British Thoracic Society

NICE National Institute for Health and Care Excellence

Healthcare Improvement Scotland | SIGN

Final

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

[J] Evidence reviews for bronchial challenge testing in response to exercise for the diagnosis of asthma

BTS/NICE/SIGN collaborative guideline NG245

November 2024

Final

Developed by BTS, NICE and SIGN

Disclaimer

The recommendations in this collaborative guideline represent the view of BTS, NICE and SIGN, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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

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Contents

1 Bronchoconstriction in response to an exercise challenge

1.1 Review question

In people under investigation for asthma, what is the diagnostic accuracy of bronchoconstriction in response to an exercise challenge?

1.1.1 Introduction

Exercise can cause bronchoconstriction (airway narrowing) in people with asthma, by various chemical and cellular mechanisms. In an exercise challenge test, spirometry is measured before and after exercise to evaluate how reactive the airways are. It is important to evaluate the evidence because it is currently the most widely available form of challenge testing in children.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

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

Table 1: PICO characteristics of diagnostic accuracy review question

Population	Inclusion: People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: • Children/young people (5-16 years old) • Adults (≥17 years old) Exclusion: • Children under 5 years old • People on steroid medication (washout period minimum of 4 weeks for inclusion) Stratified by smoking status: • Smokers • Non-smokers • Mixed population
Target condition	Asthma
Index test	Exercise challenge test (>10% FEV1 bronchoconstriction in response to exercise – within 15 mins) 1. Change in FEV1 ≥10% post-exercise (accept 15% and 12% if used by study)
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following:

	• peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) • FeNO Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis. Maximum interval between initial diagnosis and confirmation of asthma diagnosis: 12 months
Statistical measures	• Sensitivity - thresholds: upper 90, lower 10 • Specificity - thresholds: upper 80, lower 50 • Raw data to calculate 2x2 tables to calculate sensitivity and specificity • 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

One prospective cross-sectional study was included in the review (Zaczeniuk, et al., 2015) this is summarised in Table 2 below. Evidence from this study is summarised in the clinical evidence summary below in Table 3 and references in 1.3 References . The assessment of the evidence quality was conducted with emphasis on test sensitivity and specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set clinical decision thresholds as sensitivity: upper= 90% and lower= 10%, specificity: upper= 80% and lower= 50%. Values above the upper threshold indicated a test would be recommended and values below the lower threshold indicated a test is of no clinical use.

See also the study selection flow chart in Appendix C.

1.1.4.2 Excluded studies

Five studies included in the previous NICE guidance on this topic were excluded from this review. All these studies were excluded due to containing a population not relevant to this review protocol as they contained participants with a known diagnosis 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
Zaczeniuk 2015	N=90 middle-school children attending an allergic outpatient clinic because of post-exercise symptoms such as cough or shortness of breath during/after physical education classes Inclusion criteria: Aged 10-18 years with post-exercise asthma symptoms Exclusion criteria: Acute or chronic lung disease, active smoking Age, range: 10-18 years Poland	Asthma	Eight-minute submaximal exercise challenge designed to elicit 95% of predicted max heart rate. FEV_1 was measured before, immediately after, and 3, 6, 10, 15 and 30 minutes after running. Cut-off: >10% decrease in FEV_1 from baseline within 30 minutes after exercise	Diagnosis of asthma based on asthma symptoms, physical examination of the respiratory system and positive reversibility test (≥12% increase in FEV_1 after salbutamol)	Prospective cross-sectional study Strata: Children/young people ICS use: ICS naïve Smoking status: Smokers excluded Indirectness: Downgraded by two increments due to population (inclusion of both children/young people and adolescents/adults with no average reported) and index test (test duration different to protocol-specified value) indirectness

1.1.6 Summary of the diagnostic evidence

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

Table 3: Clinical evidence summary: diagnostic test accuracy of bronchial challenge testing in response to exercise for the diagnosis of asthma in children and young people

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Exercise challenge test (cut-off: >10% reduction in FEV1) vs clinician diagnosis (PPV=65.4%, NPV=79.6%)							
1 cross-sectional study	90	Very serious[1]	Not serious	Very serious[2]	Not serious	Sensitivity= 0.77 (0.61-0.89)	VERY LOW
		Very serious[1]	Not serious	Very serious[2]	Serious[3]	Specificity= 0.69 (0.54-0.81)	VERY LOW

[1] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

[2]Downgraded by two increments due to population and index test indirectness

[3] Downgraded by one increment due to the 95%CI overlapping the threshold corresponding to 'high specificity' (80%)

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 Excluded studies

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

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

1.1.8 Summary of included economic evidence

None.

1.1.9 Economic model

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

1.1.11 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

Clinical and cost effectiveness

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

Diagnostic accuracy

The committee considered the diagnostic measures of sensitivity and specificity of the index test for diagnosing asthma as well as the positive and negative predictive values where these were reported by the studies. Clinical decision thresholds were set by the committee as sensitivity/specificity 0.9 and 0.8 above which a test would be recommended and 0.1 and 0.5 below which a test is of no clinical use. The committee were interested in establishing whether there was an optimal cut-off value of bronchial challenge testing to exercise with sufficiently high sensitivity and specificity to be useful in making a diagnosis of asthma, but also in whether there are separate cut-off values which could usefully help either rule in or rule out an asthma diagnosis.

1.2.2. The quality of the evidence

Clinical and cost effectiveness

No relevant clinical studies were identified comparing the clinical effectiveness of diagnosis of asthma with bronchial challenge in response to exercise.

Diagnostic accuracy

One cross-sectional study, investigating the diagnostic accuracy of exercise challenge testing in children/young people, was included in this review. This study applied a cut-off of a fall in FEV_1 >10% from baseline up to 30 minutes following an eight-minute submaximal running challenge. The evidence identified from this study was of very low quality. Very serious risk of bias was detected due to an unclear method of patient selection, a lack of blinding when interpreting the test results, and missing outcome data. Furthermore, the evidence was downgraded for very serious indirectness due to the inclusion of a mixed group of children/young people and adolescents/adults, and index test indirectness due to the post-exercise monitoring period being 30 minutes, as opposed to 15 minutes as specified in the review protocol.

No evidence was identified for the diagnostic accuracy of bronchial challenge testing in response to an exercise challenge in adolescents/adults.

1.2.3. Benefits and harms

The evidence identified did not support the use of bronchial challenge testing in response to exercise in order to diagnose asthma in children/young people. Very low quality evidence

showed a sensitivity 0.77 and a specificity 0.69, not meeting the decision-making threshold for either outcome.

1.2.4. Cost effectiveness and resource use

No relevant published health economic analyses were identified for this review question. As the committee were concerned about the quality of the clinical evidence available, no unit costs were presented. The committee concluded that exercise testing should not be recommended in the diagnostic pathways (see evidence review 1.11).

1.2.5. Other factors the committee took into account

The committee agreed that exercise testing is rarely used in diagnosis. A formal exercise test requires specialised equipment and therefore referral to secondary care. Moreover, a rigorous test protocol would include means of controlling the temperature and humidity of inspired air, and the necessary equipment and expertise is not available in every secondary care lung function laboratory. Some members of the committee had experience of “rough and ready” exercise provocation which might involve asking a person to run up and down stairs or round part of a hospital’s grounds. Whilst this might generate a fall in a measure of lung function (FEV_1 or PEF) and therefore provide useful information, the non-standardised nature of the exercise clearly makes it impossible to set cut-off values for such a test. Potential safety concerns were also highlighted.

Although the committee did not recommend exercise testing specifically to rule asthma in or out, they acknowledged the usefulness of the test in people with unexplained exercise related breathlessness when numerous potential diagnoses were being considered.

1.2.6. Recommendations supported by the evidence review

No recommendations were made from this evidence review.

1.3 References

Zaczeniuk M, Woicka-Kolejwa K, Stelmach W, et al. (2015) Methacholine challenge testing is superior to the exercise challenge for detecting asthma in children *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 115 (6): 481-484

Appendices

Appendix A – Review protocols

Review protocol for diagnostic test accuracy and clinical and cost-effectiveness of bronchial challenge testing in response to exercise challenge

Field	Content
PROSPERO registration number	CRD42023438844
Review title	Accuracy and clinical and cost-effectiveness of bronchial challenge testing in response to exercise in diagnosis of asthma
Review question	In people under investigation for asthma, what is the diagnostic accuracy and clinical and cost-effectiveness of bronchoconstriction in response to an exercise challenge?
Objective	To evaluate the diagnostic test value of bronchoconstriction in response to an exercise challenge, in diagnosing asthma. This evidence review will have two stages: (1) Identify the clinical and cost effectiveness of diagnosis with the test (test plus treatment) (2) If evidence on clinical effectiveness is limited, the diagnostic accuracy will instead be determined
Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase

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

	Ages stratified into the following 2 groups: • Children/young people (5-16 years old) • Adults (≥17 years old) Exclusion: • Children under 5 years old • People on steroid medication (washout period minimum of 4 weeks for inclusion) Stratification: smokers vs non-smokers vs mixed population
Test	Exercise challenge test (>10% FEV1 bronchoconstriction in response to exercise – within 15 mins) 1. Change in FEV1 ≥10% post-exercise (accept 15% and 12% if used by study) NOTE: usually this is a 6-8 minute exercise challenge test (accept whatever used) <u>Stratification</u> • Different test thresholds
Reference standard	Effectiveness (test-and-treat) • Compare to each other Diagnostic accuracy • Gold standard

	Reference standard: Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) • FeNO Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold. Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis. <u>Stratification</u>: • Different reference standards Maximum interval between initial diagnosis and confirmation of asthma diagnosis: 12 months
Types of study to be included	Clinical effectiveness (test and treat): • Systematic reviews of RCTs • Parallel RCTs Published NMAs and IPDs will be considered for inclusion.

	Diagnostic test accuracy: • Cross sectional studies • Cohort studies will be included
Other exclusion criteria	• Non-English language studies. • Non comparative cohort studies • Before and after studies • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. • Not looking at occupational asthma /allergens • Not looking at tests in athletes • Not looking at other factors which influence signs/symptoms • Studies in which >10% of people are on inhaled and/or systemic corticosteroid treatment • Cross-sectional studies only included if they report sensitivity/specificity or the sensitivity and specificity can be calculated.
Context	Primary, secondary and community care settings
Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making a therefore have all been rated as critical: Clinical effectiveness (test and treat) 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)
	  ○ Acute symptoms (dichotomous outcome reported immediately post test (<10 mins))
	• Inflammatory markers; exhaled nitric oxide (continuous outcome at ≥8 weeks)
	
	Diagnostic accuracy outcomes: Asthma diagnosis
	• Sensitivity
	thresholds: upper 90, lower 10
	• Specificity
	thresholds: upper 80, lower 50

	• Raw data to calculate 2x2 tables to calculate sensitivity and specificity • Negative predictive value (NPV), Positive predictive value (PPV)
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • QUADAS-2 checklist

Strategy for data synthesis	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.	
Analysis of sub-groups	Subgroups for if heterogeneity is present: - Different reference standards	
Type and method of review	☒	Intervention
	☒	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date		
Anticipated completion date	31 July 2024	

Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☐	☐
	Formal screening of search results against eligibility criteria	☐	☐
	Data extraction	☐	☐
	Risk of bias (quality) assessment	☐	☐
	Data analysis	☐	☐
Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail asthmachronicmanagement@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
Review team members	From the National Guideline Centre: Bernard Higgins (Guideline lead) Sharon Swain (Guideline lead) Qudsia Malik (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)
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10186
Other registration details	N/A
Reference/URL for published protocol	N/A
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

Keywords	N/A	
Details of existing review of same topic by same authors	N/A	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	N/A	
Details of final publication	www.nice.org.uk	

Appendix B – Literature search strategies

In people under investigation for asthma, what is the diagnostic accuracy and clinical and cost-effectiveness of bronchoconstriction in response to an exercise challenge

B.1 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 4: 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.	Bronchial Provocation Tests/
25.	(bronchial constrict* or bronchoconstrict* or broncho constrict* or bronchoprovocation or broncho provocation).ti,ab,kf.
26.	((bronchial or airway*) adj3 (provocat* or provok* or challeng* or test* or respons* or breath*)).ti,ab,kf.
27.	((challeng* or provocat* or inhalation or inhaling) adj2 test*).ti,ab,kf.
28.	BCT.ti,ab,kf.
29.	Bronchial Hyperreactivity/
30.	((bronchial or bronchus or airway) adj2 (hyperresponsiv* or hyperreactiv* or hyper-responsiv* or hyper-reactiv*)).ti,ab,kf.
31.	or/24-30
32.	exp Histamine/
33.	Methacholine Chloride/
34.	(histamin* or methacholine*).ti,ab,kf.
35.	provocholine*.ti,ab,kf.
36.	(HCT or MCT).ti,ab,kf.
37.	or/32-36
38.	exp Mannitol/
39.	mannit*.ti,ab,kf.
40.	or/38-39
41.	exp exercise tests/
42.	(exercise adj3 (provocat* or provok* or challeng* or test* or induced or inducing or brochosospasm* or stress or tolerance* or tolerating)).ti,ab,kf.
43.	((treadmill* or step* or bike* or bicycl* or cycl* or walk*) adj2 (test* or exert*)).ti,ab,kf.
44.	ergomet*.ti,ab,kf.
45.	or/41-44
46.	31 or 37 or 40 or 45
47.	23 and 46

48.	exp "sensitivity and specificity"/
49.	(sensitivity or specificity).ti,ab.
50.	((pre test or pretest or post test) adj probability).ti,ab.
51.	(predictive value* or PPV or NPV).ti,ab.
52.	likelihood ratio*.ti,ab.
53.	likelihood function/
54.	((area under adj4 curve) or AUC).ti,ab.
55.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
56.	gold standard.ab.
57.	exp Diagnostic errors/
58.	(false positiv* or false negativ*).ti,ab.
59.	Diagnosis, Differential/
60.	(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.
61.	or/48-60
62.	Epidemiologic studies/
63.	Observational study/
64.	exp Cohort studies/
65.	(cohort adj (study or studies or analys* or data)).ti,ab.
66.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
67.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
68.	Controlled Before-After Studies/
69.	Historically Controlled Study/
70.	Interrupted Time Series Analysis/
71.	(before adj2 after adj2 (study or studies or data)).ti,ab.
72.	exp case control study/
73.	case control*.ti,ab.
74.	Cross-sectional studies/
75.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
76.	or/62-75
77.	randomized controlled trial.pt.
78.	controlled clinical trial.pt.
79.	randomi#ed.ab.
80.	placebo.ab.
81.	randomly.ab.
82.	clinical trials as topic.sh.
83.	trial.ti.
84.	or/77-83
85.	Meta-Analysis/
86.	Meta-Analysis as Topic/
87.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
88.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
89.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

90.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
91.	(search* adj4 literature).ab.
92.	(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.
93.	cochrane.jw.
94.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
95.	or/85-94
96.	47 and (61 or 76 or 84 or 95)

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.	Inhalation Test/
24.	(bronchial constrict* or bronchoconstrict* or broncho constrict* or bronchoprovocation or broncho provocation).ti,ab,kf.
25.	((bronchial or airway*) adj3 (provocat* or provok* or challeng* or test* or respons* or breath*)).ti,ab,kf.
26.	((challeng* or provocat* or inhalation or inhaling) adj2 test*).ti,ab,kf.
27.	BCT.ti,ab,kf.
28.	Bronchus hyperreactivity/
29.	((bronchial or bronchus or airway) adj2 (hyperresponsiv* or hyperreactiv* or hyper-responsiv* or hyper-reactiv*)).ti,ab,kf.
30.	or/23-29
31.	exp Histamine/
32.	Methacholine Chloride/

33.	(histamin* or methacholine*).ti,ab,kf.
34.	provocholine*.ti,ab,kf.
35.	(HCT or MCT).ti,ab,kf.
36.	or/31-35
37.	exp Mannitol/
38.	mannit*.ti,ab,kf.
39.	or/37-38
40.	exp Exercise test/
41.	(exercise adj3 (provocat* or provok* or challeng* or test* or induced or inducing or brochosospasm* or stress or tolerance* or tolerating)).ti,ab,kf.
42.	((treadmill* or step* or bike* or bicycl* or cycl* or walk*) adj2 (test* or exert*)).ti,ab,kf.
43.	ergomet*.ti,ab,kf.
44.	or/40-43
45.	30 or 36 or 39 or 44
46.	22 and 45
47.	exp "sensitivity and specificity"/
48.	(sensitivity or specificity).ti,ab.
49.	((pre test or pretest or post test) adj probability).ti,ab.
50.	(predictive value* or PPV or NPV).ti,ab.
51.	likelihood ratio*.ti,ab.
52.	((area under adj4 curve) or AUC).ti,ab.
53.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
54.	diagnostic accuracy/
55.	diagnostic test accuracy study/
56.	gold standard.ab.
57.	exp diagnostic error/
58.	(false positiv* or false negativ*).ti,ab.
59.	differential diagnosis/
60.	(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.
61.	or/47-60
62.	Clinical study/
63.	Observational study/
64.	Family study/
65.	Longitudinal study/
66.	Retrospective study/
67.	Prospective study/
68.	Cohort analysis/
69.	Follow-up/
70.	cohort*.ti,ab.
71.	69 and 70
72.	(cohort adj (study or studies or analys* or data)).ti,ab.
73.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
74.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.

75.	(before adj2 after adj2 (study or studies or data)).ti,ab.
76.	exp case control study/
77.	case control*.ti,ab.
78.	cross-sectional study/
79.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
80.	or/62-68,71-79
81.	random*.ti,ab.
82.	factorial*.ti,ab.
83.	(crossover* or cross over*).ti,ab.
84.	((doubl* or singl*) adj blind*).ti,ab.
85.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
86.	crossover procedure/
87.	single blind procedure/
88.	randomized controlled trial/
89.	double blind procedure/
90.	or/81-89
91.	Systematic Review/
92.	Meta-Analysis/
93.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
94.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
95.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
96.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
97.	(search* adj4 literature).ab.
98.	(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.
99.	cochrane.jw.
100.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
101.	or/91-100
102.	46 and (61 or 80 or 90 or 101)

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: [Bronchial Provocation Tests] this term only
#7.	(bronchial constrict* or bronchoconstrict* or "broncho constrict*" or bronchoprovocat* or "broncho provocat*"):ti,ab
#8.	((bronchial or airway*) near/3 (provocat* or provok* or challeng* or test* or respons* or breath*)):ti,ab
#9.	((challeng* or provocat* or inhalation or inhaling) near/2 test*):ti,ab
#10.	BCT:ti,ab
#11.	MeSH descriptor: [Bronchial Hyperreactivity] this term only

#12.	((bronchial or bronchus or airway) near/2 (hyperresponsiv* or hyperreactiv* or "hyper responsiv*" or "hyper reactiv*")):ti,ab
#13.	(or #6-#12)
#14.	MeSH descriptor: [Histamine] explode all trees
#15.	MeSH descriptor: [Methacholine Chloride] explode all trees
#16.	(histamin* or methacholine*):ti,ab
#17.	provocholine*:ti,ab
#18.	(HCT or MCT):ti,ab
#19.	(or #14-#18)
#20.	MeSH descriptor: [Mannitol] explode all trees
#21.	mannit*:ti,ab
#22.	(or #20-#21)
#23.	MeSH descriptor: [Exercise Test] explode all trees
#24.	(exercise near/3 (provocat* or provok* or challeng* or test* or induced or inducing or brochosospasm* or stress or tolerance* or tolerating)):ti,ab
#25.	((treadmill* or step* or bike* or bicycl* or cycl* or walk*) near/2 (test* or exert*)):ti,ab
#26.	ergomet*:ti,ab
#27.	(or #23-#26)
#28.	#13 or #19 or #22 or #27
#29.	#5 and #28

Epistemonikos search terms

1.	(title:((bronchial constrict* OR bronchoconstrict* OR "broncho constrict*" OR bronchoprovocat* OR "broncho provocat*")) OR abstract:((bronchial constrict* OR bronchoconstrict* OR "broncho constrict*" OR bronchoprovocat* OR "broncho provocat*"))) OR (title:((bronchial OR airway*) AND (provocat* OR provok* OR challeng* OR test* OR respons* OR breath*)) OR abstract:((bronchial OR airway*) AND (provocat* OR provok* OR challeng* OR test* OR respons* OR breath*))) OR (title:((challeng* OR provocat* OR inhalation OR inhaling) AND test*) OR abstract:((challeng* OR provocat* OR inhalation OR inhaling) AND test*)) OR (title:(bronchial OR bronchus OR airway) AND (hyperresponsiv* OR hyperreactiv* OR hyper-responsiv* OR hyper-reactiv*) OR abstract:(bronchial OR bronchus OR airway) AND (hyperresponsiv* OR hyperreactiv* OR hyper-responsiv* OR hyper-reactiv*)) OR (title:((histamin* OR methacholine*)) OR abstract:((histamin* OR methacholine*))) OR (title:(provocholine*) OR abstract:(provocholine*)) OR (title:(mannit*) OR abstract:(mannit*)) OR (title:(exercise AND (provocat* OR provok* OR challeng* OR test* OR induced OR inducing OR brochosospasm* OR stress OR tolerance* OR tolerating)) OR abstract:(exercise AND (provocat* OR provok* OR challeng* OR test* OR induced OR inducing OR brochosospasm* OR stress OR tolerance* OR tolerating))) OR (title:((treadmill* OR step* OR bike* OR bicycl* OR cycl* OR walk*) AND (test* OR exert*)) OR abstract:((treadmill* OR step* OR bike* OR bicycl* OR cycl* OR walk*) AND (test* OR exert*))) OR (title:(ergomet*) OR abstract:(ergomet*)) AND (title:(asthma*) OR abstract:(asthma*))

B.2 Health economic literature search strategy

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

Table 5: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 29 Dec 2023	
	Modelling 1946 – 29 Dec 2023	
Embase (OVID)	Health Economics 1 January 2014 – 29 Dec 2023	Health economics studies Quality of life studies Modelling Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 29 Dec 2023	
	Modelling 1974 – 29 Dec 2023	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 29 Dec 2023	English language

Medline (Ovid) search terms

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

8.	Anecdotes as Topic/
9.	comment/
10.	case reports/
11.	(letter or comment*).ti.
12.	or/4-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animals/ not humans/
16.	exp Animals, Laboratory/
17.	exp Animal Experimentation/
18.	exp Models, Animal/
19.	exp Rodentia/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/14-20
22.	3 not 21
23.	limit 22 to English language
24.	quality-adjusted life years/
25.	sickness impact profile/
26.	(quality adj2 (wellbeing or well being)).ti,ab.
27.	sickness impact profile.ti,ab.
28.	disability adjusted life.ti,ab.
29.	(qal* or qtime* or qwb* or daly*).ti,ab.
30.	(euroqol* or eq5d* or eq 5*).ti,ab.
31.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
32.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
33.	(hui or hui1 or hui2 or hui3).ti,ab.
34.	(health* year* equivalent* or hye or hyes).ti,ab.
35.	discrete choice*.ti,ab.
36.	rosser.ti,ab.
37.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
38.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
39.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
40.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
41.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
42.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
43.	or/24-42
44.	exp models, economic/
45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/

48.	monte carlo method/
49.	exp Decision Theory/
50.	(markov* or monte carlo).ti,ab.
51.	econom* model*.ti,ab.
52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	Economics/
55.	Value of life/
56.	exp "Costs and Cost Analysis"/
57.	exp Economics, Hospital/
58.	exp Economics, Medical/
59.	Economics, Nursing/
60.	Economics, Pharmaceutical/
61.	exp "Fees and Charges"/
62.	exp Budgets/
63.	budget*.ti,ab.
64.	cost*.ti.
65.	(economic* or pharmaco?economic*).ti.
66.	(price* or pricing*).ti,ab.
67.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
68.	(financ* or fee or fees).ti,ab.
69.	(value adj2 (money or monetary)).ti,ab.
70.	or/54-69
71.	23 and 43
72.	23 and 53
73.	23 and 70

Embase (Ovid) search terms

1.	exp Asthma/
2.	asthma*.ti,ab.
3.	1 or 2
4.	letter.pt. or letter/
5.	note.pt.
6.	editorial.pt.
7.	case report/ or case study/
8.	(letter or comment*).ti.
9.	(conference abstract or conference paper).pt.
10.	or/4-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11

13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice or rodent*).ti.
20.	or/12-19
21.	3 not 20
22.	limit 21 to English language
23.	quality adjusted life year/
24.	"quality of life index"/
25.	short form 12/ or short form 20/ or short form 36/ or short form 8/
26.	sickness impact profile/
27.	(quality adj2 (wellbeing or well being)).ti,ab.
28.	sickness impact profile.ti,ab.
29.	disability adjusted life.ti,ab.
30.	(qal* or qtime* or qwb* or daly*).ti,ab.
31.	(euroqol* or eq5d* or eq 5*).ti,ab.
32.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
33.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
34.	(hui or hui1 or hui2 or hui3).ti,ab.
35.	(health* year* equivalent* or hye or hyes).ti,ab.
36.	discrete choice*.ti,ab.
37.	rosser.ti,ab.
38.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
39.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
40.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
41.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
42.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
43.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
44.	or/23-43
45.	statistical model/
46.	exp economic aspect/
47.	45 and 46
48.	*theoretical model/
49.	*nonbiological model/
50.	stochastic model/
51.	decision theory/
52.	decision tree/

53.	monte carlo method/
54.	(markov* or monte carlo).ti,ab.
55.	econom* model*.ti,ab.
56.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
57.	or/47-56
58.	health economics/
59.	exp economic evaluation/
60.	exp health care cost/
61.	exp fee/
62.	budget/
63.	funding/
64.	budget*.ti,ab.
65.	cost*.ti.
66.	(economic* or pharmaco?economic*).ti.
67.	(price* or pricing*).ti,ab.
68.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
69.	(financ* or fee or fees).ti,ab.
70.	(value adj2 (money or monetary)).ti,ab.
71.	or/58-70
72.	22 and 44
73.	22 and 57
74.	22 and 71

NHS EED and HTA (CRD) search terms

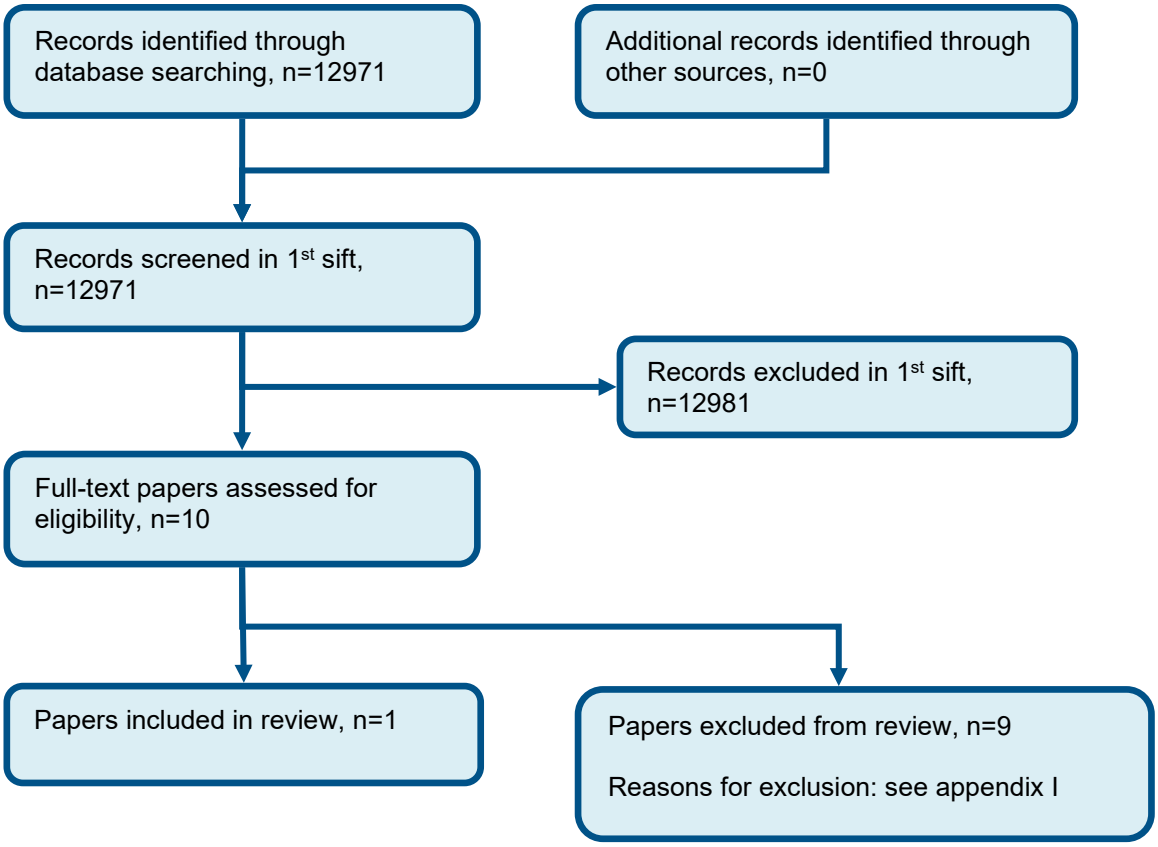
#1.	MeSH DESCRIPTOR Asthma EXPLODE ALL TREES
#2.	(asthma*)
#3.	#1 OR #2

INAHTA search terms

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

Appendix C –Diagnostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of bronchial challenge testing in response to exercise challenge



Appendix D –Diagnostic evidence

Reference	**Zaczeniuk 2015 (Zaczeniuk et al., 2015)**
Study type	Prospective cross-sectional study
Study methodology	Data source: Middle-school children attending an allergic outpatient clinic because of post-exercise symptoms such as cough and shortness of breath during after physical education classes Recruitment: January 2013-December 2014, method not reported
Number of patients	n = 90
Patient characteristics (per protocol)	Age, range: 10-18 years Gender: 37.6% male, 62.4% female Smoking status: Active smokers excluded Ethnicity: Not reported ICS use: Therapy naïve Setting: Secondary care Country: Poland Inclusion criteria: Aged 10-18 years, post-exercise asthma symptoms Exclusion criteria: Acute or chronic lung diseases, active smoking
Target condition(s)	Asthma
Index test(s) and reference standard	Index test Exercise-induced bronchoconstriction was tested using a motor-driven treadmill according to American Thoracic Society and European Respiratory Society guidelines. The children were instructed to run for 8 minutes with a submaximal exercise load. The exercise test consisted of a 2- minute warmup and 6 minutes of steady-state running on a treadmill inclined to produce a heart rate at least 95% of the

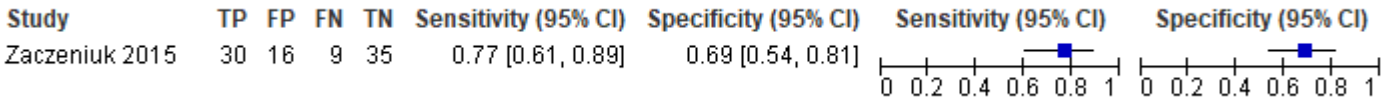
<table>
<tr><td>Reference</td><td colspan="4">Zaczeniuk 2015 (Zaczeniuk et al., 2015)</td></tr>
<tr><td></td><td colspan="4">maximum predicted for age. The slope of the treadmill was 5.5%. Small adjustments in workload were made, if necessary, to achieve targeted heart rates. Nasal clips were used during the test, and heart rate was continuously monitored. FEV_1 was measured before running, immediately after, and 3, 6, 10, 15, 20 and 30 minutes after running. Maximum percentage of decrease in FEV1 after exercise challenge test was calculated by the following formula: ([pre-exercise FEV_1 - lowest postexercise FEV_1] / pre-exercise FEV_1) x 100. Exercise induced bronchoconstriction was defined as a decrease in FEV_1 greater than 10% from baseline within 30 minutes after the exercise.

<u>Reference standard</u>
Diagnosis of asthma was established by symptoms of asthma, physical examination findings of the respiratory system, and positive reversibility test findings. Positive reversibility test result was defined as improvement of at least 12% of pre-bronchodilator FEV_1 after administration of salbutamol.

Time between measurement of index test and reference standard: One-week</td></tr>
<tr><td>2×2 table</td><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td></tr>
<tr><td></td><td>Index test +</td><td>30</td><td>16</td><td>46</td></tr>
<tr><td></td><td>Index test −</td><td>9</td><td>35</td><td>44</td></tr>
<tr><td></td><td>Total</td><td>39</td><td>51</td><td>90</td></tr>
<tr><td>Statistical measures</td><td colspan="4"><u>Index text</u>
Sensitivity: 0.77 (95%CI 0.61-0.89)
Specificity: 0.69 (95%CI 0.54-0.81)
PPV: 65.4%
NPV: 79.6%</td></tr>
<tr><td>Source of funding</td><td colspan="4">This study was supported by the National Science Centre and the Medical University of Lodz.</td></tr>
<tr><td>Limitations</td><td colspan="4">Risk of bias: Downgraded by two increments due to concerns arising from patient selection (recruitment method unclear), the interpretation of the index test and reference standard (unclear if blinded) and the flow and timing of patients through the study (11 patients excluded due to missing test data)
Indirectness: Downgraded by two increments due to population (inclusion of both children/young people and adolescents/adults with no average reported) and index test (>10% reduction in FEV_1 measured over 30 minutes, protocol specified 15 minutes) indirectness</td></tr>
</table>

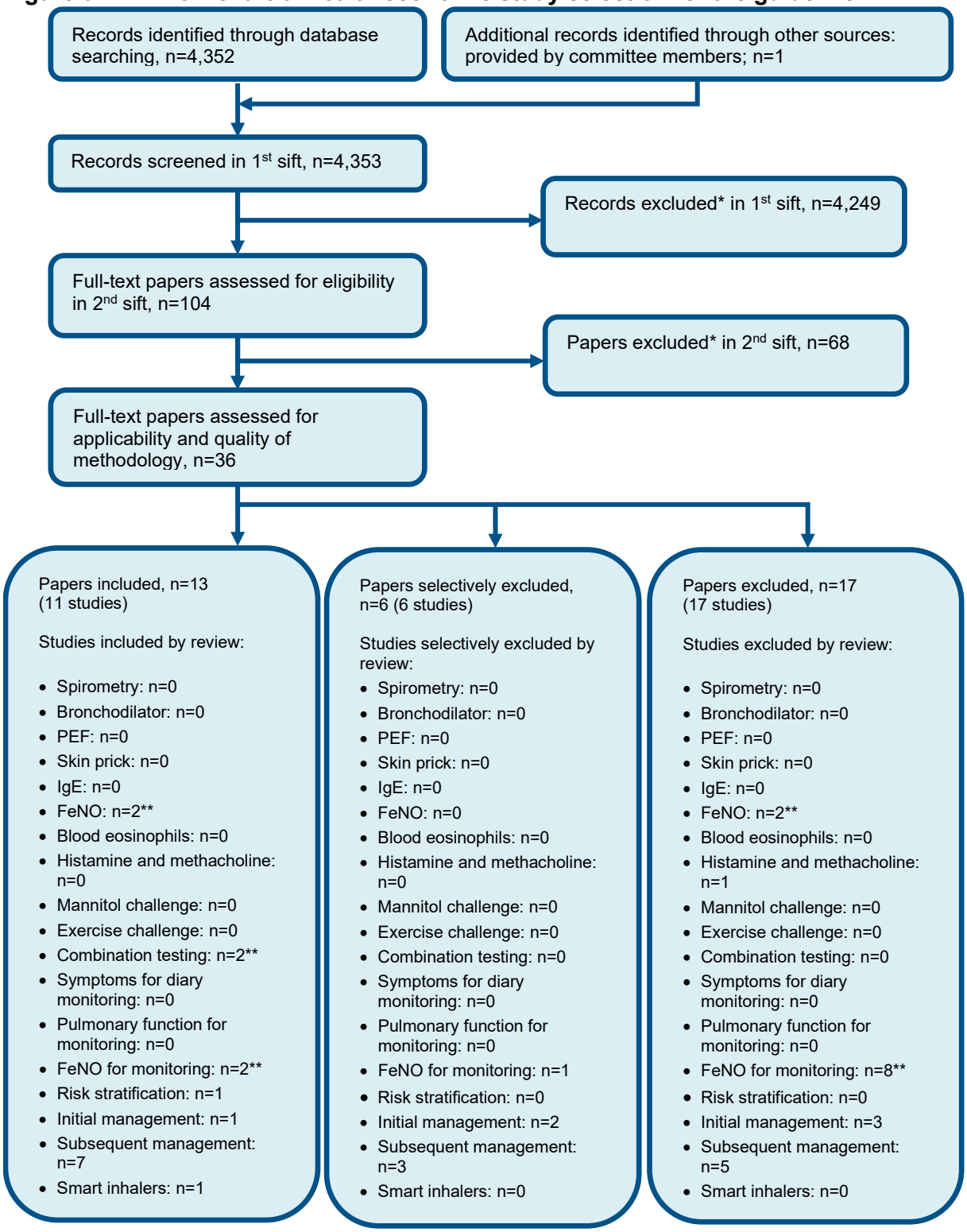
Appendix E - Forest plots

Figure 2: Exercise challenge test (cut-off: >10% reduction in FEV_1) vs clinician diagnosis in children and young people



Appendix F – Economic evidence study selection

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



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

** Includes studies that are in multiple reviews

Appendix G – Economic evidence tables

None.

Appendix H – Excluded studies

Clinical studies

Table 6: Studies excluded from the clinical review

Study	Code [Reason]
Ahmed, Safia and Handa, Ajay (2021) Diagnostic value of bronchoprovocation challenge with adenosine monophosphate versus exercise testing in early diagnosis of asthma. Medical journal, Armed Forces India 77(1): 46-50	- Reference standard not relevant to this review protocol *Objective test (adenosine monophosphate challenge) used without clinician diagnosis*
Csonka, Leon, Tikkakoski, Antti, Tikkakoski, Anna P et al. (2023) Relation of changes in PEF and FEV1 in exercise challenge in children. Clinical physiology and functional imaging	- Population not relevant to this review protocol *56% of participants diagnosed with asthma prior to study entry*
Feng, Yong, Zhang, Shiyao, Shang, Yunxiao et al. (2022) The Use of Exercise Challenge Testing and Fractional Exhaled Nitric Oxide in Diagnosis of Chest Tightness Variant Asthma in Children. International archives of allergy and immunology 183(7): 762-769	- Reference standard not relevant to this review protocol *Clinical improvement with treatment used as reference standard. No objective test.*
Gerald, L.B., Redden, D., Turner-Henson, A. et al. (2002) A multi-stage asthma screening procedure for elementary school children. Journal of Asthma 39(1): 29-36	- Population not relevant to this review protocol *Participants not presenting with respiratory symptoms*
Haby, M M, Anderson, S D, Peat, J K et al. (1994) An exercise challenge protocol for epidemiological studies of asthma in children: comparison with histamine challenge. The European respiratory journal 7(1): 43-9	- Population not relevant to this review protocol *Participants not presenting with respiratory symptoms*
Haby, M M, Peat, J K, Mellis, C M et al. (1995) An exercise challenge for epidemiological studies of childhood asthma: validity and repeatability. The European respiratory journal 8(5): 729-36	- Duplicate reference
Henriksen, Anne Hildur, Tveit, Kjerst Hafstad, Holmen, Turid Lingaas et al. (2002) A study of the association between exercise-induced wheeze and exercise versus methacholine-induced bronchoconstriction in adolescents. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 13(3): 203-8	- Reference standard not relevant to this review protocol *Objective test (methacholine challenge) without clinician diagnosis*

Study	Code [Reason]
Luntsov, A. and Skorokhodkina, O. (2012) A diagnostic program for bronchial asthma including allergen challenge and exercise bronchoprovocation testing in young patients. Allergy: European Journal of Allergy and Clinical Immunology 67(suppl96): 454	- Conference abstract
Reier-Nilsen, Tonje, Stang, Julie Sorbo, Flatsetoy, Hanne et al. (2023) Unsupervised field-based exercise challenge tests to support the detection of exercise-induced lower airway dysfunction in athletes. BMJ open sport & exercise medicine 9(3): e001680	- Population not relevant to this review protocol *43% of participants diagnosed with asthma prior to study entry*

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 7: Studies excluded from the health economic review

Reference	Reason for exclusion
None	