseline, showing a moderate sensitivity of 0.41 and high specificity of 0.86. This evidence was limited by the small number of participants included and due to risk of bias arising from a lack of clarity on blinding of the test results. Nonetheless, this evidence was of better quality compared to the other evidence identified in this review.

It was noted that the study of Fortuna et al., excluded people with "systemic manifestations" of atopy but did not define exactly what this meant leading to some uncertainty about the generalisability of this study. Louis et al., used methacholine challenge testing as part of their reference standard definition of asthma, which excludes people with a low baseline FEV_1 since, for safety reasons, methacholine challenge cannot be performed when FEV_1 is too low (this study used <70% predicted FEV_1 as the safety threshold).

The results are in keeping with the committee's clinical experience. Bronchodilator reversibility can only be demonstrated when the person being tested has some reduction in their FEV_1 at baseline and as this will not be the case much of the time, even in people with asthma, sensitivity of the test is likely to be low. However, the test shows acceptable specificity as long as the reversibility cut-off value is set at a reasonable level. The committee agreed that reversibility of either 12% of baseline FEV_1 level or 10% of predicted normal were appropriate cut-off thresholds (with the proviso that in adults the increase from baseline should also be at least 200mls).

The committee also noted the absence of evidence in children and young people.

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 bronchodilator reversibility diagnostic test was presented to aid committee consideration of cost effectiveness. The unit cost of undertaking a bronchodilator reversibility test for diagnostic purposes was £39.16 – £41.01 and included the health care professional time for conducting the test and interpreting the result (£31.69), salbutamol either reusable or not (£0 – £1.89), spacer (£3.83) and the equipment and consumables required for the spirometry tests (£3.60).

The committee agreed that this test would be conducted, and results interpreted by a practice nurse (band 5) and would take on average 30 minutes. The nurse will need to be fully trained and accredited to conduct spirometry testing and the spirometer would need daily calibration. The duration for testing and unit cost for the practice nurse account for both these elements.

The equipment and consumables costs per spirometry test were estimated in the spirometry evidence review and used here. Two spirometry tests are required for the bronchodilator reversibility test.

The person will take 400 µg (4 puffs) salbutamol through a single use spacer after the first spirometry. The committee discussed whether the full cost of a salbutamol inhaler should be included or only the required 400 µg. The rationale for including the full inhaler cost was that the same inhaler cannot be used on different people due to infection control concerns. Furthermore, although the inhaler could then be used as treatment if the person is diagnosed with asthma, thus absorbing part of the cost of a full inhaler, salbutamol may not be the recommended treatment for that individual. The main concern with including the cost of a full inhaler related to the carbon footprint of such an approach. It was noted that in secondary care, nebulised salbutamol was sometimes used, thus negating the need to use a whole inhaler per person. The committee were unable to reach a consensus and therefore a range of costs was presented for salbutamol to account for both scenarios.

The committee considered bronchodilator response test alongside or in combination with a variety of other tests for asthma within a diagnostic algorithm for both adults and children (see evidence review 1.11). Bronchodilator response was found to be a cost-effective test in adults and recommended as part of a diagnostic algorithm. Although BDR was not found to be cost-effective in a diagnostic algorithm in children, the committee acknowledged that children with non-atopic asthma could be underdiagnosed without a reversibility test. Hence, they recommended to measure BDR in children with a negative FeNO result.

1.2.5 Other factors the committee took into account

Historically FEV_1 reversibility has been calculated as a percentage change from the baseline FEV_1 value. This has the effect of making any given percentage increase more easily achievable when starting FEV_1 is lower. It is therefore preferable to stipulate that the increase in FEV_1 with bronchodilator should be related to the predicted FEV_1 as recommended by a recent joint ERS/ATS statement. (Stanojevic, et al., 2022) Although the committee agreed with this principle, they also noted that it has not been widely adopted as yet and so quoted two different means of expressing reversibility in their recommendation.

1.2.6 Recommendations supported by this evidence review

Recommendations 1.2.2 and 1.2.5.

1.3 References

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Appendices

Appendix A – Review protocol

Review protocol for diagnostic test accuracy and clinical and cost-effectiveness of bronchodilator response for diagnosis of asthma

Field	Content
PROSPERO registration number	CRD42023437194
Review title	The accuracy of bronchodilator response in the diagnosis of asthma
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of bronchodilator response (using PEF or FEV1)?
Objective	To evaluate the diagnostic test accuracy of bronchodilator response (using PEF or FEV1) in diagnosing asthma This evidence review will have two stages: (1) Identify the clinical and cost effectiveness of diagnosis with the test (test plus treatment) (2) If evidence on clinical effectiveness is limited, the diagnostic accuracy will instead be determined
Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • Diagnostic 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).

Condition or domain being studied	Asthma
Population	Inclusion: People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: • Children and young people (5-16 years old) • Adults (≥17 years) Exclusion: Children under 5 years old People on steroid inhalers (washout period minimum of 4 weeks for inclusion) Stratification Smokers' vs non-smokers vs mixed populations
Test	Bronchodilator response, measured using the following: o PEF o L/min o Change in PEF (as % of initial PEF) o FEV1 o change in FEV1 % initial and/or change in FEV1 litres o Change in FEV1 % predicted (∆FEV1 %pred) Exclusions: o Change in absolute litres alone o Standardised residual (SR)-FEV1 o Change in FEV1 % of possible maximal response (∆FEV1 %max) <u>Stratification</u> Different test thresholds (FEV1) • <12% • ≥12%
Reference standard	Effectiveness (test-and-treat) • Compare to each other Diagnostic accuracy • 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);

	• 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 diagnosis and confirmation of 'asthma' diagnosis: 12 months
Types of study to be included	Clinical effectiveness (test and treat): • Systematic reviews of RCTs • Parallel RCTs Published NMAs and IPDs will be considered for inclusion. Diagnostic test accuracy: Cross sectional studies and cohort studies will be included.
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 looking at occupational asthma /allergens • Studies in which >10% of people are on inhaled and/or systemic corticosteroid treatment • Not looking at occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring bronchodilator • Cross-sectional studies were included if they reported sensitivity or specificity, or the sensitivity and specificity could be calculated.
Context	Primary, secondary and community care settings
Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making a therefore have all been rated as critical: Clinical effectiveness (test and treat) • Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at ≥6 months, latest timepoint if more than one)

	• 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; at ≥6 months; continuous outcome
	• Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks)
	
	Diagnostic accuracy outcomes: Asthma diagnosis
	• Sensitivity (thresholds: upper 90%, lower 10%)
	• Specificity (thresholds: upper 80%, lower 50%)
	• Raw data to calculate 2x2 tables to calculate sensitivity and specificity
	• Positive predictive value (PPV) and negative predictive value (NPV)

Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments

	Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • QUADAS-2 checklist
Strategy for data synthesis	<u>Test and treat:</u> Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. WinBUGS will be used for network meta-analysis, if possible given the data identified. <u>Diagnostic accuracy:</u> Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention will be placed on specificity determined by the committee to be the primary outcome for decision making. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.

Analysis of sub-groups	N/A		
Type and method of review	☒	Intervention	
	☒	Diagnostic	
	☐	Prognostic	
	☐	Qualitative	
	☐	Epidemiologic	
	☐	Service Delivery	
	☐	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date			
Anticipated completion date	31 July 2024		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☐	☐
	Formal screening of search results against eligibility criteria	☐	☐
	Data extraction	☐	☐
	Risk of bias (quality) assessment	☐	☐
	Data analysis	☐	☐
Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail asthmachronicmanagement@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
Review team members	From the National Guideline Centre: Bernard Higgins (Guideline lead) Sharon Swain (Guideline lead) Toby Sands (Systematic reviewer) Alfredo Mariani (Senior health economist) Lina Gulhane (Head of information specialists)		

	Stephen Deed (Information specialist) Amy Crisp (Senior project manager) Melina Vasileiou (Senior systematic reviewer)	
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.	
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10186	
Other registration details	N/A	
Reference/URL for published protocol		
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	N/A	
Details of existing review of same topic by same authors	N/A	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	N/A	

Details of final publication	www.nice.org.uk

Health economic review protocol

Table 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 bronchodilator response (using PEF or FEV1)?

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.	exp *Spirometry/
25.	(spiromet* or spirograph* or spriogram* or pneumotachograph* or bronchospiromet* or microspiromet* or bronchospirograph*).ti,ab,kf.
26.	(volume* adj2 (time or curve*)).ti,ab,kf.
27.	(flow* adj2 (volume* or loop*)).ti,ab,kf.
28.	or/24-27
29.	*Vital Capacity/
30.	(forced adj2 (vital or capacity)).ti,ab,kf.
31.	FVC.ti,ab,kf.
32.	or/29-31
33.	*Forced Expiratory Volume/
34.	(forced adj2 (expiratory or expiration or exhal* or volume*)).ti,ab,kf.
35.	(FEV or FEV1*).ti,ab,kf.
36.	or/33-35
37.	*Peak Expiratory Flow Rate/
38.	(peak adj2 flow*).ti,ab,kf.
39.	(PEF or PEFR* or PFR* or PEFV).ti,ab,kf.
40.	or/37-39
41.	*Respiratory Function Tests/
42.	((pulmonary function or respiratory function) adj2 (test* or measure*)).ti,ab,kf.
43.	or/41-42
44.	(bronchoreversibility or broncho reversibility).ti,ab,kf.
45.	(reversibility adj2 (test* or respons* or respond*)).ti,ab,kf.
46.	((bronchodilator* or broncho dilator* or bronchial or broncholytic*) adj3 (test* or revers* or respons* or respond*)).ti,ab,kf.
47.	(BDR or BDT).ti,ab,kf.
48.	or/44-47
49.	28 or 32 or 36 or 40 or 43 or 48
50.	23 and 49
51.	exp "sensitivity and specificity"/

52.	(sensitivity or specificity).ti,ab.
53.	((pre test or pretest or post test) adj probability).ti,ab.
54.	(predictive value* or PPV or NPV).ti,ab.
55.	likelihood ratio*.ti,ab.
56.	likelihood function/
57.	((area under adj4 curve) or AUC).ti,ab.
58.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
59.	gold standard.ab.
60.	exp Diagnostic errors/
61.	(false positiv* or false negativ*).ti,ab.
62.	Diagnosis, Differential/
63.	(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.
64.	or/51-63
65.	randomized controlled trial.pt.
66.	controlled clinical trial.pt.
67.	randomi#ed.ab.
68.	placebo.ab.
69.	randomly.ab.
70.	clinical trials as topic.sh.
71.	trial.ti.
72.	or/65-71
73.	Meta-Analysis/
74.	Meta-Analysis as Topic/
75.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
76.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
77.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
78.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
79.	(search* adj4 literature).ab.
80.	(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.
81.	cochrane.jw.
82.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
83.	or/73-82
84.	Epidemiologic studies/
85.	Observational study/
86.	exp Cohort studies/
87.	(cohort adj (study or studies or analys* or data)).ti,ab.
88.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
89.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
90.	Controlled Before-After Studies/
91.	Historically Controlled Study/
92.	Interrupted Time Series Analysis/

93.	(before adj2 after adj2 (study or studies or data)).ti,ab.
94.	exp case control study/
95.	case control*.ti,ab.
96.	Cross-sectional studies/
97.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
98.	or/84-97
99.	50 and (64 or 72 or 83 or 98)

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.	*Spirometry/ or *Spirography/ or *Bronchospirography/ or *Pneumotachygraphy/
24.	(spiromet* or spirograph* or spriogram* or pneumotachograph* or bronchospiromet* or microspiromet* or bronchospirograph*).ti,ab,kf.
25.	(volume* adj2 (time or curve*)).ti,ab,kf.
26.	(flow* adj2 (volume* or loop*)).ti,ab,kf.
27.	or/23-26
28.	*Vital Capacity/
29.	(forced adj2 (vital or capacity)).ti,ab,kf.
30.	FVC.ti,ab,kf.
31.	or/28-30
32.	*Forced Expiratory Volume/
33.	(forced adj2 (expiratory or expiration or exhal* or volume*)).ti,ab,kf.
34.	(FEV or FEV1*).ti,ab,kf.
35.	or/32-34

36.	*Peak Expiratory Flow/
37.	(peak adj2 flow*).ti,ab,kf.
38.	(PEF or PEFR* or PFR* or PEFV).ti,ab,kf.
39.	or/36-38
40.	*Lung Function Test/
41.	((pulmonary function or respiratory function) adj2 (test* or measure*)).ti,ab,kf.
42.	or/40-41
43.	(bronchoreversibility or broncho reversibility).ti,ab,kf.
44.	(reversibility adj2 (test* or respons* or respond*)).ti,ab,kf.
45.	((bronchodilator* or broncho dilat* or bronchial or broncholytic*) adj3 (test* or revers* or respons* or respond*)).ti,ab,kf.
46.	(BDR or BDT).ti,ab,kf.
47.	or/43-46
48.	27 or 31 or 35 or 39 or 42 or 47
49.	22 and 48
50.	exp "sensitivity and specificity"/
51.	(sensitivity or specificity).ti,ab.
52.	((pre test or pretest or post test) adj probability).ti,ab.
53.	(predictive value* or PPV or NPV).ti,ab.
54.	likelihood ratio*.ti,ab.
55.	((area under adj4 curve) or AUC).ti,ab.
56.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
57.	diagnostic accuracy/
58.	diagnostic test accuracy study/
59.	gold standard.ab.
60.	exp diagnostic error/
61.	(false positiv* or false negativ*).ti,ab.
62.	differential diagnosis/
63.	(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.
64.	or/50-63
65.	random*.ti,ab.
66.	factorial*.ti,ab.
67.	(crossover* or cross over*).ti,ab.
68.	((doubl* or singl*) adj blind*).ti,ab.
69.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
70.	crossover procedure/
71.	single blind procedure/
72.	randomized controlled trial/
73.	double blind procedure/
74.	or/65-73
75.	Systematic Review/
76.	Meta-Analysis/
77.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
78.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.

79.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
80.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
81.	(search* adj4 literature).ab.
82.	(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.
83.	cochrane.jw.
84.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
85.	or/75-84
86.	Clinical study/
87.	Observational study/
88.	Family study/
89.	Longitudinal study/
90.	Retrospective study/
91.	Prospective study/
92.	Cohort analysis/
93.	Follow-up/
94.	cohort*.ti,ab.
95.	93 and 94
96.	(cohort adj (study or studies or analys* or data)).ti,ab.
97.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
98.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
99.	(before adj2 after adj2 (study or studies or data)).ti,ab.
100.	exp case control study/
101.	case control*.ti,ab.
102.	cross-sectional study/
103.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
104.	or/86-92,95-103
105.	49 and (64 or 74 or 85 or 104)

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: [Spirometry] explode all trees
#7.	(spiromet* or spirograph* or spriogram* or pneumotachograph* or bronchospiromet* or microspiromet* or bronchospirograph*):ti,ab,kw
#8.	(volume* near/2 (time or curve*)):ti,ab,kw
#9.	(flow* near/2 (volume* or loop*)):ti,ab,kw
#10.	(or #6-#9)
#11.	MeSH descriptor: [Vital Capacity] this term only

#12.	(forced near/2 (vital or capacity)):ti,ab,kw
#13.	FVC:ti,ab,kw
#14.	(or #11-#13)
#15.	MeSH descriptor: [Forced Expiratory Volume] this term only
#16.	(forced near/2 (expiratory or expiration or exhal* or volume*)):ti,ab,kw
#17.	(FEV or FEV1*):ti,ab,kw
#18.	(or #15-#17)
#19.	MeSH descriptor: [Peak Expiratory Flow Rate] this term only
#20.	(peak near/2 flow*):ti,ab,kw
#21.	(PEF or PEFR* or PFR* or PEFV):ti,ab,kw
#22.	(or #19-#21)
#23.	MeSH descriptor: [Respiratory Function Tests] this term only
#24.	((pulmonary function or respiratory function) near/2 (test* or measure*)):ti,ab,kw
#25.	(or #23-#24)
#26.	(bronchoreversibility or broncho reversibility):ti,ab,kw
#27.	(reversibility near/2 (test* or respons* or respond*)):ti,ab,kw
#28.	((bronchodilator* or broncho dilator* or bronchial or broncholytic*) near/3 (test* or revers* or respons* or respond*)):ti,ab,kw
#29.	(BDR or BDT):ti,ab,kw
#30.	(or #26-#29)
#31.	#10 or #14 or #18 or #22 or #25 or #30
#32.	#5 and #31

Epistemonikos search terms

1.	(advanced_title_en:((advanced_title_en:(asthma) OR advanced_abstract_en:(asthma))) OR advanced_abstract_en:((advanced_title_en:(asthma) OR advanced_abstract_en:(asthma)))) AND (advanced_title_en:(spiromet* OR spirograph* OR spriogram* OR pneumotachograph* OR bronchospiromet* OR microspiromet* OR bronchospirograph* OR "forced vital capacity" OR FVC OR "forced expiratory volume" OR FEV1 OR "peak expiratory flow" OR PEFR* OR PFR* OR PEFV OR bronchoreversibility OR "broncho reversibility" OR "reversibility test*" OR "bronchodilator* respons*" OR "broncho dilator* respons*" OR BDR OR "bronchodilator* test*" OR "broncho dilator* test*" OR BDT) OR advanced_abstract_en:(spiromet* OR spirograph* OR spriogram* OR pneumotachograph* OR bronchospiromet* OR microspiromet* OR bronchospirograph* OR "forced vital capacity" OR FVC OR "forced expiratory volume" OR FEV1 OR "peak expiratory flow" OR PEFR* OR PFR* OR PEFV OR bronchoreversibility OR "broncho reversibility" OR "reversibility test*" OR "bronchodilator* respons*" OR "broncho dilator* respons*" OR BDR OR "bronchodilator* test*" OR "broncho dilator* test*" OR BDT))

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

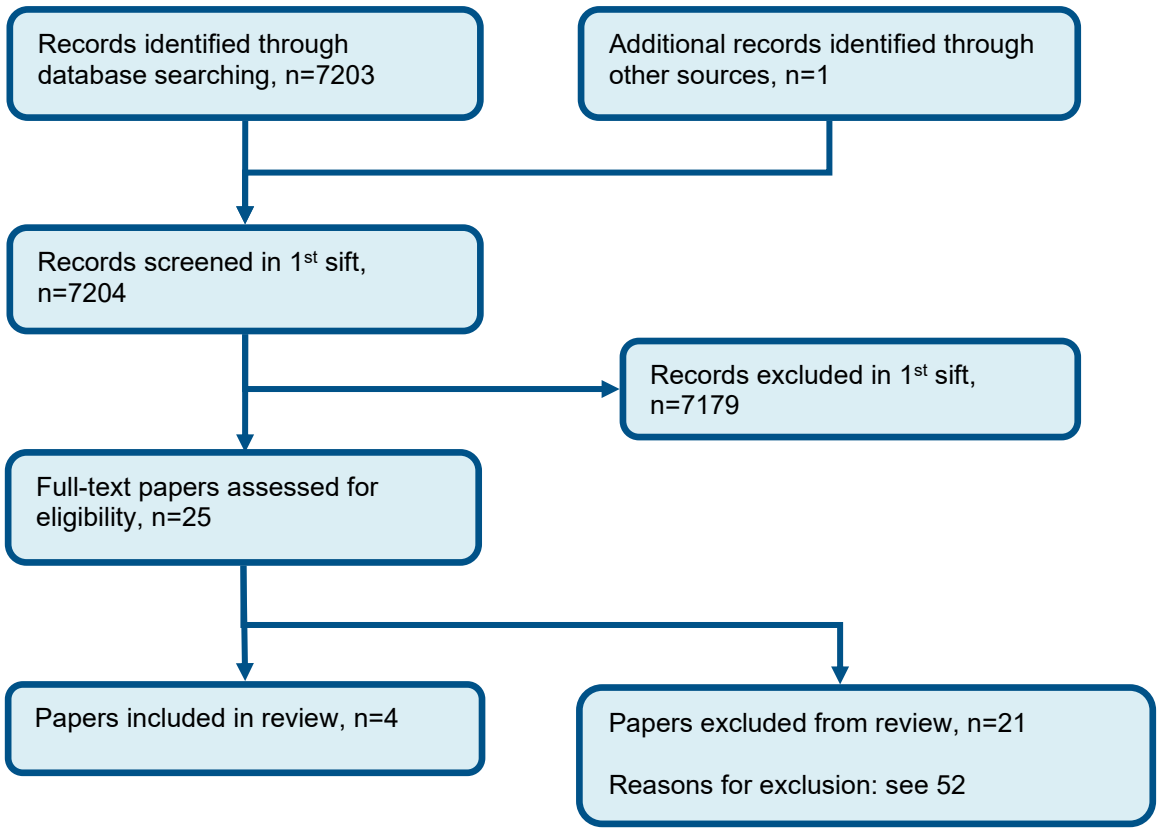
INAHTA search terms

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

Appendix C –Diagnostic evidence study selection

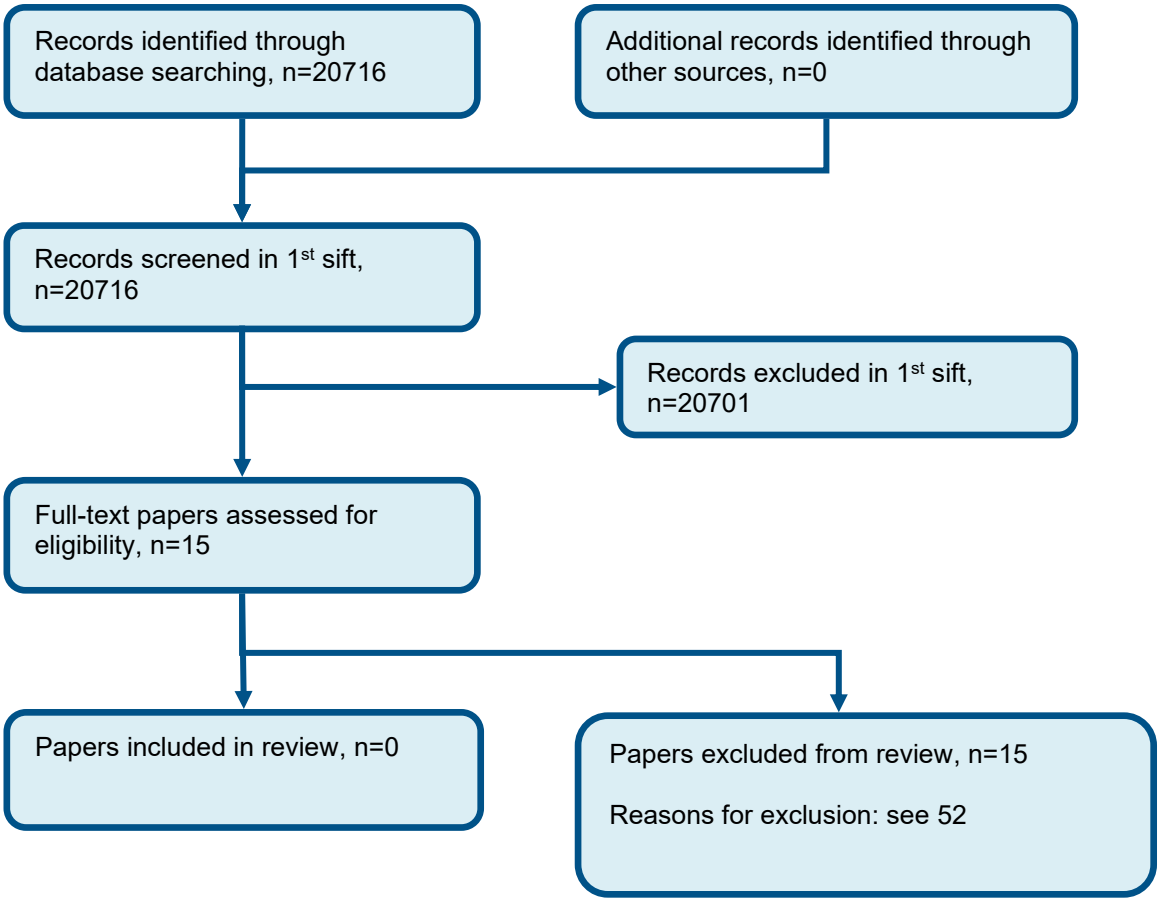
Diagnostic test accuracy of bronchodilator response

Figure 1: Flow chart of clinical study selection for the review of diagnostic test accuracy of bronchodilator reversibility for diagnosis of asthma



Clinical and cost effectiveness of bronchodilator response

Figure 2: Flow chart of clinical study selection for the review of clinical and cost effectiveness of bronchodilator response in people suspected of asthma



Appendix D –Diagnostic evidence

Diagnostic test accuracy of bronchodilator response

Reference	**Fortuna 2007 (Fortuna et al., 2007)**
Study type	Prospective cross-sectional diagnostic study
Study methodology	Data source: Consecutive patients referred to respiratory medicine outpatient clinic for asthma diagnosis Recruitment: Consecutive
Number of patients	n = 50
Patient characteristics	Age, mean (range): asthma diagnosis: 38 (18-64), non-asthma diagnosis: 37 (18-68) years Gender (male to female ratio): 21:29 Ethnicity: Not reported Smoking status: 14% current smokers Atopy: Mean induced sputum eosinophil count: 3.16% Setting: Secondary care Country: Spain Inclusion criteria: patients referred to hospital-based respiratory medicine outpatient clinic for diagnosis with a clinical history suggestive of asthma (dry cough, wheezing, and shortness of breath) Exclusion criteria: patients with conditions that could affect FeNO or Eos% measurement for reasons other than asthma: subjects with symptoms of respiratory tract infection in the previous 6 weeks or with systemic manifestations of atopy (rash, digestive symptoms, etc.) and patients who had received treatment with inhaled or oral corticosteroids in the last 4 weeks
Target condition(s)	Asthma

<table>
<tr><td>Reference</td><td colspan="5">Fortuna 2007 (Fortuna et al., 2007)</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5">Index test
A positive bronchodilator response was defined as an increase in FEV_1 ≥15% and/or ≥200 mL from baseline after inhalation of 400 µg of salbutamol.

Cut-off: FEV_1 increase of ≥15% and/or ≥200 mL from baseline (pre-specified)

Reference standard
A subject who presented with a clinical history suggestive of asthma and a positive methacholine challenge test was diagnosed with asthma. The methacholine challenge was performed according to international guidelines as a dose–response test of increasing doses of methacholine chloralhydrate (0.1–32 mg/mL) every 5 min. The test was stopped when the highest concentration (32 mg/mL) was tolerated, or if a fall of 20% in FEV1 from baseline was induced after methacholine was inhaled. A methacholine challenge test was considered positive if the PD20 was ≤16 mg/mL.

Time between measurement of index test and reference standard: 1 day</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td>Prevalence= 44%</td></tr>
<tr><td></td><td>Index test +</td><td>9</td><td>4</td><td>13</td><td></td></tr>
<tr><td></td><td>Index test −</td><td>13</td><td>24</td><td>37</td><td></td></tr>
<tr><td></td><td>Total</td><td>22</td><td>28</td><td>50</td><td></td></tr>
<tr><td>Statistical measures</td><td colspan="5">Index text
Sensitivity: 0.41 (95%CI 0.21-0.64
Specificity: 0.86 (95%CI 0.67-0.96)
PPV: 69%
NPV: 65%</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: Serious due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded)
Indirectness: None</td></tr>
<tr><td>Comments</td><td colspan="5">Sensitivity and specificity calculated from reported 2x2 tables</td></tr>
</table>

<table>
<tr><td>Reference</td><td>Kim 2012 (Kim et al., 2012)</td></tr>
<tr><td>Study type</td><td>Retrospective diagnostic cohort study</td></tr>
<tr><td>Study methodology</td><td>Data source: Chart review of asthma, COPD and asthma-COPD overlap patients

Recruitment: Not stated</td></tr>
</table>

Reference	Kim 2012 (Kim et al., 2012)
Number of patients	n = 514
Patient characteristics	Age, mean (SD): asthma cohort: 48 (16), COPD cohort: 65 (8) years Gender (male to female ratio): asthma cohort: 49% male, COPD cohort: 91.7% Smoking status: asthma cohort: 16.6% current smokers, COPD cohort: 30.1% current smokers Atopy: asthma cohort: 141/306 atopic, COPD cohort: 13/141 atopic Ethnicity: Not reported Setting: Secondary care Country: Republic of Korea Inclusion criteria: Adults with chronic obstructive airways disorders included in an asthma cohort or a COPD cohort; all had at least one chronic persistent respiratory symptom (dyspnoea, cough, sputum production or wheeze) for >3 months or repetition of the symptom for >3 months Exclusion criteria: Patients with tuberculous destroyed lungs, bronchiectasis or lung resection
Target condition(s)	Asthma
Index test(s) and reference standard	Index test Post-bronchodilator spirometry was performed 10 –15 min after inhalation of 400 µg of albuterol; an increase in FEV_1 that was both ≥200 mL and 12% above the pre-bronchodilator FEV1 was considered clinically important. The use of bronchodilators was prohibited for at least 4 days before the test. Cut-off: FEV_1 increase of ≥12% and 200 mL from baseline (pre-specified) Reference standard Clinical diagnosis by specialists in allergy or pulmonary departments (no definitive diagnostic criteria). Tests included: Methacholine challenge Airway hyperresponsiveness was assessed by methacholine challenge. An AHR-positive response was defined as a PC20 (provocational concentration of methacholine that produced a 20% decrease in FEV_1) of <16 mg/mL.

<table>
<tr><td>Reference</td><td colspan="5">Kim 2012 (Kim et al., 2012)</td></tr>
<tr><td></td><td colspan="5">Skin prick tests
Skin prick tests employing 12 common allergens were employed for detection of atopy. The panel consisted of house dust mites (Dermatophagoides pteronyssinus, D. farinae); cat fur; moulds (Aspergillus fumigatus, Alternaria tenuis); various pollens (tree pollen mixture 1 [alder, hazel, popular, elm, and willow tree] and 2 [birch, beech, oak, and plane tree], grass pollen mixture [velvet grass, orchard grass, rye grass, timothy grass, Kentucky blue grass, and meadow grass], mug wort, and ragweed); German cockroach (Blattella germanica); and 2-spotted spider mite; plus a negative control and histamine.

History
frequency of emergency department visits and admissions to hospital during the previous year. The smoking history was evaluated; subjects who had a positive lifetime history of cigarette smoking but do not now smoke were considered as ex-smokers, and those who had smoked cigarettes on 5 or more days within the past 30 days were current smokers

Time between measurement of index test and reference standard: Not reported</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="4">Prevalence= 71.8%</td></tr>
<tr><td></td><td>Index test +</td><td>62</td><td>56</td><td>118</td></tr>
<tr><td></td><td>Index test −</td><td>307</td><td>89</td><td>396</td></tr>
<tr><td></td><td>Total</td><td>369</td><td>145</td><td>514</td></tr>
<tr><td>Statistical measures</td><td colspan="5">Sensitivity: 0.17 (95%CI 0.13-0.21)
Specificity: 0.72 (95%CI 0.65-0.78)
PPV: 53%
NPV: 22%</td></tr>
<tr><td>Source of funding</td><td colspan="5">None reported</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: Downgraded by two increments due to very serious risk of bias due to concerns arising from the method of patient selection (not stated how they selected patients from the respective cohorts), lack of clarity if the index test and reference standard were interpreted without knowledge of one another (blinding) and concerns due to the patient flow through the study (790 asthma/COPD patients enrolled, 514 in analyses)
Indirectness: Downgraded by one increment due to population indirectness (unclear pre-trial ICS treatment status)</td></tr>
<tr><td>Comments</td><td colspan="5">Sensitivity and specificity calculated from reported 2x2 tables</td></tr>
</table>

Reference	**Louis 2020 (Louis et al., 2020)**
Study type	Retrospective cross-sectional diagnostic study
Study methodology	Data source: Asthma clinic database of patients referred by two asthma-dedicated respiratory physicians for a diagnosis of asthma

Reference	Louis 2020 (Louis et al., 2020)
	Recruitment: Method not specified; people investigated from June 2006 – November 2018
Number of patients	n = Subset of 194 untreated patients from the patient database of 1610
Patient characteristics	Age, mean (SD): 49 (16) Gender (male to female ratio): 70:124 Smoking status: 56% non-smokers, 21% ex-smokers, 22% current smokers Atopy: 85 atopic, 100 non-atopic (no data for 9 participants) Ethnicity: Not reported Setting: Secondary care Country: Belgium Inclusion criteria: Intermittent or chronic respiratory symptoms, referred to an asthma clinic by two asthma physicians for diagnosis who had not yet received treatment, FEV_1 ≥70% of predicted Exclusion criteria: None reported
Target condition(s)	Asthma
Index test(s) and reference standard	Index test Patients received 400 µg inhaled salbutamol administered by a metered-dose inhaler with a spacer one puff at a time into the spacer and spirometry was performed again 15 minutes later Cut-offs: ≥12% and 200 mL increase in FEV_1 from baseline or ≥9% increase in % predicted FEV_1 (pre-specified) Reference standard The methacholine challenge was performed by using a jet nebulizer activated by an airflow rate of 6 L/minute and delivering 0.3 mL/ minute. Each patient successively inhaled for 1 minute quadrupling methacholine concentration starting from 0.06 mg/mL until a maximal concentration of 16 mg/mL. FEV1 was measured 30 and 90 seconds after each inhaled concentration and the best value was retained. The test was stopped if FEV1 had dropped by at least 20% from the baseline value. The PC20M was calculated by linear interpolation from the last 2 points of the curve. *** for data analysis in this review, only positive values at the cut-off specified in the protocol were extracted (PC20 ≤8 mg/mL) ***

Reference	**Louis 2020 (Louis et al., 2020)**				
	Time between measurement of index test and reference standard: 7-14 days				
2×2 table reversibility ≥12% and 200 mL		Reference standard +	Reference standard −	Total	Prevalence= 72.6%
	Index test +	32	7	39	
	Index test −	109	46	155	
	Total	141	53	194	
2×2 table reversibility ≥9% predicted		Reference standard +	Reference standard −	Total	
	Index test +	49	13	62	
	Index test −	92	40	132	
	Total	141	53	194	
Statistical measures	<u>Index text: reversibility ≥12% and 200 mL</u> Sensitivity: 0.23 (95%CI 0.16-0.31) Specificity: 0.87 (95%CI 0.75-0.95) PPV: 82% NPV: 30% <u>Index text: reversibility ≥9% predicted</u> Sensitivity: 0.30 (95%CI 0.23-0.39) Specificity: 0.79 (95%CI 0.67-0.88) PPV: 75% NPV: 35%				
Source of funding	Federal grant from the Belgian Government				
Limitations	Risk of bias: Downgraded by two increments due to high risk of bias arising from concerns due to the patient selection process (unclear how the 194 were selected from the 1610 available), and concerns due to the interpretation of the index test and reference standard (unclear if the results were interpreted by a blinded assessor) Indirectness: Downgraded by one increment due to indirectness of the reference standard (unclear if clinician diagnosis is involved or just an objective test)				
Comments	Sensitivity and specificity calculated from reported 2x2 tables				

Reference	**Simpson 2024 (Simpson et al., 2024)**
Study type	Prospective cross-sectional diagnostic accuracy study

Reference	Simpson 2024 (Simpson et al., 2024)
Study methodology	Data source: People referred by general practitioners in Greater Manchester having presented with symptoms suggestive of asthma Recruitment: Not reported
Number of patients	n = 118
Patient characteristics	Age, mean (SD): 36 (12) Gender (male to female ratio): 43:75 Smoking status: 40 (35%) current or ex-smokers Atopy: 75/115 (65%) with ≥1 positive skin prick test result Ethnicity: Not reported Setting: Asthma clinic Country: UK Inclusion criteria: Presenting with symptoms of wheeze, chest tightness, cough and/or breathlessness Exclusion criteria: Aged >70 years, inhaled or oral corticosteroid use within 4 weeks, antibiotic use within 2 weeks, smoking history >10 pack years, other significant lung disease, suspected alternative lung disease upon inspection of clinical history and initial physical examination
Target condition(s)	Asthma
Index test(s) and reference standard	Index test Spirometry was repeated 15 minutes following administration of 400 µg of inhaled salbutamol from a metered dose inhaler via a large-volume spacer. Absolute and percentage change in FEV_1 and FVC were calculated to give bronchodilator reversibility. Cut-offs: FEV_1 increase by ≥12% and 200 mL, >10% of predicted increase Reference standard Expert panel objective evidence review was used as the reference standard. All evidence, including history, physical examination, Asthma Control Questionnaire, and all test results before and after ICS, was reviewed by at least three physicians (a minimum of two senior asthma physicians) with a diagnosis reached by consensus. Index test data were available to the assessors of the reference standard. Not

<table>
<tr><td>Reference</td><td colspan="5">Simpson 2024 (Simpson et al., 2024)</td></tr>
<tr><td></td><td colspan="5">all participants completed all aspects of the study, but all evaluable data were assessed including raw data (such as flow volume loops, dose-response curves, peak flow diaries), to take account of uncertainty and inherent biological variability. Participants were assigned a diagnosis of “asthma” or “not asthma” or were excluded from further analyses if a clear diagnosis was not possible.

Time between measurement of index test and reference standard: 8-12 weeks</td></tr>
<tr><td rowspan="5">2×2 table FEV₁ increase by ≥12% and 200 mL</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="5">Prevalence= 59.3%</td></tr>
<tr><td>Index test +</td><td>29</td><td>0</td><td>29</td></tr>
<tr><td>Index test −</td><td>41</td><td>48</td><td>89</td></tr>
<tr><td>Total</td><td>70</td><td>48</td><td>118</td></tr>
<tr><td></td></tr>
<tr><td rowspan="5">2×2 table FEV₁ increase by >10% of predicted</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td><td rowspan="5"></td></tr>
<tr><td>Index test +</td><td>30</td><td>2</td><td>32</td></tr>
<tr><td>Index test −</td><td>40</td><td>46</td><td>86</td></tr>
<tr><td>Total</td><td>70</td><td>48</td><td>118</td></tr>
<tr><td></td></tr>
<tr><td>Statistical measures</td><td colspan="5"><u>Index text FEV₁ increase by ≥12% and 200 mL</u>
Sensitivity: 0.41 (95%CI 0.30-0.54)
Specificity: 1.00 (95%CI 0.93-1.00)
PPV: 100% (88-100)
NPV: 54% (49-59)

<u>Index text FEV₁ increase by >10% of predicted</u>
Sensitivity: 0.43 (95%CI 0.31-0.55)
Specificity: 0.96 (95%CI 0.85-0.99)
PPV: 94% (79-98)
NPV: 53% (48-58)</td></tr>
<tr><td>Source of funding</td><td colspan="5">Supported by the Manchester NIHR Biomedical Research Centre, Asthma UK/Innovate and Northwest Lung Centre Charity</td></tr>
<tr><td>Limitations</td><td colspan="5">Risk of bias: Downgraded by two increments due to concerns arising from the method of participant selection (recruitment method not reported) and the interpretation of the index test and reference standard (clinicians had access to index test results whilst making the reference standard diagnosis)
Indirectness: Downgraded by one increment due to population (mixed smoking status of participants) indirectness</td></tr>
</table>

Clinical and cost effectiveness of bronchodilator response

No clinical evidence identified.

Appendix E – Forest plots

Coupled sensitivity and specificity forest plots

Adults with mixed smoking status

Figure 3: Bronchodilator reversibility with 400 µg salbutamol (cut-off FEV_1 increase of both ≥200 mL and 12% above the pre-bronchodilator value) vs expert panel diagnosis with multiple diagnostic tests or methacholine challenge test with/without clinician decision

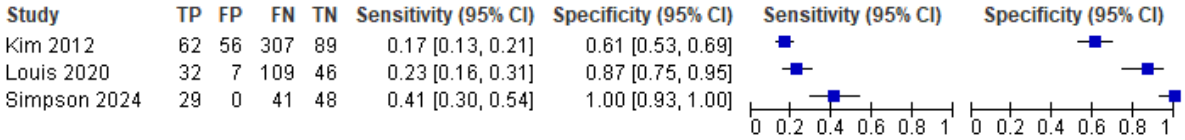


Figure 4: Bronchodilator reversibility with 400 µg salbutamol (cut-off FEV_1 increase >10% of predicted) vs expert panel diagnosis with multiple diagnostic tests

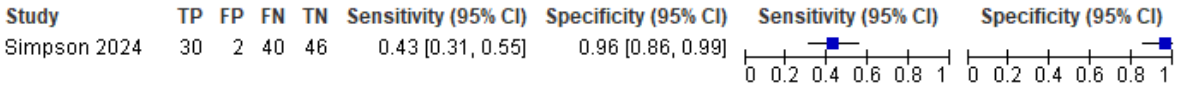


Figure 5: Bronchodilator reversibility with 400 µg salbutamol (cut-off: ≥9% increase predicted FEV_1) vs methacholine bronchial challenge test

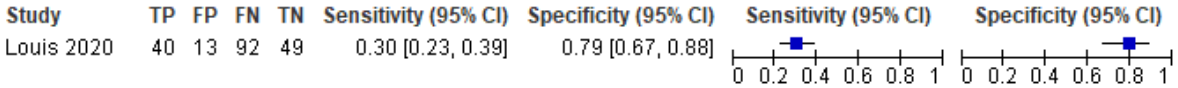


Figure 6: Bronchodilator reversibility with 400 µg salbutamol (cut-off: increase in FEV_1 ≥15% and/or ≥200 mL from baseline) vs clinician diagnosis and methacholine bronchial challenge test

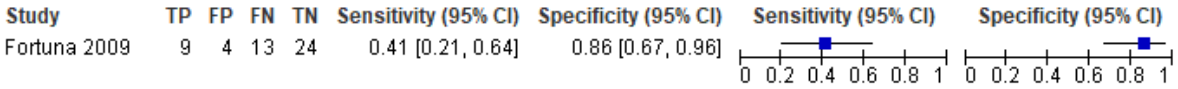
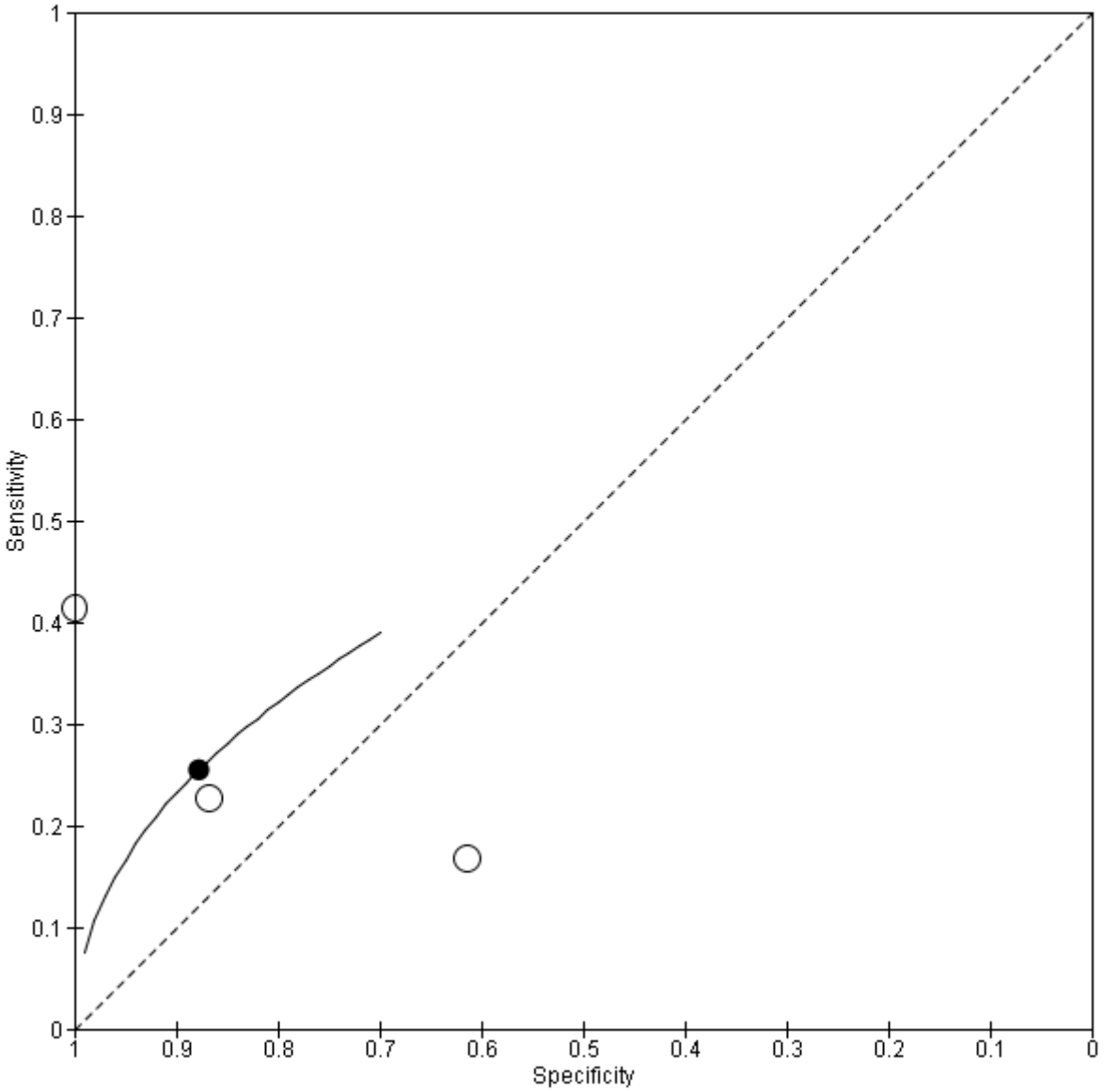


Figure 7: Bronchodilator reversibility with 400 µg salbutamol (cut-off FEV_1 increase of both ≥200 mL and 12% above the pre-bronchodilator value) vs expert panel diagnosis with multiple diagnostic tests or methacholine challenge test with/without clinician decision

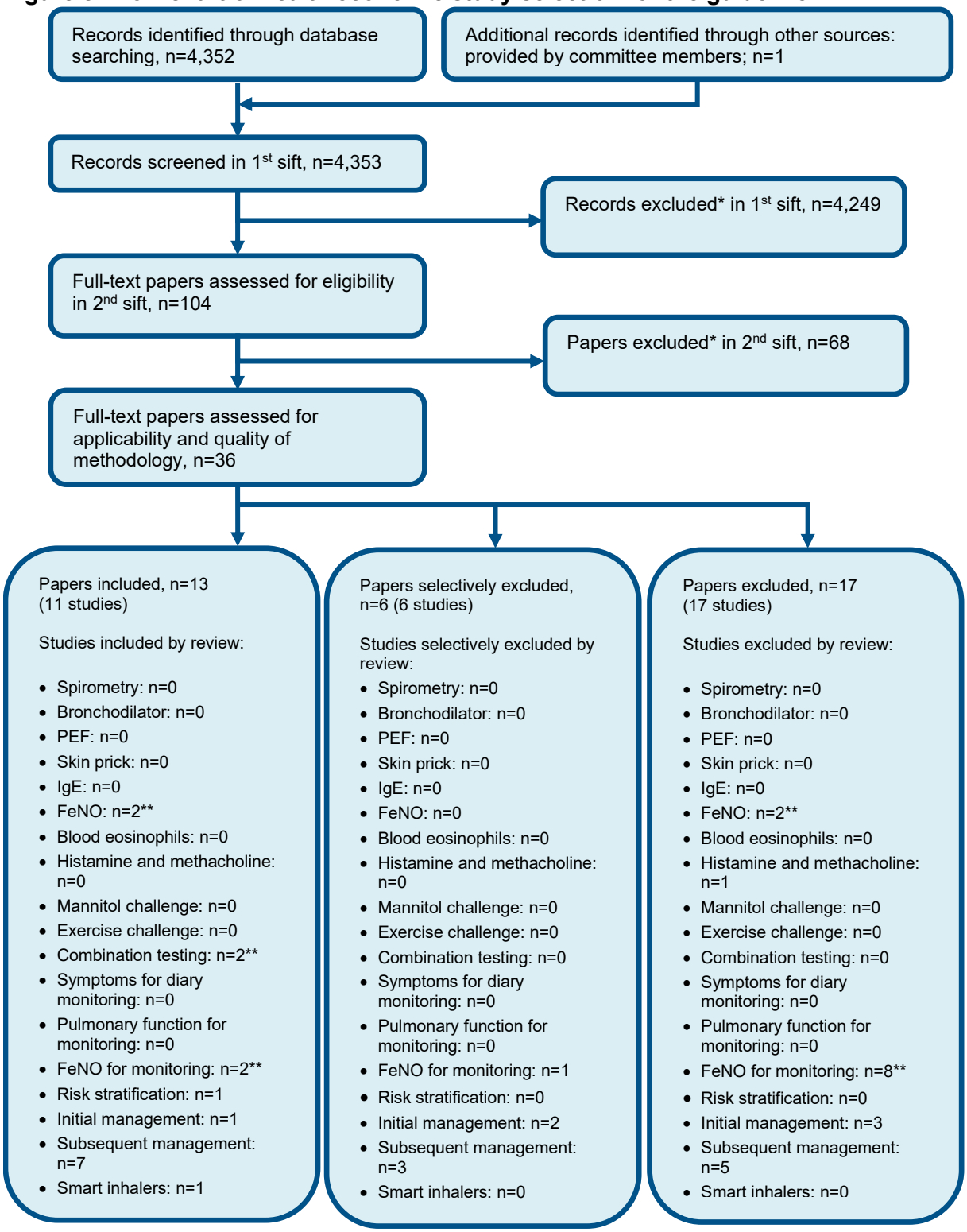


Clinical and cost effectiveness of bronchodilator response

No clinical evidence identified.

Appendix F – Economic evidence study selection

Figure 8: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language
** Includes studies that are in multiple reviews

Appendix G – Economic evidence tables

None.

Appendix H – Excluded studies

Clinical studies

Diagnostic test accuracy of bronchodilator response

Table 8: Studies excluded from the clinical review

Study	Code [Reason]
Backer, V.; Sverrild, A.; Porsbjerg, C. (2014) FENO and AHR mannitol in patients referred to an out-of-hospital asthma clinic: a real-life study. Journal of Asthma 51(4): 411-6	- Index test not relevant to this review protocol
Batmaz, S. B., Kuyucu, S., Arikoglu, T. et al. (2016) Impulse oscillometry in acute and stable asthmatic children: a comparison with spirometry. Journal of Asthma 53(2): 179-86	- Population not relevant to this review protocol
Bobrowska-Korzeniowska, M., Brzozowska, A., Jerzynska, J. et al. (2020) Usefulness of sRtot and Rint in bronchodilator testing in the diagnosis of asthma in children. Postepy Dermatologii I Alergologii 37(5): 685-689	- Population not relevant to this review protocol
Boutin, B., Koskas, M., Guillo, H. et al. (2015) Forced expiratory flows' contribution to lung function interpretation in schoolchildren. European Respiratory Journal 45(1): 107-15	- Population not relevant to this review protocol
Brand PL, Quanjer PH, Postma DS et al. (1992) Interpretation of bronchodilator response in patients with obstructive airways disease. The Dutch Chronic Non-Specific Lung Disease (CNSLD) Study Group. Thorax 47(6): 429-436	- Population not relevant to this review protocol *Inhaled corticosteroid washout period not appropriate for this review protocol (>4 weeks required, >2 weeks specified)*
Cavallazzi, R. S., Polivka, B. J., Beatty, B. L. et al. (2020) Current Bronchodilator Responsiveness Criteria Underestimate Asthma in Older Adults. Respiratory Care 65(8): 1104-1111	- Population not relevant to this review protocol
Chhabra SK (2005) Acute bronchodilator response has limited value in differentiating bronchial asthma from COPD. The Journal of asthma : official journal of the Association for the Care of Asthma 42(5): 367-372	- Population not relevant to this review protocol *Corticosteroid washout period not appropriate for this preview protocol (oral/inhaled treatment allowed to continue throughout study)*

Study	Code [Reason]
Feng, M.; Yang, X.; He, Y. (2019) Effects of bronchial provocation test and bronchial dilation test for the diagnosis of lung diseases. Artificial Cells, Nanomedicine and Biotechnology 47(1): 1452-1457	- Population not relevant to this review protocol
Fillard, Anouchka, Licari, Amelia, Molinari, Nicolas et al. (2023) Sensitivity of FEV1 and Clinical Parameters in Children With a Suspected Asthma Diagnosis. The journal of allergy and clinical immunology. In practice 11(1): 238-247	- Population not relevant to this review protocol *All participants had asthma, not suspected*
Guo, X. X., Liu, X. F., Wang, A. L. et al. (2020) The Clinical Role of Changes of Maximum Expiratory Flow at 25% and 50% of Vital Capacity before and after Bronchodilator Reversibility Test in Diagnosing Asthma. Current Medical Science 40(4): 677-682	- Population not relevant to this review protocol
Hopp, R. J. and Pasha, M. A. (2016) A literature review of the evidence that a 12% improvement in FEV1 is an appropriate cut-off for children. Journal of Asthma 53(4): 413-8	- Systematic review used as source of primary studies
Kang, X. H.; Wang, W.; Cao, L. (2019) A clinical study to determine the threshold of bronchodilator response for diagnosing asthma in Chinese children. World Journal of Pediatrics 15(6): 559-564	- Population not relevant to this review protocol
Mamyrbekova, Saltanat, Iskakova, Gulnara, Faizullina, Kamila et al. (2022) The diagnostic accuracy of spirometry versus peak expiratory flow test for follow-up of adult asthma patients at primary care level. Allergy and asthma proceedings 43(5): e58-e64	- Reference standard in study does not match that specified in protocol *Reference standard (clinician diagnosis) included assessment of pulmonary function tests (index test)*
Pino, J. M., García-Río, F., Prados, C. et al. (1996) Value of the peak expiratory flow in bronchodynamic tests. Allergol Immunopathol (Madr) 24(2): 54-7	- Reference standard in study does not match that specified in protocol *Bronchodilator response used as both index test and reference standard, using either FEV1 or PEF increase as the diagnostic criteria*
Quadrelli SA; Roncoroni AJ; Montiel GC (1999) Evaluation of bronchodilator response in patients with airway obstruction. Respiratory medicine 93(9): 630-636	- Population not relevant to this review protocol *Washout period of inhaled corticosteroids not appropriate for this review protocol (>4 weeks required, 12h specified)*

Study	Code [Reason]
Raywood, E., Lum, S., Aurora, P. et al. (2016) The bronchodilator response in preschool children: A systematic review. Pediatric Pulmonology 51(11): 1242-1250	- Population not relevant to this review protocol
Tan, D. J., Lodge, C. J., Lowe, A. J. et al. (2021) Bronchodilator reversibility as a diagnostic test for adult asthma: findings from the population-based Tasmanian Longitudinal Health Study. Erj Open Research 7(1)	- Population not relevant to this review protocol
Tomita, Katsuyuki, Sano, Hiroyuki, Chiba, Yasutaka et al. (2013) A scoring algorithm for predicting the presence of adult asthma: a prospective derivation study. Primary care respiratory journal : journal of the General Practice Airways Group 22(1): 51-8	- Inadequate ICS washout period *24-hour ICS washout applied*
Tuomisto, L. E., Ilmarinen, P., Lehtimaki, L. et al. (2019) Immediate bronchodilator response in FEV1 as a diagnostic criterion for adult asthma. European Respiratory Journal 53(2): 02	- Review article but not a systematic review
Vilozni, D., Hakim, F., Livnat, G. et al. (2016) Assessment of Airway Bronchodilation by Spirometry Compared to Airway Obstruction in Young Children with Asthma. Canadian Respiratory Journal 2016: 5394876	- Population not relevant to this review protocol
Yadollahzadeh, M., Hashemian, S. M., Kiani, A. et al. (2019) Diagnostic values of bronchodilator response versus 9-question questionnaire for asthma. Advances in Respiratory Medicine 87(5): 269-275	- Reference standard in study does not match that specified in protocol

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Table 9: Studies excluded from the clinical review

Study	Code [Reason]
Backer, V., Groth, S., Dirksen, A. et al. (1991) Sensitivity and specificity of the histamine challenge test for the diagnosis of asthma in an unselected sample of children and adolescents. European Respiratory Journal 4(9): 1093-100	- Population not relevant to this review protocol *Random population sample - not people presenting with respiratory symptoms*

Study	Code [Reason]
Beach, J., Russell, K., Blitz, S. et al. (2007) A systematic review of the diagnosis of occupational asthma. Chest 131(2): 569-78	- Systematic review used as source of primary studies
Berkman, N., Avital, A., Breuer, R. et al. (2005) Exhaled nitric oxide in the diagnosis of asthma: comparison with bronchial provocation tests. Thorax 60(5): 383-8	- Study does not contain an intervention relevant to this review protocol *No bronchodilator reversibility tests applied*
Biswas, P. N.; Shivpuri, D. N.; Agarwal, M. K. (1973) Evaluation of bronchial sensitivity test in diagnosis of bronchial asthma. Indian Journal of Chest Diseases 15(2): 117-22	- Population not relevant to this review protocol *Participants already diagnosed with asthma*
Brand, P. L., Quanjer, P. H., Postma, D. S. et al. (1992) Interpretation of bronchodilator response in patients with obstructive airways disease. The Dutch Chronic Non-Specific Lung Disease (CNSLD) Study Group. Thorax 47(6): 429-36	- Study design not relevant to this review protocol *Not a randomised trial*
Chhabra, S. K. (2005) Acute bronchodilator response has limited value in differentiating bronchial asthma from COPD. Journal of Asthma 42(5): 367-72	- Population not relevant to this review protocol *Participants already diagnosed with asthma/COPD*
Cockcroft, D. W., Murdock, K. Y., Berscheid, B. A. et al. (1992) Sensitivity and specificity of histamine PC20 determination in a random selection of young college students. Journal of Allergy & Clinical Immunology 89(1pt1): 23-30	- Population not relevant to this review protocol *Random sample of university students - not people presenting with respiratory symptoms*
Ghodrati, S., Hormati, A., Mousavi, N. N. et al. (2011) Comparison of FEV1 and PEF values in cough variant asthma during methacholine challenge test. Journal of Zanjan University of Medical Sciences and Health Services 19(77): 3	- Study not reported in English
Goldstein, M. F., Veza, B. A., Dunsky, E. H. et al. (2001) Comparisons of peak diurnal expiratory flow variation, postbronchodilator FEV(1) responses, and methacholine inhalation challenges in the evaluation of suspected asthma. Chest 119(4): 1001-10	- Study design not relevant to this review protocol *Not a randomised trial*
Griese, M.; Kusenbach, G.; Reinhardt, D. (1990) Histamine release test in comparison to standard tests in diagnosis of childhood allergic asthma. Annals of Allergy 65(1): 46-51	- Population not relevant to this review protocol *Participants already diagnosed with asthma*

Study	Code [Reason]
Hunter, C. J., Brightling, C. E., Woltmann, G. et al. (2002) A comparison of the validity of different diagnostic tests in adults with asthma. Chest 121(4): 1051-7	- Population not relevant to this review protocol *Participants already diagnosed with asthma*
Kim, T. B., Oh, Y. M., Chang, Y. S. et al. (2012) The reality of an intermediate type between asthma and COPD in practice. Respiratory Care 57(8): 1248-1253	- Population not relevant to this review protocol *Participants already diagnosed with asthma/COPD*
Linna, O. (1998) Sensitivity of peak expiratory flow rate for diagnosing bronchial obstruction on methacholine inhalation challenge in school-aged asthmatic children. Acta Paediatrica 87(6): 635-7	- Study design not relevant to this review protocol *Not a randomised trial*
Perpina, M., Pellicer, C., de Diego, A. et al. (1993) Diagnostic value of the bronchial provocation test with methacholine in asthma. A Bayesian analysis approach. Chest 104(1): 149-54	- Population not relevant to this review protocol *Participants already diagnosed with respiratory illness*
Quadrelli, S. A.; Roncoroni, A. J.; Montiel, G. C. (1999) Evaluation of bronchodilator response in patients with airway obstruction. Respiratory Medicine 93(9): 630-6	- Population not relevant to this review protocol *Participants already diagnosed with asthma/COPD*

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.