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 reviews for diagnostic test accuracy of spirometry in people suspected of asthma

BTS/NICE/SIGN collaborative guideline <number>

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1. Spirometry

1.1 Review question

In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of spirometry in diagnosing asthma?

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. Spirometry is a measure of lung function. The procedure involves blowing under maximal effort into an instrument (spirometer), the majority of which nowadays provide calculated measurements of air flows and volumes. These measurements can then be used to quantify airflow obstruction (usually due to narrowing of the airways, as seen typically in uncontrolled asthma) and restriction (not typically seen in asthma, but in other lung disease such as pulmonary fibrosis). Spirometry is therefore potentially useful in establishing a diagnosis of asthma and this evidence review was carried out to determine its clinical and cost-effectiveness as a diagnostic test.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

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

Table 1: PICO characteristics of diagnostic accuracy review question

Population	People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: • Children and young people (5-16 years old) • Adults (≥17 years old) Exclusion: Children under 5 years old People on steroid inhalers (washout period minimum of 4 weeks for inclusion)
Target condition	Asthma
Index test	Spirometry measures (report separately) 1. Airflow obstruction, defined as either: a. FEV1/FVC ratio (<70%) b. FEV1/FVC ratio < lower limit of normal (LLN) Secondary outcome (if no data for above): in children only: 2. Reduced FEV1, defined as either: a. < 80% predicted b. < LLN
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (e.g. more than 20% variability as indication of a positive test)

	• bronchodilator reversibility (e.g. an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test) • bronchial hyper-responsiveness (e.g. 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. Maximum time between index test and reference standard: 12 months
Statistical measures	Diagnostic accuracy outcomes: • Sensitivity thresholds: upper 90, lower 10 • Specificity thresholds: upper 80, lower 50 • Raw data to calculate 2x2 tables to calculate sensitivity and specificity • Negative predictive value (NPV), Positive predictive value (PPV)
Study design	• Cross-sectional studies • Cohort studies

1.1.3 Methods and process

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

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

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

Six cross-sectional diagnostic studies were included in the review; (Bai, et al., 2023, Bao, et al., 2021, Eom, et al., 2020, Louis, et al., 2023, Nekoee, et al., 2020, Smith, et al., 2004) this is summarised in Table 2 below. Evidence from these studies is summarised below in Table 4 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 for sensitivity as 0.10, below which a test would be of no clinical use, and 0.90, above which a test would be recommended. For specificity these thresholds were set as 0.50, below which a test would be of no clinical use, and 0.80, above which a test would be recommended.

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

Five studies from the previous NICE guidance on this topic were excluded from the current review. Two of these studies were excluded due to not containing a relevant index test (FEV_1

only, not FEV_1/FVC in an adult population), one due to using an inappropriate study design (index test and reference standard 18 months apart), one due to containing a population that was not relevant to the current review protocol (inhaled corticosteroid washout period 12 hours) and one not containing a reference standard that was relevant to the current review protocol (objective test without clinician diagnosis in a population with an unclear pre-test probability of asthma).

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
Bai 2023 (Bai et al., 2023)	Adults with chronic cough (>8 weeks) attending a Pulmonary and Critical Care Department with an FEV1 >80% of predicted N=283 Mean age (SD): CVA; 47.8 (15.9), nCVA; 44.6 (15.2) years China	Cough variant asthma vs non-asthma chronic cough	FEV1/FVC Cut-off: 78.79% of predicted	Asthma as per Chinese diagnosis guidelines: chronic cough, often with significant night cough, positive bronchial provocation test and positive response to anti-asthma treatment	Prospective cross-sectional study Strata: Adults ICS use: none within a month Smoking status: non-smokers Indirectness: downgraded by one increment due to index test (LLN not used as cut-off) indirectness
Bao 2021 (Bao et al., 2021)	Adults with an FEV1 >80%, normal CT scan results and recurrent variable symptoms of dyspnoea, cough, wheeze or chest tightness for >8 weeks referred to a pulmonary outpatient clinic N= 692 Mean age (SD): positive MCT; 43.90 (12.56), negative MCT: 43.80 (14.90)	Airway hyperresponsiveness to methacholine	FEV1/FVC Cut-off: 84.67% of predicted	Airway hyperresponsiveness was diagnosed using methacholine challenge testing	Retrospective cross-sectional study Strata: adults ICS use: none within a month Smoking status: non-smokers Indirectness: downgraded by two increments due to index test (LLN not used as cut-off) and reference standard (unclear clinician decision in

Study	Population	Target condition	Index test	Reference standard	Comments
	China				diagnosis) indirectness
Eom 2020 (Eom et al., 2020)	Consecutive patients referred to an outpatient clinic for the diagnosis of asthma. Inclusion criteria: 8-16 years old with respiratory symptoms for at least 1-month. Exclusion criteria: symptoms of respiratory tract infection or other systemic or inflammatory disease, receiving inhaled short-acting β-2-agonists within 8 hours or receiving regular controller medication within a month N= 275; mean age (range): 11.5 (10.7-12.3) years South Korea	Asthma	Lung function assessed using ATS/ERS recommendations. %pred. FEV_1, FEF25-75 and FEV_1/FVC reported. Cut-offs: %pred. FEV_1: 88.4% FEV_1/FVC: 85.3%	Assessed by a paediatric pulmonologist after ≥6 months of follow-up. Asthma was diagnosed according to the Global Initiative for Asthma guidelines (symptoms and exacerbations) Spirometry was used to determine presence of variable expiratory airflow limitation, which was confirmed by increase in FEV1 of more than 12% in response to a rapid-acting bronchodilator at any time during the follow-up period, increase in FEV1 of more than 12% from baseline after 4 weeks of anti-inflammatory treatment, and/or variation in FEV1 of more than 12% between visits	Prospective cross-sectional study Strata: Children and young people ICS use: 1-month washout Smoking status: 45.2% and 40.6% exposed to cigarette smoking in non-asthma and asthma groups, respectively Indirectness: FEV_1/FVC downgraded by one increment due to index test (LLN not used as cut-off) indirectness
Louis 2023 (Louis et al., 2023)	Adults seeking medical attention at an asthma clinic, in whom asthma was suspected	Asthma	FEV_1/FVC ratio Cut-off: 75 and 78%	Asthma was diagnosed as per GINA guidelines, combining symptoms with	Prospective cross-sectional study Strata: Age: Adults

Study	Population	Target condition	Index test	Reference standard	Comments
	N= 303; mean age; 51 (16) years Belgium			bronchodilator reversibility and/or methacholine bronchial challenge tests	Smoking status: Mixed ICS use: Treatment naïve Indirectness: Downgraded by one increment due to index test (cut-offs other than 70% or LLN used) indirectness
Nekoee 2020 (Nekoee et al., 2020)	Database record of patients who had been referred to an asthma clinic with respiratory symptoms suggestive of asthma by two respiratory physicians N= 702; mean age: 51 years Location not reported	Asthma	FEV_1/FVC Cut-off: 76%	Asthma was diagnosed by a positive result with a bronchodilator test (≥12% and 200 mL) or methacholine challenge test (≥20% fall in FEV_1 with ⩽8 $mg \cdot mL^{-1}$)	Retrospective cross-sectional study Strata: Adults ICS use: Treatment naïve Smoking status: Mixed (57% never, 24% ex, 19% current Indirectness: Downgraded by two increments due to index test (LLN or 70% not used as cut-offs) and reference standard (unclear clinician involvement in diagnosis) 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 UK	Asthma	FEV_1/FVC Cut-offs: <70%, <75%, <LLN, <70% or LLN, <LLN with reduced FEV_1	Diagnosis by an expert panel, including at least three asthma clinicians with access to history, physical examination, ACQ, and all test results before and after ICS	Prospective cross-sectional study Strata: Adults ICS use: 4-week washout Smoking status: Mixed (40 (35%) current or ex-smokers)

Study	Population	Target condition	Index test	Reference standard	Comments
					Indirectness: Downgraded by one increment due to index test (for thresholds that were not LLN or 70%) indirectness
Smith 2004 (Smith et al., 2004)	Consecutive patients aged 8–75 years referred by their family practitioner for asthma diagnosis. Inclusion criteria: people having respiratory symptoms in the preceding 4 weeks. Exclusion criteria: used oral or inhaled corticosteroid in the preceding 4 weeks or had a typical respiratory tract infection in the previous 6 weeks N= 47; mean age (range): 35.3 (9-72) years New Zealand	Asthma	For FEV_1 the cut point used to define "abnormal" was 80%. For the FEV_1/FVC ratio two cut points were used: 80 and 70%.	Relevant symptom history (present in all patients), using American Thoracic Society criteria, and a positive test for BHR and/or a positive response to hypertonic saline. Cut-off Provocative dose of hypertonic saline resulting in a 15% fall in FEV_1 of less than 20 ml and increase in FEV_1 of ≥12% after receiving albuterol	Prospective cross-sectional study Strata: Adults ICS use: 4-week washout Smoking status: Mixed Indirectness: Downgraded by two increments due index test (LLN not used as cut-off) and population (mixed children and adolescents/young people) indirectness

1 See Appendix D for full evidence tables.

2 **1.1.6 Summary of the diagnostic evidence**

3 The assessment of the evidence quality was conducted with emphasis on test sensitivity and
4 specificity as this was identified by the committee as the primary measure in guiding
5 decision-making. The committee set clinical decision thresholds as sensitivity upper =0.90
6 and lower= 0.10 and specificity upper= 0.80 and lower= 0.50. Above these thresholds a test
7 could be recommended, and below the lower a test would be deemed of no clinical use. No
8 pooling was possible due to fewer than three studies reporting the same diagnostic
9 threshold.

Table 3: Clinical evidence summary: diagnostic test accuracy for spirometry in adults

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
FEV1/FVC ratio (cut-off: 70%) vs clinician diagnosis with hypertonic saline provocation test							
1 cross-sectional study	47	Serious[1]	Not serious	Very serious[2]	Not serious	Sensitivity: 0.35 (0.14-0.62)	VERY LOW
		Serious[1]	Not serious	Very serious[2]	Not serious	Specificity: 1.00 (0.88-1.00)	VERY LOW
FEV_1/FVC ratio (cut-off: <70%) vs expert panel diagnosis with multiple diagnostic tests							
1 cross-sectional study	118	Very serious[3]	Not serious	Not serious	Not serious	Sensitivity: 0.30 (0.20-0.42)	LOW
		Very serious[3]	Not serious	Not serious	Not serious	Specificity: 0.96 (0.86-0.99)	LOW
FEV1/FVC ratio (cut-off: 75%) vs clinician diagnosis with bronchodilator reversibility and/or methacholine bronchial challenge test							
1 cross-sectional study	303	Very serious[3]	Not serious	Serious[4]	Not serious	Sensitivity= 0.39 (0.32-0.47)	VERY LOW
		Very serious[3]	Not serious	Serious[4]	Serious[5]	Specificity= 0.83 (0.75-0.89)	VERY LOW
FEV_1/FVC ratio (cut-off: <75%) vs expert panel diagnosis with multiple diagnostic tests							
1 cross-sectional study	118	Very serious[3]	Not serious	Serious[4]	Not serious	Sensitivity: 0.49 (0.36-0.61)	VERY LOW
		Very serious[3]	Not serious	Serious[4]	Serious[5]	Specificity: 0.90 (0.77-0.97)	VERY LOW
FEV1/FVC (cut-off: 76%) vs diagnosis with bronchodilator reversibility or methacholine bronchial challenge tests							
1 cross-sectional study	702	Very serious[6]	Not serious	Very serious[7]	Not serious	Sensitivity: 0.51 (0.46-0.56)	VERY LOW
		Very serious[6]	Not serious	Very serious[7]	Not serious	Specificity: 0.76 (0.71-0.80)	VERY LOW
FEV1/FVC ratio (cut-off: 78%) vs clinician diagnosis with bronchodilator reversibility and/or methacholine bronchial challenge test							
1 cross-sectional study	303	Very serious[8]	Not serious	Serious[4]	Not serious	Sensitivity= 0.54 (0.44-0.64)	VERY LOW
		Very serious[8]	Not serious	Serious[4]	Serious	Specificity= 0.79 (0.66-0.88)	VERY LOW
FEV1/FVC (cut-off: 78.79%) vs clinician diagnosis and histamine bronchial provocation test							
1 cross-sectional study	283	Very serious[9]	Not serious	Serious[4]	Not serious	Sensitivity: 0.52 (0.40-0.64)	VERY LOW
		Very serious[9]	Not serious	Serious[4]	Not serious	Specificity: 0.83 (0.77-0.87)	VERY LOW
FEV1/FVC ratio (cut-off: 80%) vs clinician diagnosis with hypertonic saline provocation test							
1 cross-sectional study	47	Serious[1]	Not serious	Very serious[2]	Not serious	Sensitivity: 0.47 (0.23-0.72)	VERY LOW
		Serious[1]	Not serious	Very serious[2]	Serious[5]	Specificity: 0.80 (0.61-0.92)	VERY LOW
FEV1/FVC (cut-off: 84.76%) vs diagnosis with methacholine bronchial challenge test							
1 cross-sectional study	692	Very serious[8]	Not serious	Very serious[7]	Not serious	Sensitivity: 0.66 (0.59-0.74)	VERY LOW
		Very serious[8]	Not serious	Very serious[7]	Not serious	Specificity: 0.68 (0.63-0.72)	VERY LOW
FEV_1/FVC ratio (cut-off: <LLN) vs expert panel diagnosis with multiple diagnostic tests							

1 cross-sectional study	118	Very serious[3]	Not serious	Not serious	Not serious	Sensitivity: 0.37 (0.26-0.50)	LOW
		Very serious[3]	Not serious	Not serious	Not serious	Specificity: 0.96 (0.86-0.99)	LOW
FEV_1/FVC ratio (cut-off: <70% or LLN) vs expert panel diagnosis with multiple diagnostic tests							
1 cross-sectional study	118	Very serious[3]	Not serious	Not serious	Not serious	Sensitivity: 0.39 (0.27-0.51)	LOW
		Very serious[3]	Not serious	Not serious	Not serious	Specificity: 0.96 (0.86-0.99)	LOW
FEV_1/FVC ratio (cut-off: <LLN with reduced FEV_1) vs expert panel diagnosis with multiple diagnostic tests							
1 cross-sectional study	118	Very serious[3]	Not serious	Not serious	Not serious	Sensitivity: 0.47 (0.35-0.59)	LOW
		Very serious[3]	Not serious	Not serious	Not serious	Specificity: 0.94 (0.83-0.99)	LOW

1. *Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded)*
2. *Downgraded by one increment due to index test (paper did not report standard spirometry was performed to and/or 70% or LLN not used as cut-off) and population (mixed age group: children and young people and adults) indirectness*
3. *Downgraded by two increments due to concerns arising from the method of participant selection (method not reported) and interpretation of the index test and reference standard (unclear if blinded/unblinded)*
4. *Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high specificity' (80%)*
5. *Downgraded by two increments due to concerns arising from patient selection (method of selection not reported), unclear interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of participants through the study (not all participants were diagnosed with the same reference standard)*
6. *Downgraded by two increments due to index test (paper did not report standard spirometry was performed to and lower limit of normal not used as cut-off) and reference standard (unclear if clinician decision was involved in diagnosis) indirectness*
7. *Downgraded by two increments due to concerns arising from the method of participant selection (method not reported), interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of participants through the study (data only reported for training cohort (n=166), not including validation cohort)*
8. *Downgraded by two increments due to concerns arising from selection bias (recruitment method not reported) and interpretation of the index test and reference standard (unclear if blinded)*

Table 4: Clinical evidence summary: diagnostic test accuracy for spirometry in children and young people

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
% Predicted FEV1 (cut-off: 88.4%) vs clinician diagnosis with bronchodilator reversibility							
1 cross-sectional study	275	Not serious	Not serious	Serious[1]	Not serious	Sensitivity: 0.68 (0.61-0.75)	MODERATE
		Not serious	Not serious	Serious[1]	Serious[2]	Specificity: 0.76 (0.66-0.85)	LOW
FEV1/FVC ratio (cut-off: 85.3%) vs clinician diagnosis with bronchodilator reversibility							
1 cross-sectional study	275	Not serious	Not serious	Serious[2]	Not serious	Sensitivity: 0.73 (0.66-0.79)	MODERATE
		Not serious	Not serious	Serious[2]	Not serious	Specificity: 0.65 (0.54-0.76)	MODERATE

1. *Downgraded by one increment due to indirectness of the index test (protocol-specified cut-off not used)*
2. *Downgraded by one increment due to the confidence interval overlapping the upper threshold for 'high specificity' (80%)*

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

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

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

1.1.8 Summary of included economic evidence

None

1.1.9 Economic model

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

1.1.10 Unit costs

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

Table 5: Spirometry per-test cost

Resource	Quantity	Unit costs	Total cost	Source
MicroLab with integral printer and spirometry PC software	1/2100 [(a)]	£1,174.13 per spirometer	£0.62	NHS Supply Chain Catalogue(NHS Supply Chain Catalogue., 2022)
Calibration syringe 3 litre	1/2100 [(a)]	£231.69 per syringe	£0.12	NHS Supply Chain Catalogue(NHS Supply Chain Catalogue., 2022)
Bacterial filter plus mouthpiece	1	£1.06 per filter and mouthpiece	£1.06	NHS Supply Chain Catalogue(NHS Supply Chain Catalogue., 2022)
Time of practice nurse	20 minutes	£63.38 per hour	£21.13	PSSRU 2022(Jones, et al.)
Total cost			£22.93	

Note: all prices are VAT-exclusive

a) Assuming that the equipment would last for 7 years and used on average 2100 times during that period(MicroDirect, 2019). Annuatisation was undertaken assuming a rate of 3.5%.

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

Test and treat

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

Diagnostic accuracy

The committee considered the diagnostic measures of sensitivity and specificity of the index test for diagnosing asthma as well as the positive and negative predictive values where these were reported by the studies. Equal emphasis was placed upon both sensitivity and specificity. Clinical decision thresholds were set by the committee as sensitivity/specificity 0.9 and 0.8 above which a test could 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 from spirometry readings with sufficiently high sensitivity and specificity to be useful in making a diagnosis of asthma, but also in whether there are 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 spirometry measures with physician diagnosis of asthma based on symptoms plus an objective test from any of the following: peak flow variability (e.g. more than 20% variability as indication of a positive test), bronchodilator reversibility (e.g. an improvement in FEV1 of more than or equal to 12% plus an increase in volume of more than or equal to 200mls as indication of a positive test), bronchial hyper-responsiveness (e.g. histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) or FeNO.

Diagnostic accuracy studies

Seven prospective cross-sectional studies were included in the diagnostic accuracy evidence for spirometry. One study was in children and young people and six studies were conducted in adults. The study conducted in children and young people reported two spirometric measures, FEV_1, with positivity determined as 88.4% of predicted, and FEV_1/FVC ratio with positivity determined as 85.3%. The evidence in adults was all for FEV_1/FVC ratio, with cut-off values ranging from 70% to 84.76%.

The quality of the evidence for children and young people ranged from moderate to low as a result of downgrading due to index test indirectness, namely due to using cut-offs (chosen based on optimal threshold) that were different to the protocol-specified cut-offs. Additionally, some imprecision was seen in the specificity estimates for FEV_1 as a percentage of predicted values.

The quality of the evidence for the adult population was all very low quality. All evidence was downgraded by at least one increment due to risk of bias, most frequently due to concerns arising from the method of participant selection and a lack of clarity over blinding of assessors. Additionally, all evidence was downgraded by at least one increment due to indirectness. This was mostly due to reporting thresholds different to those specified in the review protocol, not reporting the standards the spirometry was performed to, or lacking clarity over the involvement of a clinician decision in the final asthma diagnosis.

1.2.3 Benefits and harms

Diagnostic accuracy review:

Children and young people

Clinical evidence for the diagnostic accuracy of FEV_1 in children and young people using a cut-off of 88.4% predicted to detect asthma showed a moderate sensitivity (0.68) and specificity (0.76) although there was some imprecision in the effect for specificity with the upper limit of the confidence interval crossing the higher threshold set for specificity. In the same population, FEV_1/FVC ratio with a cut-off of 85.3% also showed a moderate sensitivity (0.73) and specificity (0.65) for asthma. The committee noted that the cut-off for FEV_1 was not the same as the widely accepted cut-off value for defining airflow obstruction as specified in the review protocol (<70%). However, although widely used, the figure of <70% is known to be an oversimplification, and preference now is to use standardised residual values if these are available. This approach would set a higher cut-off value as the definition of airflow obstruction in children.

Adults

Low to very low-quality evidence from two studies reported FEV_1/FVC ratio with a cut-off of 70% in adults, showing low sensitivities ranging from 0.30-0.35 and very high specificities ranging from 0.95-1.00. Evidence was downgraded by at least one increment due to risk of bias arising from concerns surrounding the method of participant selection and/or a lack of clarity over the blinding of assessors. Evidence from one study was downgraded by two increments due to indirectness arising from not reporting the standard spirometry was conducted to and including a mixed population of adults and children and young people.

Very low-quality evidence from two studies reported FEV_1/FVC ratio with a cut-off of 75% in adults, showing low-moderate sensitivities ranging from 0.39-0.49 and high specificities ranging from 0.83-0.90. Evidence from both studies was downgraded by two increments due to risk of bias arising from concerns surrounding the method of participant selection and a lack of clarity over the blinding of assessors. Furthermore, all evidence was downgraded by one increment due to using a cut-off that was different to those specified in the present review protocol (70% or LLN). One of these studies also reported the diagnostic accuracy of FEV_1/FVC ratio with a cut-off of 78%, showing a moderate sensitivity of 0.54 and a moderate specificity of 0.79. This evidence was also of very low quality due to the aforementioned reasons.

A separate study reported FEV_1/FVC ratio with a cut-off of 76% in adults, showing a moderate sensitivity of 0.51 and a moderate specificity of 0.76, albeit with very low certainty. This evidence was limited due to very serious risk of bias arising from an unclear method of recruitment, unclear blinding, and not all participants having the same reference standard due to some receiving a bronchodilator reversibility test, whilst others were diagnosed with a methacholine challenge test. Furthermore, this study was downgraded due to indirectness as a result of not reporting the protocol used for the spirometry measurements and because it was not clear whether the reference standard involved a clinician decision.

Very low-quality evidence from one study reported FEV_1/FVC ratio with a cut-off of 80%, showing a moderate sensitivity of 0.47 and a high specificity of 0.80. Whilst this evidence suggests that this is a valuable test for ruling asthma in, the committee were aware that the data was not without limitations, largely due to the small sample of 47 participants. Additionally, serious risk of bias arose due to a lack of blinding, and indirectness was present due to incomplete reporting of the protocol used for the spirometry measurements and the inclusion of a mixture of children/young people and adults.

Very low-quality evidence from one study reported FEV_1/FVC ratio with a cut-off of 78.79% in adults, showing a moderate sensitivity of 0.52 and a high specificity of 0.83. This evidence was limited due to risk of bias arising from an unclear method of recruitment and unclear blinding, in addition to indirectness due to using a cut-off that was different to that specified in this review protocol (<70% or <LLN).

Very low-quality evidence from one study reported FEV_1/FVC ratio with a cut-off of 84.76% in adults, showing a moderate sensitivity of 0.66 and a moderate specificity of 0.68. This evidence was limited due to risk of bias arising from an unclear recruitment method and unclear blinding, as well as indirectness due to not reporting the protocol used for the spirometry measurements and using a cut-off that was different to that specified in this review protocol (<70% or <LLN).

Low quality evidence from a single study reported the diagnostic accuracy of FEV_1/FVC ratio using three different cut-offs that included LLN. Using LLN as a single cut-off resulted in a moderate sensitivity of 0.37 and a very high specificity of 0.96. Including 70% as an alternative to LLN increased sensitivity to 0.39 whilst maintaining specificity at 0.96. Using a different approach, with LLN as the cut-off in combination with reduced FEV_1, resulted in a moderate sensitivity of 0.47 and a very high specificity of 0.94. All of this evidence was at very high risk of bias due to a lack of clarity surrounding the participant selection method, and a lack of blinding of the index test and reference standard. Nonetheless, all three of these cut-offs met the clinical decision making threshold for specificity, suggesting that these are suitable thresholds for ruling asthma in, but with poor sensitivity suggesting they are not suitable for ruling a diagnosis out.

Overall, the committee agreed the evidence was poor both in terms of quality and quantity with little data in adults meeting the review protocol. However, the conclusions of the included evidence are in keeping with the committee's clinical experience in showing high specificity but low sensitivity of spirometry as a test for asthma. This is predictable since asthma is a disease of variable airflow obstruction, and because of that variability many people with asthma will have normal spirometry at the time the test is performed. The committee noted that in clinical practice spirometry readings are not taken in isolation but in combination with other diagnostic tests in order to diagnose asthma. The committee therefore recommended against using spirometry as a standalone test for asthma but emphasised the importance of spirometry in assessing other causes of breathlessness which must be distinguished from asthma, in particular COPD which is a common alternate cause of breathlessness in adults.

Although some evidence of moderate quality was available for children, the committee did not feel able to recommend the routine use of spirometry as a standalone test. A factor in this was due to the difficulty many children have in performing spirometry, especially at younger ages. Furthermore, many staff in general practice are not trained in paediatric spirometry. Given the aforementioned difficulties of conducting spirometry in paediatric populations, testing would require that children are referred to secondary care (until such times as diagnostic hubs are widely available). Despite the practical arguments presented against spirometry for children and young people, the committee did not wish to recommend against the use of spirometry. The committee agreed that spirometry may have a role when children are referred to secondary care, particularly in older children.

1.2.4 Cost effectiveness and resource use

No relevant published health economic analyses were identified for this review question. The unit cost of spirometry was presented to aid committee consideration of cost effectiveness. The unit cost of undertaking a spirometry for diagnostic purposes was £22.93 and included the health care professional time for conducting the test and interpreting the result (£21.13) and the equipment and consumables required for the spirometry (£1.80).

With regards to staff time, the committee agreed that the test could be undertaken and interpreted by a general practice nurse (band 5) trained and accredited in spirometry testing. There was discussion that in some settings the spirometry could be conducted and interpreted by a health care assistant (band 3 or 4) who is fully trained and accredited to do so, but the committee agreed this is less common. The committee discussed the time required for the practice nurse to undertake the test and interpret the results and noted that this can be variable depending on the person's age and ability as well as the health care professional's experience in conducting the test. The committee agreed that on average 20 minutes was appropriate. The training and accreditation required for conducting this test can take considerable time, the training course is 6 months and re-accreditation is required every 3 years. The unit cost for a practice nurse used in the costing does include pre-registration qualifications but does not necessarily include this training.

In terms of equipment and consumables, the per test cost of the spirometer and calibration syringe were calculated by assuming that the equipment would last for 7 years and used on average 2100 times during that period (this assumes 300 tests conducted a year). Annuitisation was undertaken assuming a rate of 3.5%. In addition to these capital costs, the unit cost of a mouthpiece (including a bacterial filter) and thermal printer paper were included.

The committee considered spirometry 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). Spirometry with bronchodilator reversibility was found to be a cost-effective test to be included in the diagnostic algorithm for adults and recommended in both adults and children (see evidence review 1.2).

1.2.5 Other factors the committee took into account

The role of spirometry in diagnosing asthma cannot be divorced from its role in assessing people with symptoms which are suggestive of asthma but also compatible with other diagnoses. This is particularly important in adults in relation to COPD, which is excluded by normal spirometry.

In children, as noted above, there are practical problems in obtaining diagnostic spirometry in primary care because the majority of practices do not have staff members trained in paediatric spirometry.

1.2.6 Recommendations supported by this evidence review

No recommendations were made from this evidence review.

1.3 References

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Appendices

Appendix A – Review protocols

Diagnostic test accuracy of spirometry

Review protocol for diagnostic test accuracy and clinical and cost-effectiveness of spirometry in diagnosing asthma

ID	Field	Content
0.	PROSPERO registration number	CRD42023435438
1.	Review title	Accuracy and clinical and cost-effectiveness of spirometry for diagnosis of asthma.
2.	Review question	In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of spirometry?
3.	Objective	To evaluate the diagnostic test accuracy of spirometry in diagnosing asthma. This evidence review will have two stages: (1) Identify the clinical and cost effectiveness of diagnosis with the test (test plus treatment) (2) If evidence on clinical effectiveness is limited, the diagnostic accuracy will instead be determined
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos

		Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Asthma
6.	Population	Inclusion: People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: • Children and young people (5-16 years old) • Adults (≥17 years old)

		Exclusion: Children under 5 years old People on steroid inhalers (washout period minimum of 4 weeks for inclusion)
7.	Test	• Spirometry measures (report separately) 9. Airflow obstruction, defined as either: a. FEV1/FVC ratio (<70%) b. FEV1/FVC ratio < lower limit of normal (LLN) Secondary outcome (if no data for above): in children only: 10. Reduced FEV1, defined as either: a. < 80% predicted b. < LLN Pre bronchodilator values (applies for all above measures) • FEV1 and FVC should be performed using the following criteria: ○ Forced expiratory volume (FEV1) - patients perform manoeuvre until 3 readings are within e.g. 5% and/ 150ml of each other (maximum 8 attempts) the measured value being the best of these 3 readings. ○ Forced vital capacity (FVC) - patients perform manoeuvre until 3 readings are within e.g. 5% and/150ml of each other (maximum 8 attempts) the measured value being the best of these 3 readings.
8.	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 (e.g. more than 20% variability as indication of a positive test); • bronchodilator reversibility (e.g. an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (e.g. histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) 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.
9.	Types of study to be included	Clinical effectiveness (test and treat): • Systematic reviews of RCTs • Parallel RCTs Published NMAs and IPDs will be considered for inclusion. Diagnostic test accuracy:

		• Cross sectional studies • Cohort studies will be included
10.	Other exclusion criteria	• Non-English language studies. • Non comparative cohort studies • Before and after studies • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. • Not looking at occupational asthma /allergens
11.	Context	Primary and secondary settings
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making a therefore have all been rated as critical: Clinical effectiveness (test and treat) outcomes: • Severe asthma exacerbations (defined as asthma exacerbations requiring oral corticosteroid use (dichotomous outcome at ≥6 months) • Mortality (dichotomous outcome at ≥6 months) • Quality of life (QOL; validated scale, including asthma specific questionnaires AQLQ; health-related) (continuous outcome at ≥3 months) • Asthma control assessed by a validated questionnaire (ACQ, ACT, St George's respiratory) (continuous outcome at ≥3 months) • Hospital admissions (dichotomous outcome at ≥6 months)

		• Reliever/rescue medication use (continuous outcome at ≥3 months)
		• Lung function (change in FEV1 or morning PEF – average over at least 7 days for morning PEF) (continuous outcome at ≥3 months). *Note: Extract FEV1 %pred over litres if both are reported. If only litres is reported, extract and analyse separately (do not extract both). For children, only use FEV1 %pred.*
		• Adverse events
		  ○ Linear growth (continuous outcome at ≥1 year),
		  ○ Pneumonia frequency (dichotomous outcome at ≥3 months)
		  ○ Adrenal insufficiency as defined by study, including short synacthen test and morning cortisol (dichotomous outcome at ≥3 months)
		  ○ Bone mineral density (continuous outcome at ≥6 months)
		• Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks)
		
		Diagnostic accuracy outcomes:
		• Sensitivity thresholds: upper 90, lower 10
		• Specificity thresholds: upper 80, lower 50
		• Raw data to calculate 2x2 tables to calculate sensitivity and specificity
		• Negative predictive value (NPV), Positive predictive value (PPV)

13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

		The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • QUADAS-2 checklist
15.	Strategy for data synthesis	Diagnostic intervention (test and treat): 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. Diagnostic accuracy: Where possible data will be meta-analysed where appropriate (if at least 3 studies reporting data at the same diagnostic threshold) in WinBUGS. Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Heterogeneity will be assessed by visual inspection of the sensitivity and specificity plots and summary area under

		the curve (AUC) plots. Particular attention will be placed on specificity determined by the committee to be the primary outcome for decision making. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.			
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Different reference standards • Micro-spirometry vs Diagnostic spirometry			
17.	Type and method of review	☒	Intervention		
		☒	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
18.	Language	English			
19.	Country	England			
20.	Anticipated or actual start date	18 June 2023			
21.	Anticipated completion date	31 July 2024			
22.	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	☐	☐
23.	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		
24.	Review team members	From the National Guideline Centre: Bernard Higgins (Guideline lead) Sharon Swain (Guideline lead) Qudsia Malik (Senior systematic reviewer) Clare Jones (Senior systematic reviewer) Toby Sands (Systematic reviewer) Alfredo Mariani (Senior health economist)		

		Lina Gulhane (Head of information specialists) Stephen Deed (Information specialist) Amy Crisp (Senior project manager)
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10186
28.	Other registration details	N/A
29.	Reference/URL for published protocol	N/A
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts

		• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Spirometry, Asthma	
32.	Details of existing review of same topic by same authors	N/A	
33.	Current review status	N/A	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	N/A	
35.	Details of final publication	www.nice.org.uk	

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1 Health economic review protocol

2 Table 6: Health economic review protocol

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

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

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Appendix B - Literature search strategies

In people under investigation for asthma, what is the diagnostic test accuracy and clinical and cost-effectiveness of spirometry in diagnosing asthma?

Clinical search literature search strategy

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

Table 7: Database parameters, filters and limits applied

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

Medline (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter/
5.	editorial/
6.	news/

7.	exp historical article/
8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	exp *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)

1 **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)

1

2 **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

1 **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))

2

1 Health economics literature search strategy

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

9 **Table 8: Database parameters, filters and limits applied**

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

1 **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

1 **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

1

2 **NHS EED and HTA (CRD) search terms**

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

3 **INAHTA search terms**

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

1

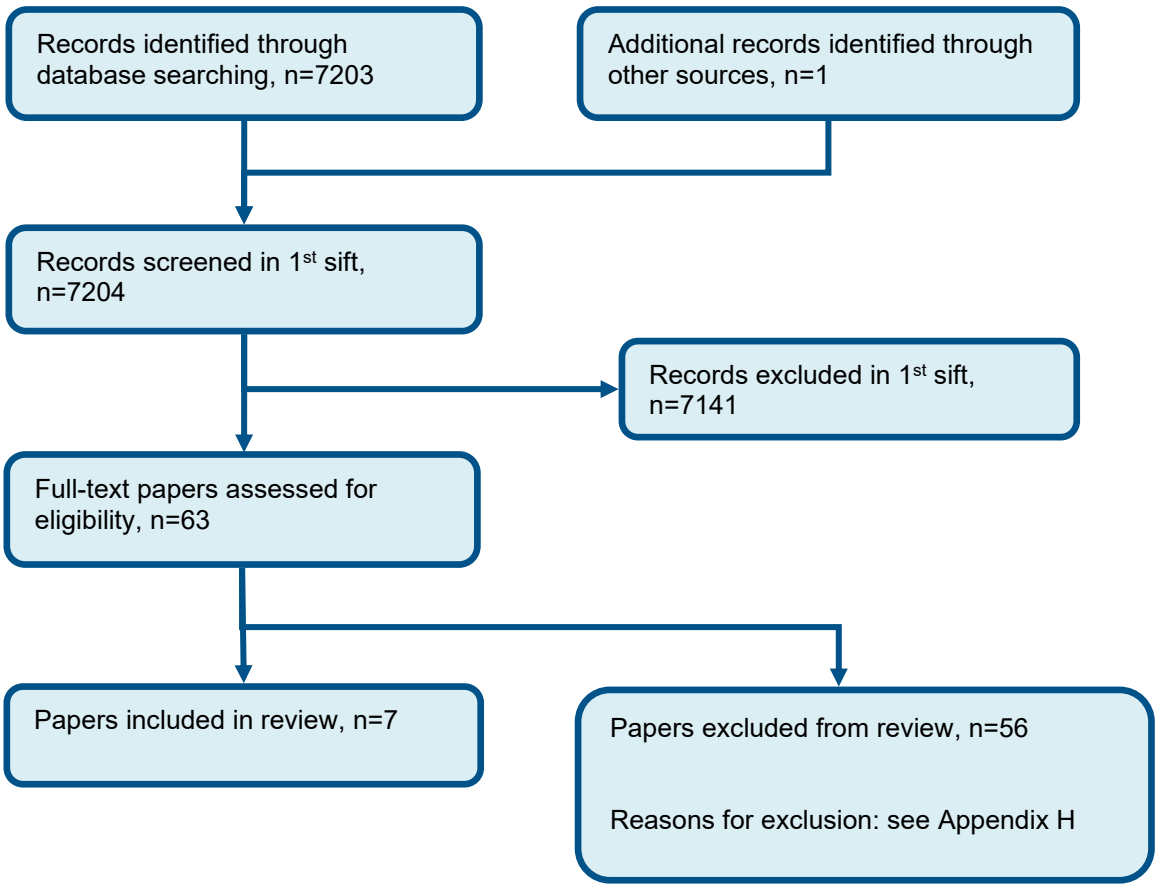
2

3

Appendix C –Evidence study selection

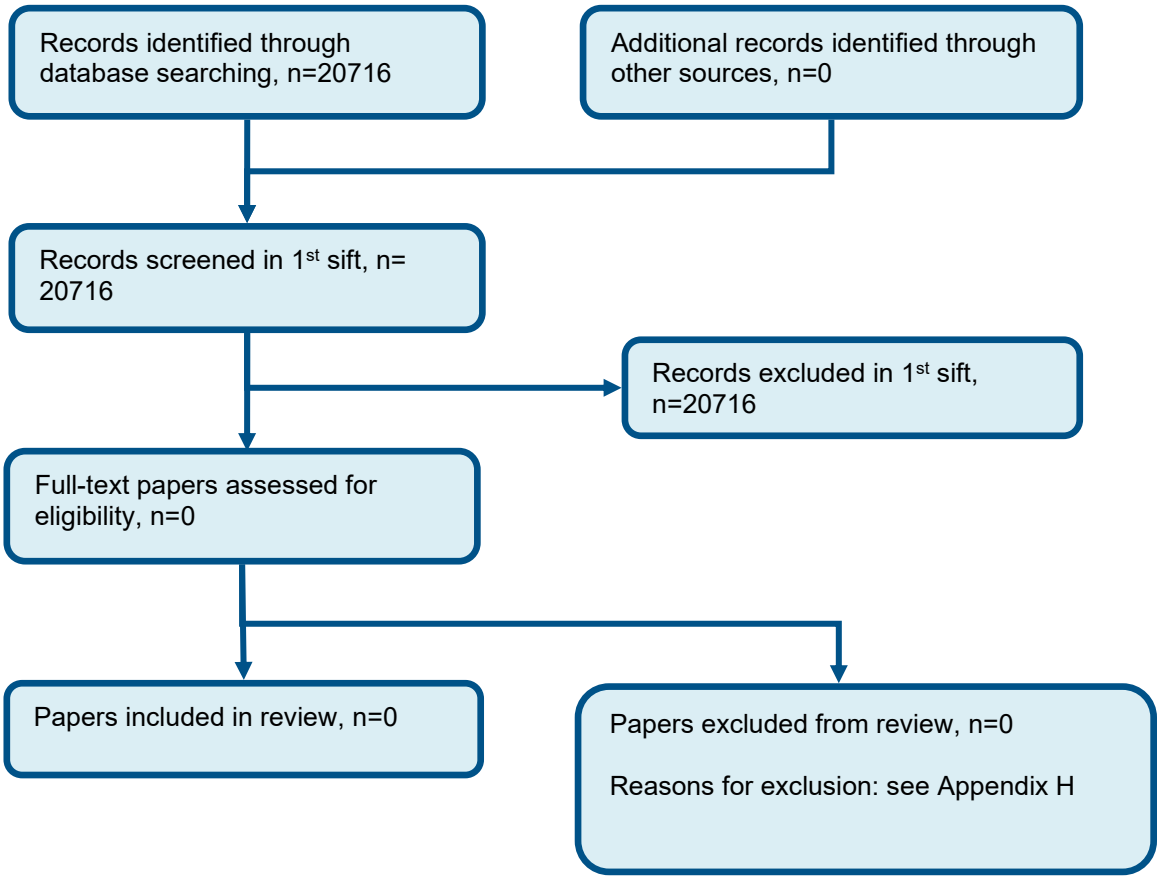
Diagnostic test accuracy of spirometry

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



Clinical and cost effectiveness of spirometry

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



1 Appendix D –Evidence tables

2 Diagnostic test accuracy of spirometry

Reference	**Bai 2023 (Bai et al., 2023)**
Study type	Cross-sectional diagnostic study
Study methodology	Data source: patients attending the Department of Pulmonary and Critical Care Medicine Recruitment: not reported
Number of patients	n = 283
Patient characteristics	Age, mean (SD): cough variant asthma (CVA); 47.8 (15.9) years, non-cough variant asthma (NCVA); 44.6 (15.2) years Gender (male to female ratio): CVA; 27:44, NCVA; 85:127 Smoking status: non-smokers ICS use: none within a month Ethnicity: not reported Setting: secondary care Country: China Inclusion criteria: >18 years of age, cough lasting at least 8 weeks, normal chest radiograph, FEV1/FVC >70% of predicted and FEV1 >80% of predicted and no corticosteroid use in the past month Exclusion criteria: current smoker or ex-smoker within 2 years, pregnant or lactating, acute upper respiratory tract infection within 8 weeks, use of corticosteroids within a month, or use of montelukast or LABAs within a week, severe cardiac insufficiency, severe liver and kidney insufficiency, mental and cognitive dysfunction, hearing and communication impairment and multiple causes of chronic cough
Target condition(s)	Cough variant asthma or non-asthma chronic cough
Index test(s) and reference standard	Index test Spirometry assessments were made with a spirometer in accordance with the specifications and performance criteria recommended in the ATS/ ERS

Reference	**Bai 2023 (Bai et al., 2023)**
Study type	Cross-sectional diagnostic study
Study methodology	Data source: patients attending the Department of Pulmonary and Critical Care Medicine Recruitment: not reported
Number of patients	n = 283
Patient characteristics	Age, mean (SD): cough variant asthma (CVA); 47.8 (15.9) years, non-cough variant asthma (NCVA); 44.6 (15.2) years Gender (male to female ratio): CVA; 27:44, NCVA; 85:127 Smoking status: non-smokers ICS use: none within a month Ethnicity: not reported Setting: secondary care Country: China Inclusion criteria: >18 years of age, cough lasting at least 8 weeks, normal chest radiograph, FEV1/FVC >70% of predicted and FEV1 >80% of predicted and no corticosteroid use in the past month Exclusion criteria: current smoker or ex-smoker within 2 years, pregnant or lactating, acute upper respiratory tract infection within 8 weeks, use of corticosteroids within a month, or use of montelukast or LABAs within a week, severe cardiac insufficiency, severe liver and kidney insufficiency, mental and cognitive dysfunction, hearing and communication impairment and multiple causes of chronic cough
Target condition(s)	Cough variant asthma or non-asthma chronic cough
	Cut-off: FEV_1/FVC: 78.79% (optimal threshold)

Reference	**Bai 2023 (Bai et al., 2023)**
Study type	Cross-sectional diagnostic study
Study methodology	Data source: patients attending the Department of Pulmonary and Critical Care Medicine Recruitment: not reported
Number of patients	n = 283
Patient characteristics	Age, mean (SD): cough variant asthma (CVA); 47.8 (15.9) years, non-cough variant asthma (NCVA); 44.6 (15.2) years Gender (male to female ratio): CVA; 27:44, NCVA; 85:127 Smoking status: non-smokers ICS use: none within a month Ethnicity: not reported Setting: secondary care Country: China Inclusion criteria: >18 years of age, cough lasting at least 8 weeks, normal chest radiograph, FEV1/FVC >70% of predicted and FEV1 >80% of predicted and no corticosteroid use in the past month Exclusion criteria: current smoker or ex-smoker within 2 years, pregnant or lactating, acute upper respiratory tract infection within 8 weeks, use of corticosteroids within a month, or use of montelukast or LABAs within a week, severe cardiac insufficiency, severe liver and kidney insufficiency, mental and cognitive dysfunction, hearing and communication impairment and multiple causes of chronic cough
Target condition(s)	Cough variant asthma or non-asthma chronic cough
	Reference standard Diagnosis of cough variant asthma in accordance with Chinese national guidelines: chronic cough, often with significant night cough, positive bronchial provocation test and positive response to anti-asthma treatment

Reference	**Bai 2023 (Bai et al., 2023)**
Study type	Cross-sectional diagnostic study
Study methodology	Data source: patients attending the Department of Pulmonary and Critical Care Medicine Recruitment: not reported
Number of patients	n = 283
Patient characteristics	Age, mean (SD): cough variant asthma (CVA); 47.8 (15.9) years, non-cough variant asthma (NCVA); 44.6 (15.2) years Gender (male to female ratio): CVA; 27:44, NCVA; 85:127 Smoking status: non-smokers ICS use: none within a month Ethnicity: not reported Setting: secondary care Country: China Inclusion criteria: >18 years of age, cough lasting at least 8 weeks, normal chest radiograph, FEV1/FVC >70% of predicted and FEV1 >80% of predicted and no corticosteroid use in the past month Exclusion criteria: current smoker or ex-smoker within 2 years, pregnant or lactating, acute upper respiratory tract infection within 8 weeks, use of corticosteroids within a month, or use of montelukast or LABAs within a week, severe cardiac insufficiency, severe liver and kidney insufficiency, mental and cognitive dysfunction, hearing and communication impairment and multiple causes of chronic cough
Target condition(s)	Cough variant asthma or non-asthma chronic cough
	Bronchial provocation test

Reference	**Bai 2023 (Bai et al., 2023)**
Study type	Cross-sectional diagnostic study
Study methodology	Data source: patients attending the Department of Pulmonary and Critical Care Medicine Recruitment: not reported
Number of patients	n = 283
Patient characteristics	Age, mean (SD): cough variant asthma (CVA); 47.8 (15.9) years, non-cough variant asthma (NCVA); 44.6 (15.2) years Gender (male to female ratio): CVA; 27:44, NCVA; 85:127 Smoking status: non-smokers ICS use: none within a month Ethnicity: not reported Setting: secondary care Country: China Inclusion criteria: >18 years of age, cough lasting at least 8 weeks, normal chest radiograph, FEV1/FVC >70% of predicted and FEV1 >80% of predicted and no corticosteroid use in the past month Exclusion criteria: current smoker or ex-smoker within 2 years, pregnant or lactating, acute upper respiratory tract infection within 8 weeks, use of corticosteroids within a month, or use of montelukast or LABAs within a week, severe cardiac insufficiency, severe liver and kidney insufficiency, mental and cognitive dysfunction, hearing and communication impairment and multiple causes of chronic cough
Target condition(s)	Cough variant asthma or non-asthma chronic cough
	Histamine bronchial provocation tests were performed with the Jaeger APS Pro system by using a Medic-Aid sidestream nebulizer, following the recommendations of the ATS/ERS. Provocative dose causing a 20% fall in FEV1 was recorded, and bronchial hyperresponsiveness was defined as present if PD20-FEV1 <7.8 μmol.

Reference	**Bai 2023 (Bai et al., 2023)**
Study type	Cross-sectional diagnostic study
Study methodology	Data source: patients attending the Department of Pulmonary and Critical Care Medicine Recruitment: not reported
Number of patients	n = 283
Patient characteristics	Age, mean (SD): cough variant asthma (CVA); 47.8 (15.9) years, non-cough variant asthma (NCVA); 44.6 (15.2) years Gender (male to female ratio): CVA; 27:44, NCVA; 85:127 Smoking status: non-smokers ICS use: none within a month Ethnicity: not reported Setting: secondary care Country: China Inclusion criteria: >18 years of age, cough lasting at least 8 weeks, normal chest radiograph, FEV1/FVC >70% of predicted and FEV1 >80% of predicted and no corticosteroid use in the past month Exclusion criteria: current smoker or ex-smoker within 2 years, pregnant or lactating, acute upper respiratory tract infection within 8 weeks, use of corticosteroids within a month, or use of montelukast or LABAs within a week, severe cardiac insufficiency, severe liver and kidney insufficiency, mental and cognitive dysfunction, hearing and communication impairment and multiple causes of chronic cough
Target condition(s)	Cough variant asthma or non-asthma chronic cough
	Time between measurement of index test and reference standard: Not reported

Reference	**Bai 2023 (Bai et al., 2023)**				
Study type	Cross-sectional diagnostic study				
Study methodology	Data source: patients attending the Department of Pulmonary and Critical Care Medicine Recruitment: not reported				
Number of patients	n = 283				
Patient characteristics	Age, mean (SD): cough variant asthma (CVA); 47.8 (15.9) years, non-cough variant asthma (NCVA); 44.6 (15.2) years Gender (male to female ratio): CVA; 27:44, NCVA; 85:127 Smoking status: non-smokers ICS use: none within a month Ethnicity: not reported Setting: secondary care Country: China Inclusion criteria: >18 years of age, cough lasting at least 8 weeks, normal chest radiograph, FEV1/FVC >70% of predicted and FEV1 >80% of predicted and no corticosteroid use in the past month Exclusion criteria: current smoker or ex-smoker within 2 years, pregnant or lactating, acute upper respiratory tract infection within 8 weeks, use of corticosteroids within a month, or use of montelukast or LABAs within a week, severe cardiac insufficiency, severe liver and kidney insufficiency, mental and cognitive dysfunction, hearing and communication impairment and multiple causes of chronic cough				
Target condition(s)	Cough variant asthma or non-asthma chronic cough				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 25%
	Index test +	37	37	74	

Reference	**Bai 2023 (Bai et al., 2023)**				
Study type	Cross-sectional diagnostic study				
Study methodology	Data source: patients attending the Department of Pulmonary and Critical Care Medicine Recruitment: not reported				
Number of patients	n = 283				
Patient characteristics	Age, mean (SD): cough variant asthma (CVA); 47.8 (15.9) years, non-cough variant asthma (NCVA); 44.6 (15.2) years Gender (male to female ratio): CVA; 27:44, NCVA; 85:127 Smoking status: non-smokers ICS use: none within a month Ethnicity: not reported Setting: secondary care Country: China Inclusion criteria: >18 years of age, cough lasting at least 8 weeks, normal chest radiograph, FEV1/FVC >70% of predicted and FEV1 >80% of predicted and no corticosteroid use in the past month Exclusion criteria: current smoker or ex-smoker within 2 years, pregnant or lactating, acute upper respiratory tract infection within 8 weeks, use of corticosteroids within a month, or use of montelukast or LABAs within a week, severe cardiac insufficiency, severe liver and kidney insufficiency, mental and cognitive dysfunction, hearing and communication impairment and multiple causes of chronic cough				
Target condition(s)	Cough variant asthma or non-asthma chronic cough				
	Index test −	34	175	209	
	Total	71	212	283	

Statistical measures	Sensitivity: 0.52 (95%CI 0.40-0.64) Specificity: 0.83 (95%CI 0.77-0.87) PPV: 50% NPV: 84%
Source of funding	Supported by the National Natural Science Foundation of China, the Project of Science and Technology Commission of Shanghai Municipality, the Program of Shanghai Academic Research Leader and the Fund of Shanghai Youth Talent Support Program
Limitations	Risk of bias: Very serious risk of bias due to selection bias (unclear recruitment method) and concerns arising from interpretation of the index test and reference standard (unclear if blinded) Indirectness: Downgraded by one increment due to index test (protocol specified 70% or LLN as cut-off) indirectness
Comments	2x2 data calculated using sensitivity, specificity and prevalence (25%) reported in the paper

1

Reference	**Bao 2021 (Bao et al., 2021)**
Study type	Retrospective cross-sectional study
Study methodology	Data source: Retrospective data of adults with recurrent variable symptoms of dyspnoea, cough, wheeze, or chest tightness of at least 8 weeks' duration who were referred to the Pulmonary Outpatient Clinic of Shanghai General Hospital Recruitment: Not reported
Number of patients	n = 692
Patient characteristics	Age, mean (SD): Positive MCT: 43.90 (14.56), negative MCT: 43.80 (14.90) Gender (male to female ratio): Positive MCT; 53:117, negative MCT; 203:319 Smoking status: Non-smokers ICS use: None within a month Ethnicity: Not reported Setting: Pulmonary outpatient department (secondary care) Country: China Inclusion criteria: Aged 18-75 years, recurrent variable symptoms of dyspnoea, cough, wheeze, or chest tightness for >8 weeks, normal high-resolution CT and FEV1 >80% of predicted Exclusion criteria: Respiratory tract infection within 8 weeks, abnormal haemoglobin, platelets or neutrophils, use of montelukast, LABAs, theophylline, anticholinergics or corticosteroids within 4 weeks, concomitant severe systemic diseases, smoking history >10 pack years, current smokers and those who had quit within 2 years
Target condition(s)	Bronchial hyperresponsiveness to methacholine
Index test(s) and reference standard	Index test Retrospective spirometry data was use for this study. No information on protocol or standard used to conduct measurements Cut-off: FEV_1/FVC: 84.76% (optimal threshold) Reference standard

Reference	**Bao 2021 (Bao et al., 2021)**				
	Methacholine challenge testing was used with a cut-off of ≤0.48 mg to indicate airway hyperresponsiveness. Time between measurement of index test and reference standard: Not reported				
2×2 table % Predicted FEV_1 (cut-off: 88.4%)		Reference standard +	Reference standard −	Total	Prevalence= 24.5%
	Index test +	113	169	282	
	Index test −	57	353	410	
	Total	170	522	692	
Statistical measures	Index text Sensitivity: 0.66 (95%CI 0.59-0.74) Specificity: 0.68 (95%CI 0.63-0.72) PPV: 40% NPV: 86%				
Source of funding	Supported by the National Natural Science Foundation of China; Appropriate technique application Program of Shanghai Municipal Health system, Scientific and Technological Innovation program funded by Science and Technology Commission of Shanghai municipality and the Program of Shanghai Municipal Health System				
Limitations	Risk of bias: Very serious due to concerns arising from patient selection (recruitment method not reported), unclear interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of the study (interval between index test and reference standard not reported) Indirectness: Downgraded by two increments due to index test (paper did not report standard spirometry was performed to, and protocol specified LLN as the cut-off) and reference standard (unclear clinician decision in diagnosis) indirectness				
Comments	2x2 tables calculated using sensitivity, specificity and prevalence (24.5%) data reported in paper				

1

Reference	**Eom 2020 (Eom et al., 2020)**
Study type	Prospective cross-sectional study
Study methodology	Data source: Patients referred to an outpatient clinic for diagnosis of asthma Recruitment: Consecutive
Number of patients	n = 275
Patient characteristics	Age, mean (95%CI): Non-asthma diagnosis: 11.5 (10.7-12.3), asthma diagnosis: 11.6 (11.1-12.1)

Reference	**Eom 2020 (Eom et al., 2020)**				
	Gender (male to female ratio): Non-asthma diagnosis 30:54, asthma diagnosis: 65:126 Exposure to cigarette smoke: Non-asthma diagnosis: 45.2%, asthma diagnosis: 40.6% Atopy: Not reported Ethnicity: Not reported Setting: Secondary care Country: South Korea Inclusion criteria: 8-16 years of age presenting with respiratory symptoms including cough, wheezing, or breathlessness for at least 1 month duration. Exclusion criteria: Symptoms of respiratory tract infection or those with other systemic or inflammatory disease, receiving inhaled short-acting β2-agonists within 8 hours and receiving a regular treatment with controller medications for 1 month or more before evaluation.				
Target condition(s)	Asthma				
Index test(s) and reference standard	Index test Spirometry: Lung function was measured by a spirometer according to the ATS/ERS recommendations. FVC, FEV1, FEF25-75 and FEV1/FVC were obtained from the best of three reproducible forced expiratory manoeuvres. Percent predicted values were calculated based on the Third National Health and Nutrition Examination Survey (NHANES III). Cut-off: FEV_1= 88.4%, FEV_1/FVC= 85.3% (optimal threshold) Reference standard Asthma was assessed by a paediatric pulmonologist after at least 6 months of follow-up. The diagnosis of asthma was determined according to the Global Initiative for Asthma guidelines and was based on the patient's history of two or more clinical exacerbations of respiratory symptoms such as wheezing, shortness of breath and chest tightness or cough. Furthermore, spirometry was used to determine presence of variable expiratory airflow limitation, which was confirmed by increase in FEV1 of more than 12% in response to a rapid-acting bronchodilator at any time during the follow-up period, increase in FEV1 of more than 12% from baseline after 4 weeks of anti- inflammatory treatment, and/or variation in FEV1 of more than 12% between visits. Children who did not have these characteristics and had never used asthma medication in the previous year were not considered to have asthma. Time between measurement of index test and reference standard: at least 6 months				
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 69.5%

Reference	**Eom 2020 (Eom et al., 2020)**			
% Predicted FEV_1 (cut-off: 88.4%)	Index test +	130	20	150
	Index test −	61	64	125
	Total	191	84	275
2×2 table FEV_1/FVC (cut-off: 85.3%)		Reference standard +	Reference standard −	Total
	Index test +	139	29	168
	Index test −	52	55	107
	Total	191	84	275
Statistical measures	Index text FEV_1 (% predicted) cut-off 88.4 Sensitivity: 0.68 (95%CI 0.61-0.75) Specificity: 0.76 (95%CI 0.66-0.85) PPV: 87% NPV: 51% Index text FEV_1/FVC (%) cut-off 85.3 Sensitivity: 0.73 (95%CI 0.66-0.79) Specificity: 0.65 (95%CI 0.54-76) PPV: 83% NPV: 52%			
Source of funding	None declared			
Limitations	Risk of bias: Not serious Indirectness: FEV_1/FVC downgraded by one increment due to index test (lower limit of normal not used as the cut-off) indirectness			
Comments	2x2 tables calculated using sensitivity, specificity and prevalence (69%) data reported in paper			

1

Reference	**Louis 2023 (Louis et al., 2023)**
Study type	Prospective cross-sectional study
Study methodology	Data source: Adult patients investigated at an asthma clinic of Liege University Recruitment: Not reported
Number of patients	n = 303 (split into a training (n=166) and validation (n=137) cohort. Only data from the training cohort is available for the optimal threshold analysis).

Reference	**Louis 2023 (Louis et al., 2023)**				
Patient characteristics	Age, mean (SD): 51 (16) years Gender (male:female ratio): 121:182 Smoking status: 62 smokers, 84 ex-smokers, 157 non-smokers Atopy: 136 atopic Ethnicity: Not reported Setting: Secondary care Country: Belgium Inclusion criteria: Untreated patients aged ≥18 years who sought medical attention and in whom asthma was suspected Exclusion criteria: None specified				
Target condition	Asthma				
Index test(s) and reference standard	Index test: Lung function testing was performed by spirometry, according to ATS/ERS standards Cut-off: 75% (pre-specified) and 78% (optimal threshold) Reference standard As per GINA guidelines, asthma diagnosis was based on the presence of typical symptoms (wheezing, dyspnoea, cough, sputum production and chest tightness) combined with ⩾12% and ⩾200 mL FEV_1 reversibility after inhalation of 400 µg salbutamol and/or a PC20 methacholine causing a 20% fall in FEV_1 ⩽8 mg·mL−1 when FEV_1 is ⩾70% predicted Time between measurement of index test and reference standard: 1-2 weeks				
2×2 table FEV_1/FVC <75%		Reference standard +	Reference standard −	Total	Prevalence= 61.1%
	Index test +	73	20	93	
	Index test −	112	98	210	
	Total	185	118	303	
2×2 table		Reference standard +	Reference standard −	Total	Prevalence= 63.3%

Reference	**Louis 2023 (Louis et al., 2023)**				
FEV_1/FVC <78%	Index test +	57	13	70	
	Index test −	48	48	96	
	Total	105	61	166	
Statistical measures	FEV_1/FVC <75% Sensitivity: 0.39 (95%CI 0.32-0.47) Specificity: 0.83 (95%CI 0.75-0.89) PPV: 78% NPV: 47% FEV_1/FVC <78% Sensitivity: 0.54 (95%CI 0.44-0.64) Specificity: 0.79 (95%CI 0.66-0.88) PPV: 82% NPV: 50%				
Source of funding	Funding from the European Union, FEDER APPS INTERREG				
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from the method of participant recruitment (method not reported) and the interpretation of the index test and reference standard (unclear if blinded). Additionally, 78% cut-off has further concerns due to the flow and timing of participants through the study, including data on the training cohort (n=166) only, not including the validation cohort. Indirectness: Downgraded by one increment due to index test (lower limit of normal or <70% not used as the cut-off)				
Comments	2x2 data for 78% cut-off calculated from sensitivity, specificity and prevalence (63.3%) reported in paper				

1

Reference	**Nekoee 2020 (Nekoee et al., 2020)**
Study type	Retrospective cross-sectional diagnostic accuracy study
Study methodology	Data source: Retrospective study of database data of untreated patients referred to an asthma clinic by two respiratory physicians for chronic or episodic respiratory symptoms suggestive of asthma Recruitment: Not reported
Number of patients	n = 702
Patient characteristics	Age, mean: 51 years Gender (% female): 58% Smoking status: 57% never smokers, 24% ex-smokers, 19% current smokers

<table>
<tr><td>Reference</td><td colspan="5">Nekoee 2020 (Nekoee et al., 2020)</td></tr>
<tr><td></td><td colspan="5">Atopy: Not reported

Ethnicity: Not reported

Setting: Asthma clinic (secondary care)

Country: Not reported

Inclusion criteria: Underwent investigations at an asthma clinic prior to receiving maintenance therapy

Exclusion criteria: None reported</td></tr>
<tr><td>Target condition(s)</td><td colspan="5">Asthma</td></tr>
<tr><td>Index test(s) and reference standard</td><td colspan="5"><u>Index test</u>
FEV_1/FVC – method/protocol followed to obtain measurements not reported

Cut-off: 76% (optimal threshold)

<u>Reference standard</u>
Asthma was diagnosed by either bronchodilator reversibility (⩾12% from baseline and 200 mL) and/or bronchial hyperresponsiveness to methacholine (provocative concentration causing a 20% fall in FEV_1 ⩽8 $mg \cdot mL^{-1}$). Patients who were negative tested negative to both tests

Time between measurement of index test and reference standard: 1-2 weeks</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= 49.7%</td></tr>
<tr><td></td><td>Index test +</td><td>178</td><td>85</td><td>263</td></tr>
<tr><td></td><td>Index test −</td><td>171</td><td>268</td><td>439</td></tr>
<tr><td></td><td>Total</td><td>349</td><td>353</td><td>702</td></tr>
</table>

Reference	**Nekoee 2020 (Nekoee et al., 2020)**
Statistical measures	Index text Sensitivity: 0.51 (95%CI 0.46-0.56) Specificity: 0.76 (95%CI 0.71-0.80) PPV: 68% NPV: 61%
Source of funding	Supported by a Federal Belgian Government Excellence of Science grant
Limitations	Risk of bias: Downgraded by two increments due to concerns arising from patient selection (method of selection not reported), unclear interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of participants through the study (not all participants were diagnosed with the same reference standard) Indirectness: Downgraded by two increments due to index test (paper did not report standard spirometry was performed to, and lower limit of normal or <70% not used as the cut-off) and reference standard (unclear clinician involvement in diagnosis) indirectness
Comments	2x2 data calculated from sensitivity, specificity and prevalence (49.7%) data reported in paper

1

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

Reference	**Simpson 2024 (Simpson et al., 2024)**				
	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 conducted according to the ATS/ERS guidelines. After withholding bronchodilators for at least 8 hours, participants were instructed to inhale deeply followed by maximal exhalation as quickly as possible from total lung capacity to residual volume through a spirometer. A minimum of three technically acceptable measurements were required. FVC and FEV_1 were recorded in litres and as percentage predicted from Global Lung Function Initiative equations. Cut-offs: <75%, <70%, <LLN, <70% or LLN, <LLN with reduced FEV_1 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 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				
2×2 table FEV_1/FVC ratio <70%		Reference standard +	Reference standard −	Total	Prevalence= 59.3%
	Index test +	21	2	23	
	Index test −	49	46	95	
	Total	70	48	118	
2×2 table FEV_1/FVC ratio <75%		Reference standard +	Reference standard −	Total	
	Index test +	34	5	39	
	Index test −	36	43	79	
	Total	70	48	118	

Reference	Simpson 2024 (Simpson et al., 2024)			
2×2 table FEV_1/FVC ratio <LLN		Reference standard +	Reference standard −	Total
	Index test +	26	2	28
	Index test −	44	46	90
	Total	70	48	118
2×2 table FEV_1/FVC ratio <70% or LLN		Reference standard +	Reference standard −	Total
	Index test +	27	2	29
	Index test −	43	46	89
	Total	70	48	118
2×2 table FEV_1/FVC ratio <LLN with reduced FEV_1		Reference standard +	Reference standard −	Total
	Index test +	33	3	36
	Index test −	37	45	82
	Total	70	48	118
Statistical measures	Index text FEV_1/FVC ratio <70% Sensitivity: 0.30 (95%CI 0.20-0.42) Specificity: 0.96 (95%CI 0.86-0.99) PPV: 91% (72-98) NPV: 48% (44-53) Index text FEV_1/FVC ratio <75% Sensitivity: 0.49 (95%CI 0.36-0.61) Specificity: 0.90 (95%CI 0.77-0.97) PPV: 87% (75-94) NPV: 54% (48-60) Index text FEV_1/FVC ratio <LLN Sensitivity: 0.37 (95%CI 0.26-0.50) Specificity: 0.96 (95%CI 0.86-0.99) PPV: 93% (76-98) NPV: 51% (46-56) Index text FEV_1/FVC ratio <70% or LLN Sensitivity: 0.39 (95%CI 0.27-0.51) Specificity: 0.96 (95%CI 0.86-0.99) PPV: 93% (77-98)			

Reference	Simpson 2024 (Simpson et al., 2024)
	NPV: 52% (47-57) Index text FEV_1/FVC ratio <LLN with reduced FEV_1 Sensitivity: 0.47 (95%CI 0.35-0.59) Specificity: 0.94 (95%CI 0.93-0.99) PPV: 92% (78-97) NPV: 55% (49-61)
Source of funding	Supported by the Manchester NIHR Biomedical Research Centre, Asthma UK/Innovate and Northwest Lung Centre Charity
Limitations	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 index test (where cut-offs other than LLN or 70% were used) indirectness

1

2

Reference	Smith 2004 (Smith et al.)
Study type	Prospective cross-sectional diagnostic accuracy study
Study methodology	Data source: 47 consecutive patients aged 8–75 years referred by their family practitioner to Dunedin Hospital Recruitment: Consecutive patients
Number of patients	n = 47
Patient characteristics	Age, mean (range): Diagnosed with asthma: 41.6 (9-72), without asthma: 31.8 (9-64) Gender (male to female ratio): 20: 27 Smoking status: 42 non-smokers, 5 ex-smokers Atopy: Not reported Ethnicity: Not reported Setting: Primary care

Reference	**Smith 2004 (Smith et al.)**				
	Country: New Zealand Inclusion criteria: people having respiratory symptoms in the preceding 4 weeks Exclusion criteria: used oral or inhaled corticosteroid in the preceding 4 weeks or if they had a typical respiratory tract infection in the previous 6 weeks				
Target condition(s)	Asthma				
Index test(s) and reference standard	Index test FEV_1/FVC – method/protocol followed to obtain measurements not reported Cut-offs: 80% and 70% (pre-specified) Reference standard Diagnosis of asthma was ascertained on the basis of the following: relevant symptom history (present in all patients), using American Thoracic Society criteria, and a positive test for BHR and/or a positive response to bronchodilator. These were defined as: provocative dose of hypertonic saline resulting in a 15% fall in FEV1(PD15) of less than 20 ml and an increase in FEV_1 of 12% or greater from baseline 15 minutes after inhaled albuterol, respectively Time between measurement of index test and reference standard: 2-4 weeks				
2×2 table FEV_1/FVC ratio <70%		Reference standard +	Reference standard −	Total	Prevalence= 36.1%
	Index test +	6	0	6	
	Index test −	11	30	41	
	Total	17	30	47	
2×2 table FEV_1/FVC ratio <80%		Reference standard +	Reference standard −	Total	
	Index test +	8	6	14	
	Index test −	9	24	33	
	Total	17	30	47	

Reference	Smith 2004 (Smith et al.)
Statistical measures	Index text FEV_1/FVC ratio <70% Sensitivity: 0.35 (95%CI 0.14-0.62) Specificity: 1.00 (95%CI 0.88-1.00) PPV: 100% NPV: 73% Index text FEV_1/FVC ratio <80% Sensitivity: 0.47 (95%CI 0.23-0.72) Specificity: 0.80 (95%CI 0.61-0.92) PPV: 57% NPV: 73%
Source of funding	Supported by the Otago Medical Research Foundation and the Otago Respiratory Research Trust. GlaxoSmithKline provided a personal educational grant to A.D.S. as GSK Research Fellow
Limitations	Risk of bias: Downgraded by one increment due to concerns arising from the interpretation of the index test and reference standard (unclear if blinded) Indirectness: Downgraded by two increments due to index test (paper did not report standard spirometry was performed to, and lower limit of normal not used as the cut-off) and population (mixed children and adolescents/young people) indirectness
Comments	2x2 data reported in paper, sensitivity and specificity calculated by analyst

Clinical and cost effectiveness of spirometry

No clinical evidence identified.

Appendix E – Forest plots

Diagnostic test accuracy of spirometry

Coupled sensitivity and specificity forest plots

Adults

Figure 3: FEV_1/FVC ratio (cut-off: 70%) vs clinician diagnosis and hypertonic saline provocation test or expert panel diagnosis with multiple diagnostic tests

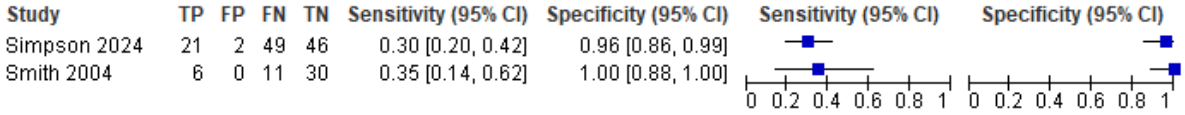


Figure 4: FEV_1/FVC ratio (cut-off: 75%) vs clinician diagnosis with bronchodilator reversibility and/or methacholine bronchial challenge test or expert panel diagnosis with multiple diagnostic tests

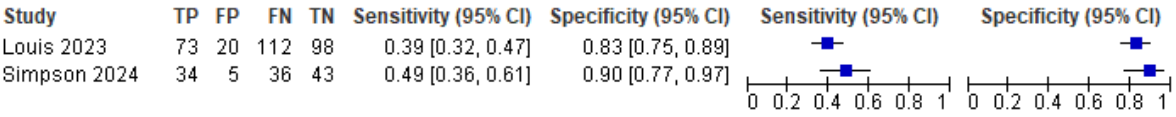


Figure 5: FEV_1/FVC ratio (cut-off: 76%) vs bronchodilator reversibility or methacholine bronchial challenge test

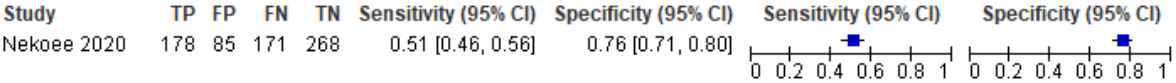


Figure 6: FEV_1/FVC ratio (cut-off: 78%) vs clinician diagnosis with bronchodilator reversibility and/or methacholine bronchial challenge test

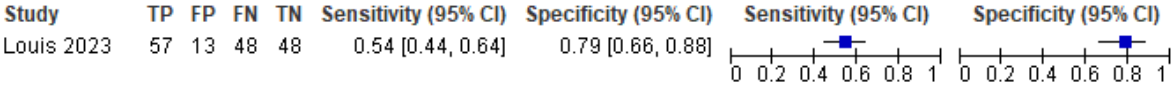


Figure 7: FEV_1/FVC ratio (cut-off: 78.79%) vs clinician diagnosis and histamine bronchial provocation test

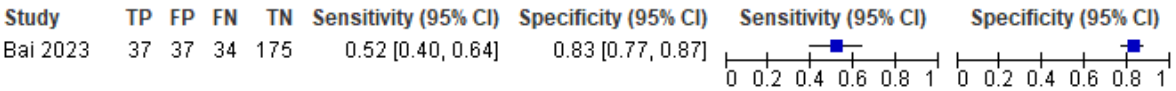
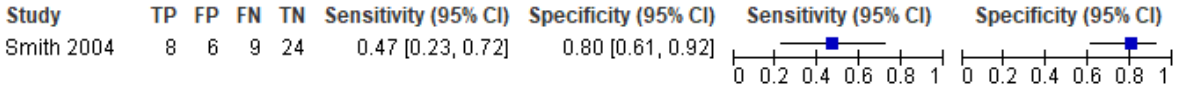
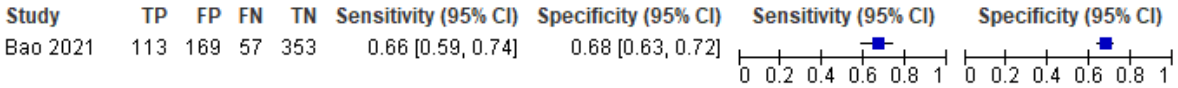


Figure 8: FEV_1/FVC ratio (cut-off: 80%) vs clinician diagnosis and hypertonic saline provocation test



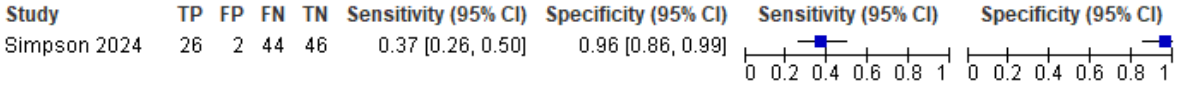
1

Figure 9: FEV_1/FVC ratio (cut-off: 84.76%) vs methacholine bronchial challenge test



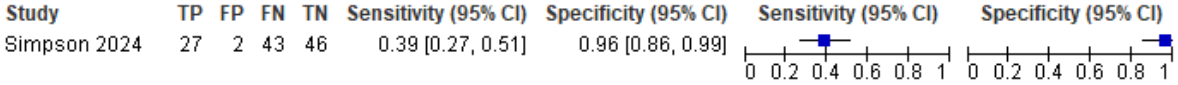
2

Figure 10: FEV_1/FVC ratio (cut-off: <LLN) vs expert panel diagnosis with multiple diagnostic tests



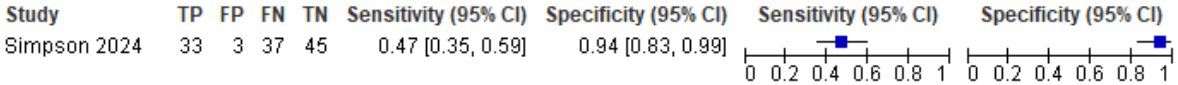
3

Figure 11: FEV_1/FVC ratio (cut-off: <70% or LLN) vs expert panel diagnosis with multiple diagnostic tests



4

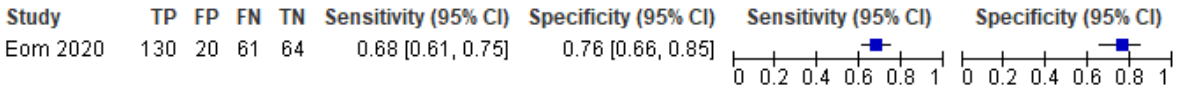
Figure 12: FEV_1/FVC ratio (cut-off: <LLN with reduced FEV_1) vs expert panel diagnosis with multiple diagnostic tests



5

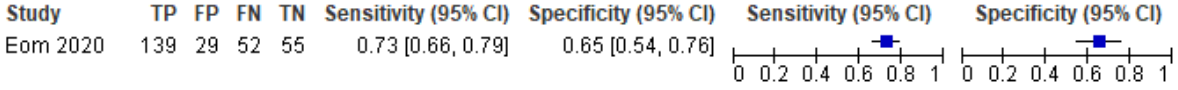
6 **Children and young people**

Figure 13: % predicted FEV_1 (cut-off: 88.4%) vs clinician diagnosis with bronchodilator reversibility



7

Figure 14: FEV_1/FVC ratio (cut-off: 85.3%) clinician diagnosis with bronchodilator reversibility



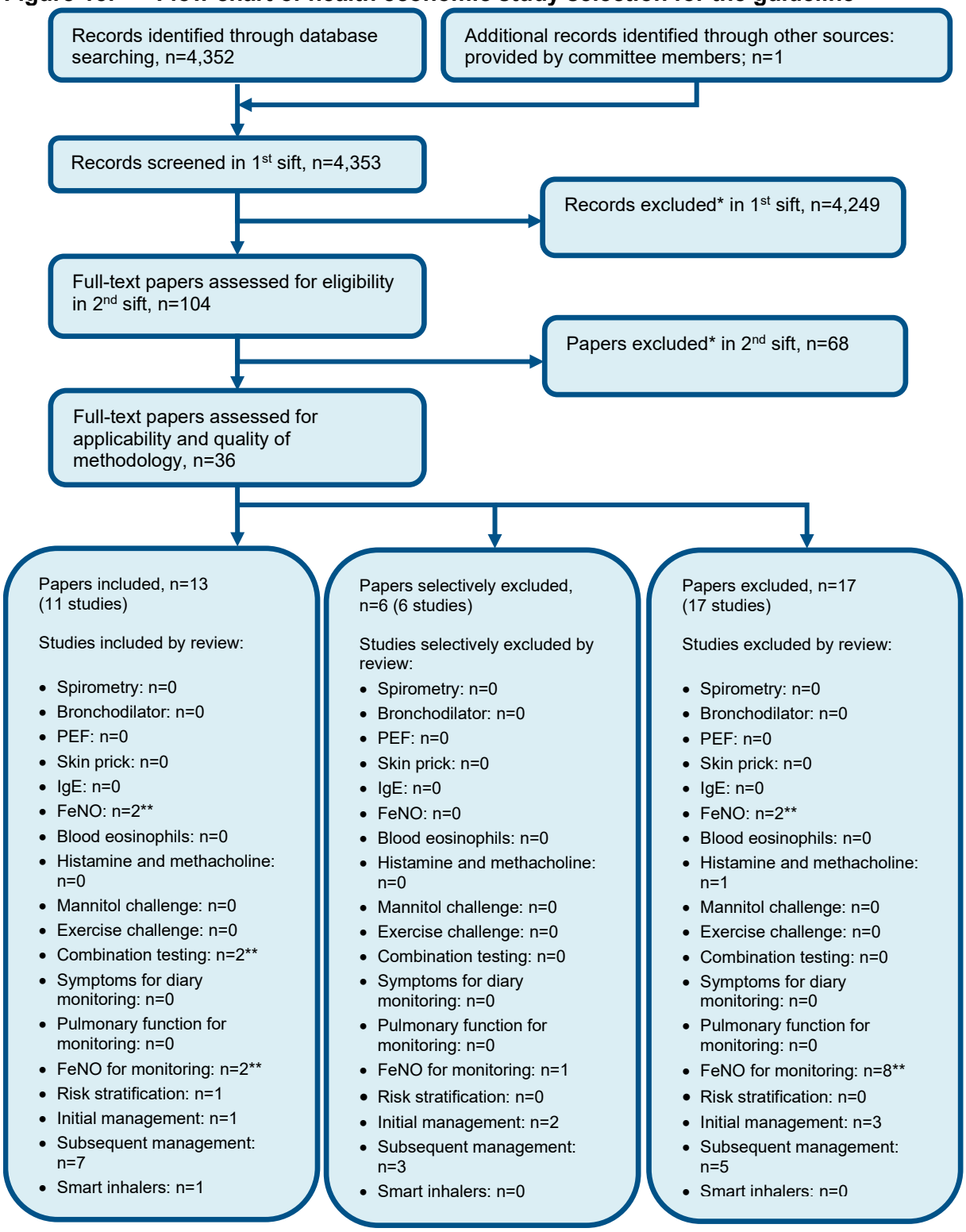
8

1 Clinical and cost effectiveness of spirometry

2 No clinical evidence identified.

Appendix F – Economic evidence study selection

Figure 15: 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 spirometry

Table 9: Studies excluded from the clinical review

Study	Code [Reason]
Abramson, M. J., Gwini, S. M., de Klerk, N. H. et al. (2020) Predictive value of non-specific bronchial challenge testing for respiratory symptoms and lung function in aluminium smelter workers. Occupational & Environmental Medicine 77(8): 535-539	- Population not relevant to this review protocol *Participants not presenting with symptoms/suspected of asthma*
Almeshari, M. A., Alobaidi, N. Y., Edgar, R. G. et al. (2020) Physiological tests of small airways function in diagnosing asthma: a systematic review. BMJ open respiratory research 7(1): 12	- Review article but not a systematic review
Almeshari, M. A.; Stockley, J.; Sapey, E. (2021) The diagnosis of asthma. Can physiological tests of small airways function help?. Chronic Respiratory Disease 18: 14799731211053332	- More recent systematic review included that covers the same topic
Arikoglu, T., Batmaz, S. B., Unlu, A. et al. (2018) The Diagnostic Value of Impulse Oscillometry and Plethysmography for the Assessment of Exercise-Induced Bronchoconstriction in Asthmatic Children. Pediatric, Allergy, Immunology, and Pulmonology 31(1): 24-31	- Population not relevant to this review protocol *Participants already diagnosed with asthma*
Backman, K., Ollikainen, H., Piippo-Savolainen, E. et al. (2018) Asthma and lung function in adulthood after a viral wheezing episode in early childhood. Clinical & Experimental Allergy 48(2): 138-146	- Population not relevant to this review protocol *Participants already diagnosed with asthma*
Badnjevic, A., Cifrek, M., Koruga, D. et al. (2015) Neuro-fuzzy classification of asthma and chronic obstructive pulmonary disease. BMC Medical Informatics & Decision Making 15suppl3: 1	- Population not relevant to this review protocol *Participants already diagnosed with asthma or COPD*
Benjelloun, H., Zaidane, S., Zaghba, N. et al. (2019) Clinical, functional and therapeutic features of asthma in the elderly. Revue Francaise d'Allergologie 59(2): 58-62	- Study not reported in English

Study	Code [Reason]
Bokov, P., Martin, C., Graba, S. et al. (2017) Bronchodilator Response Assessment of the Small Airways Obstructive Pattern. The Open Respiratory Medicine Journal 11: 47-53	- Index test in study does not match that specified in the protocol *impulse oscillometry*
Borak, J. and Lefkowitz, R. Y. (2016) Bronchial hyperresponsiveness. Occupational Medicine (Oxford) 66(2): 95-105	- Review article but not a systematic review
Borak, J.; Lefkowitz, R. Y.; Linde, B. (2018) Bronchial hyper-responsiveness: a technical update. Occupational Medicine (Oxford) 68(8): 519-522	- Review article but not a systematic review
Bougard, N., Nekoee, H., Schleich, F. et al. (2020) Assessment of diagnostic accuracy of lung function indices and FeNO for a positive methacholine challenge. Biochemical Pharmacology 179: 113981	- Population not relevant to this review protocol *Patients already receiving ICS with no washout prior to tests*
Chaiwong, W., Namwongprom, S., Liwsrisakun, C. et al. (2022) The roles of impulse oscillometry in detection of poorly controlled asthma in adults with normal spirometry. Journal of Asthma 59(3): 561-571	- Population not relevant to this review protocol *Already diagnosed with asthma*
Chawes, B. and Elenius, V. (2022) Pulmonary function testing for the diagnosis of asthma in preschool children. Current Opinion in Allergy & Clinical Immunology 22(2): 101-106	- Population not relevant to this review protocol *Pre-school children (protocol specified >5 years old)*
de Jong, C. C. M., Pedersen, E. S. L., Mozun, R. et al. (2019) Diagnosis of asthma in children: the contribution of a detailed history and test results. European Respiratory Journal 54(6): 12	- Population not relevant to this review protocol *ICS washout period not suitable (24h, protocol specified at least 4 weeks)*
Dean, B. W., Birnie, E. E., Whitmore, G. A. et al. (2018) Between-Visit Variability in FEV1 as a Diagnostic Test for Asthma in Adults. Annals of the American Thoracic Society 15(9): 1039-1046	- Population not relevant to this review protocol *Already diagnosed with asthma*
Dos Santos, K., Fausto, L. L., Camargos, P. A. M. et al. (2017) Impulse oscillometry in the assessment of asthmatic children and adolescents: from a narrative to a systematic review. Paediatric Respiratory Reviews 23: 61-67	- Study design not relevant to this review protocol *Systematic review of cohort studies including participants with pre-study diagnosis*

Study	Code [Reason]
Elenius, V., Chawes, B., Malmberg, P. L. et al. (2021) Lung function testing and inflammation markers for wheezing preschool children: A systematic review for the EAACI Clinical Practice Recommendations on Diagnostics of Preschool Wheeze. Pediatric Allergy & Immunology 32(3): 501-513	- Population not relevant to this review protocol *Pre-school children (protocol specified >5 years old)*
Francisco, B., Ner, Z., Ge, B. et al. (2015) Sensitivity of different spirometric tests for detecting airway obstruction in childhood asthma. Journal of Asthma 52(5): 505-11	- Population not relevant to this review protocol *Already diagnosed with asthma*
Gaillard, E. A., Kuehni, C. E., Turner, S. et al. (2021) European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5-16 years. European Respiratory Journal 58(5): 10	- Systematic review used as source of primary studies
Grzelewski, T., Witkowski, K., Makandjou-Ola, E. et al. (2014) Diagnostic value of lung function parameters and FeNO for asthma in schoolchildren in large, real-life population. Pediatric Pulmonology 49(7): 632-40	- Aiming to diagnose a condition not relevant to this review protocol *Aiming to diagnose allergic asthma*
Gurbeta, L., Badnjevic, A., Maksimovic, M. et al. (2018) A telehealth system for automated diagnosis of asthma and chronical obstructive pulmonary disease. Journal of the American Medical Informatics Association 25(9): 1213-1217	- Population not relevant to this review protocol *Patients in primary care - not presenting with respiratory complaints*
Heijkenskjold Rentzhog, C., Janson, C., Berglund, L. et al. (2017) Overall and peripheral lung function assessment by spirometry and forced oscillation technique in relation to asthma diagnosis and control. Clinical & Experimental Allergy 47(12): 1546-1554	- Study does not contain an intervention relevant to this review protocol *Already diagnosed with asthma*
Hou, L., Hao, H., Huang, G. et al. (2021) The value of small airway function parameters and fractional exhaled nitric oxide for predicting positive methacholine challenge test in asthmatics of different ages with FEV1 >= 80% predicted. Clinical and Translational Allergy 11(1)	- Reference standard in study does not match that specified in protocol *Objective test used as reference standard without clinical diagnosis*
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 *Already diagnosed with asthma and healthy controls with no symptoms*

Study	Code [Reason]
Jankrift, N., Kellerer, C., Magnussen, H. et al. (2021) The role of clinical signs and spirometry in the diagnosis of obstructive airway diseases: a systematic analysis adapted to general practice settings. Journal of Thoracic Disease 13(6): 3369-3382	- Study design not relevant to this review protocol *No reference standard*
Kilci, F., Uyan, Z. S., Celakil, M. E. et al. (2021) Respiratory function in children with nephrotic syndrome: Comparative evaluation of impulse oscillometry and spirometry. Pediatric Pulmonology 56(10): 3301-3309	- Full text paper not available
Knihtila, H., Kotaniemi-Syrjanen, A., Pelkonen, A. S. et al. (2017) Sensitivity of newly defined impulse oscillometry indices in preschool children. Pediatric Pulmonology 52(5): 598-605	- Population not relevant to this review protocol *Pre-school children (protocol specified >5 years old)*
Koruga, D., Baletic, N., Veres, K. T. et al. (2018) Impulse oscillometry in evaluation bronchial hyperresponsiveness in patients with persistent allergic rhinitis. Vojnosanitetski Pregled 75(1): 39-45	- Index test in study does not match that specified in the protocol *Impulse oscillometry used as index test*
Kumar, R. and Gupta, N. (2017) Exhaled nitric oxide atopy, and spirometry in asthma and rhinitis patients in India. Advances in Respiratory Medicine 85(4): 186-192	- Population not relevant to this review protocol *Already diagnosed with asthma*
Lambert, A., Drummond, M. B., Wei, C. et al. (2015) Diagnostic accuracy of FEV1/forced vital capacity ratio z scores in asthmatic patients. Journal of Allergy & Clinical Immunology 136(3): 649-653.e4	- Population not relevant to this review protocol *Already diagnosed with asthma*
Levy, M. L. (2016) Is spirometry essential in diagnosing asthma? No. British Journal of General Practice 66(650): 485	- Study design not relevant to this review protocol *Opinion piece*
Li, H., Zhang, X., Zhao, Q. et al. (2022) Assessment of Clinical Diagnostic Efficacy of Pulmonary Function Test Based on DBN-SVM of Pediatric Asthma and Cough Variant Asthma. Computational Intelligence & Neuroscience 2022: 1182114	- Population not relevant to this review protocol *Already diagnosed with asthma*
Louis, R., Satia, I., Ojanguren, I. et al. (2022) European Respiratory Society Guidelines for the	- Systematic review used as source of primary studies

Study	Code [Reason]
Diagnosis of Asthma in Adults. European Respiratory Journal 15: 15	
Metting, E. I., In 't Veen, J. C., Dekhuijzen, P. N. et al. (2016) Development of a diagnostic decision tree for obstructive pulmonary diseases based on real-life data. Erj Open Research 2(1)	- Study design not relevant to this review protocol *Prognostic study*
Miyoshi, S., Katayama, H., Matsubara, M. et al. (2020) Prediction of Spirometric Indices Using Forced Oscillometric Indices in Patients with Asthma, COPD, and Interstitial Lung Disease. International Journal of Copd 15: 1565-1575	- Population not relevant to this review protocol *Already diagnosed with asthma, COPD or ILD*
Mondal, P., Yirinec, A., Midya, V. et al. (2019) Diagnostic value of spirometry vs impulse oscillometry: A comparative study in children with sickle cell disease. Pediatric Pulmonology 54(9): 1422-1430	- Data not reported in an extractable format or a format that can be analysed *Sensitivity, specificity and 2x2 data not reported*
Mousa, H. and Kamal, E. (2018) Impulse oscillation system versus spirometry in assessment of obstructive airway diseases. Egyptian Journal of Chest Diseases and Tuberculosis 67(2): 106-112	- Population not relevant to this review protocol *Already diagnosed with asthma or COPD*
Nawaz, S. F.; Ravindrarn, M.; Kuruvilla, M. E. (2022) Asthma diagnosis using patient-reported outcome measures and objective diagnostic tests: now and into the future. Current Opinion in Pulmonary Medicine 28(3): 251-257	- Review article but not a systematic review
Parkes, E. D., Moore, V. C., Walters, G. I. et al. (2020) Diagnosis of occupational asthma from serial measurements of forced expiratory volume in 1 s (FEV1) using the Area Between Curves (ABC) score from the Oasys plotter. Occupational & Environmental Medicine 77(11): 801-805	- Population not relevant to this review protocol *Already diagnosed with asthma*
Peled, M., Ovadya, D., Cohn, J. et al. (2021) Baseline spirometry parameters as predictors of airway hyperreactivity in adults with suspected asthma. BMC Pulmonary Medicine 21(1): 153	- Index test in study does not match that specified in the protocol *Spirometry carried out, but no index tests relevant to the protocol reported*
Popović-Grle, S., Mehulić, M., Pavicić, F. et al. (2002) Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. Coll Antropol 26suppl: 119-27	- Index test in study does not match that specified in the protocol *Study reports FEV1, but not FEV1/FVC ratio*

Study	Code [Reason]
Qin, R., An, J., Xie, J. et al. (2021) FEF25-75% Is a More Sensitive Measure Reflecting Airway Dysfunction in Patients with Asthma: A Comparison Study Using FEF25-75% and FEV1. The Journal of Allergy & Clinical Immunology in Practice 9(10): 3649-3659.e6	- Population not relevant to this review protocol *Already diagnosed with asthma*
Raji, H., Haddadzadeh Shoushtari, M., Idani, E. et al. (2018) Forced Expiratory Flow at 25-75% as a Marker for Airway Hyper Responsiveness in Adult Patients with Asthma-like Symptoms. Tanaffus 17(2): 90-95	- Index test in study does not match that specified in the protocol *Spirometry carried out, but no index test relevant to the protocol reported*
Schneider, A., Gindner, L., Tilemann, L. et al. (2009) Diagnostic accuracy of spirometry in primary care. BMC Pulm Med 9: 31	- Population not relevant to this review protocol *ICS washout period not appropriate (12h, protocol specified >4 weeks)*
Shafiq, I., Uzbeck, M. H., Zoumot, Z. et al. (2021) Correlation between Reduced FEF25-75% and a Positive Methacholine Challenge Test in Adults with Nonobstructive Baseline Spirometry. Pulmonary Medicine 2021: 6959322	- Data not reported in an extractable format or a format that can be analysed *Diagnostic accuracy data only given in ROC curves*
Sivan, Y., Gadish, T., Fireman, E. et al. (2009) The use of exhaled nitric oxide in the diagnosis of asthma in school children. J Pediatr 155(2): 211-6	- Study design not relevant to this review protocol *Reference standard completed 18 months after index test (protocol specified 12 months or less)*
Stanbrook, M. B.; Chapman, K. R.; Kesten, S. (1995) Gas trapping as a predictor of positive methacholine challenge in patients with normal spirometry results. Chest 107(4): 992-5	- Index test in study does not match that specified in the protocol *No protocol index tests used in study*
Zhang, Y., Shi, H., Su, A. et al. (2022) Angle beta combined with FeNO and FEV1/FVC% for the detection of asthma in school-aged children. Journal of Asthma 59(4): 746-754	- Population not relevant to this review protocol *Already diagnosed with asthma*

Clinical and cost effectiveness of spirometry

Studies excluded from the clinical review

No studies identified for full text screening.

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.

Table 10: Studies excluded from the health economic review

Reference	Reason for exclusion
None	