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Early View

Task force report

European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5–16 years

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Title:

European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5 to 16 years

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Glossary

AHR	Airway hyperresponsiveness
BDR	Bronchodilatator reversibility
BTS/SIGN	British Thoracic Society/Scottish Intercollegiate Guidelines Network
ELF	European Lung Foundation
EtD	Evidence to Decision
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in the first second

FVC	Forced Vital Capacity
FEV_1/FVC	Ratio of FEV1 over FVC
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
ICS	Inhaled corticosteroids
LABA	Long acting $beta_2$ agonists
LLN	Lower limits of normal
LTRA	Leukotriene receptor antagonists
NICE	National Institute for Health and Care Excellence
PC_{20}	Provocative concentration leading to a fall of 20% in FEV1
PD_{20}	Provocative dose leading to a fall of 20% in FEV1
ppb	Parts per billion
PEFR	Peak Expiratory Flow Rate
SABA	Short acting $beta_2$ agonists
TF	Task Force

Abstract

Diagnosing asthma in children represents an important clinical challenge. There is no single gold standard test to confirm the diagnosis. Consequently, both over-, and under-diagnosis of asthma are frequent in children.

A Task Force (TF) supported by the European Respiratory Society has developed these evidence-based clinical practice guidelines for the diagnosis of asthma in children aged 5 to 16 years using nine PICO (Population, Intervention, Comparator and Outcome) questions. The TF conducted systematic literature searches for all PICO questions and screened the outputs from these, including relevant full text articles. All TF members approved the final decision for inclusion of research papers. The TF assessed the quality of the evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.

The TF then developed a diagnostic algorithm based on the critical appraisal of the PICO questions, preferences expressed by lay members and test availability. Proposed cut-offs were determined based on the best available evidence. The TF formulated recommendations using the GRADE Evidence to Decision framework.

Based on the critical appraisal of the evidence and the Evidence to Decision Framework the TF recommends spirometry, bronchodilator reversibility testing and FeNO as first line diagnostic tests in children under investigation for asthma. The TF recommends against diagnosing asthma in children based on clinical history alone or following a single abnormal objective test. Finally, this guideline also proposes a set of research priorities to improve asthma diagnosis in children in the future.

239 of 250 words

Twitter: International ERS clinical practice guidelines recommend a combination of objective tests including spirometry, bronchodilator reversibility, fraction of exhaled nitric oxide and bronchial challenge testing to diagnose asthma in children aged 5 to 16 years.

Introduction

Asthma is the commonest chronic respiratory condition affecting approximately 5.5 million children in the European Union. (1) In many European healthcare settings the diagnosis is based on clinical history and examination without further tests.
Several recent reports from Europe and North America have highlighted a high rate of asthma misdiagnosis, including over- and under-diagnosis. (2-10)

Misdiagnosis in children often arises because respiratory symptoms are common in this age group. These are frequently non-specific (11) and often represent episodes of viral respiratory tract infections (12,13). Some of these can be prolonged with clinical symptoms similar to asthma. Getting the correct diagnosis in children matters because over-diagnosis frequently results in over-treatment with corticosteroids (6,14) with implications for health care costs (15), the risk of unnecessary side-effects and, in some cases, delay in establishing an important alternative diagnosis. Under-diagnosis with under-treatment of asthma results in unnecessary morbidity, poor quality of life and increased mortality in low resource settings. (16,17)

Many asthma guidelines (18-20) recommend the use of objective tests to confirm the diagnosis in symptomatic patients. Spirometry, bronchodilator reversibility testing (BDR) and measurements of peak flow variability are recommended in some form by all the guidelines. UK National Institute for Health and Care Excellence (NICE) asthma guidelines also recommend the use of FeNO. (20) Recommendations on the hierarchy and timing of objective tests varies considerably between guidelines. This has resulted in variation of diagnostic tests used across Europe and across different healthcare settings within individual countries.

Importantly, to date there are no child focused evidence-based asthma diagnostic guidelines. The usual approach is to produce joint adult and paediatric asthma guidelines and this often results in extrapolation from adult data where there is a lack of evidence in children. However, tests employed in adults under investigation for asthma may not be appropriate in children and the best cut-offs for many of the tests may not be the same in children and adults. This makes child focused guidelines for the diagnosis of asthma essential.

The aim of this TF was to systematically review the evidence that supports the use of tests commonly used across Europe to diagnose asthma in children and to propose evidence-based clinical practice recommendations for the diagnosis of asthma in children aged five to 16 years.

Methods

The methods are described in detail in the supplementary material.

TF composition

The panel consisted of a multidisciplinary group including paediatricians, primary care physicians, researchers, patients and patient representatives. All members of the TF have either recognised clinical experience in the diagnosis of asthma practicing in various regions of Europe or personal experience with asthma as patients or are caregivers of children with asthma. Junior members and trainees affiliated with European paediatric asthma centres were active members of the committee (supplementary table 1).

Methodologists from the ERS provided expertise in guideline development following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach for diagnostic tests (21). Panel members disclosed potential conflicts of interest according to ERS policies at the start of the TF and prior to publication of this manuscript.

Patient and parent representatives recruited to the TF through the European Lung Foundation (ELF) were involved from the beginning. They commented on the selection and scope of the PICO questions, attended meetings, commented on the hierarchy of tests, contributed to the discussions relating to the Evidence to Decision (EtD) for each PICO question and approved the final diagnostic algorithm. All the recommended tests to support asthma diagnosis were acceptable to patients and carers.

The TF was organised into four core centres (Leicester, Zurich, Bern and Aberdeen), each with PICO leads and junior members. The core centres divided the PICO questions between themselves. The other members of the TF each aligned themselves to two or three PICO questions so that each PICO was supported by a TF subgroup consisting of a core centre and additional TF members. The numbers in each PICO TF subgroup were evenly distributed. Junior members performed the initial screening of the outputs from the systematic literature reviews, coordinated the final selection of research papers and performed the initial quality of evidence assessment for each selected research

paper. The other PICO subgroup members supported the PICO groups and were involved in selecting and approving the included research papers and reviewing the quality of the evidence. The whole TF was involved in all the key decisions such as selection of PICO questions, agreed recommendations for each PICO question, and the drafting and agreement on the diagnostic algorithm.

Formulation of the review questions

Review questions were formulated using the **P**opulation, **I**ntervention, **C**omparator and **O**utcome (PICO) format. The chairs initially proposed eight PICO questions based on common clinical practice in Europe. Early on during the TF, members discussed each PICO question to evaluate whether it should be included. The PICO questions were discussed during several rounds of telephone conferences and email discussions. Nine PICO questions were finally agreed at the first face-to-face TF meeting in 2018 (table 1).

Table 1: The list of PICO questions that this TF sought to answer with their respective comparator or reference standard.

PICO questions	**Comparator/Reference standard**
PICO 1. In children aged 5-16 years under investigation for asthma, should the presence of the symptoms wheeze, cough and breathing difficulty be used to diagnose asthma?	Doctor diagnosis of asthma **and** one of the following: Obstructive spirometry, bronchodilator reversibility, challenge testing, FeNO, two-week PEFR variability.
PICO 2. *In children aged 5-16 years under investigation for asthma, should an improvement in symptoms following a trial of preventer medication be used to diagnose asthma?*	Doctor diagnosis of asthma **and** one of the following: Obstructive spirometry, bronchodilator reversibility, challenge testing, FeNO, two-week PEFR variability.
PICO 3. *In children aged 5-16 years under investigation for asthma, should spirometry testing be used to diagnose asthma?*	Doctor diagnosis of asthma **and** one of the following: Challenge testing, bronchodilator reversibility, FeNO, two-week PEFR variability.
PICO 4. *In children aged 5-16 years under investigation for asthma, should bronchodilator reversibility (BDR) testing be used to diagnose asthma?*	Doctor diagnosis of asthma **and** one of the following: Challenge testing, FeNO, two-week PEFR variability.
PICO 5. *In children aged 5-16 years under investigation for asthma, should FeNO testing be used to diagnose asthma?*	Doctor diagnosis of asthma **and** one of the following: Obstructive spirometry, bronchodilator reversibility, challenge testing, two-week PEFR variability.

PICO 6. *In children aged 5-16 years under investigation for asthma, should peak expiratory flow rate (PEFR) variability be used to diagnose asthma?*	Doctor diagnosis of asthma **and** one of the following: Obstructive spirometry, bronchodilator reversibility, challenge testing, FeNO.
PICO 7. *In children aged 5-16 years under investigation for asthma, should allergy testing be used to diagnose asthma?**	Doctor diagnosis of asthma **and** one of the following: Obstructive spirometry, bronchodilator reversibility, challenge testing, FeNO, two-week PEFR variability.
PICO 8. *In children aged 5-16 years under investigation for asthma, should direct bronchial challenge testing including methacholine and histamine be used to diagnose asthma?*	Doctor diagnosis of asthma **and** one of the following: Obstructive spirometry, bronchodilator reversibility, FeNO, two-week PEFR variability.
PICO 9. *In children aged 5-16 years under investigation for asthma, should indirect bronchial challenge testing including exercise and mannitol be used to diagnose asthma?*	Doctor diagnosis of asthma **and** one of the following: Obstructive spirometry, bronchodilator reversibility, FeNO, two-week PEFR variability.

*food allergens were not included

Systematic literature review

For each PICO question, a systematic literature review was carried out and eligible papers had to include the diagnostic test in question plus at least one other objective test. For each question, the outcomes were diagnostic accuracy; sensitivity and specificity.

Librarians experienced with systematic reviews based at University Hospitals Leicester (UK) performed the systematic literature searches for all PICO questions covering the period from 1st January 1980 to 31st August 2019. They searched the Medline (via OVID), Cochrane and Embase databases. Supplementary searches were undertaken by checking the references of included papers and by asking TF members if they were aware of additional papers not identified by the searches. The full details of all the searches are provided in the supplementary material.

Screening of search results

At least two TF members from each core group reviewed all the titles and abstracts identified by each of the literature searches. They agreed on the inclusion of full-text manuscripts. The screening results were shared with the TF PICO group for comments. The whole TF discussed and agreed the

final selection of studies included for each PICO question during a face-to-face meeting. Research papers were only included if all the TF members agreed that they fulfilled the *a priori* inclusion criteria. PRISMA flow diagrams showing the search process for each PICO question are available in supplementary figure 1A-H. Tables listing all the full-text articles, which were screened, are shown in in the supplementary material.

Study designs: In clinical practice, caregivers bring children with respiratory symptoms to the doctor. These symptoms may be compatible with a diagnosis of asthma. Confirming or refuting the diagnosis represents a clinical challenge due to the absence of a gold standard test. Therefore, we only included studies that replicated this clinical scenario and included studies that had followed consecutive patients with relevant respiratory symptoms referred for asthma diagnosis. The diagnosis was then either confirmed or excluded using objective tests. This approach also allowed us to calculate the sensitivity and specificity of the index test. We excluded case control studies for this reason. We included cohort studies.

Reference standard

In the absence of a universally accepted reference standard for the diagnosis of asthma, the TF agreed to accept a "doctor diagnosis of asthma" supported by at least one abnormal comparator test as the standard with which to compare the index test of interest for each PICO. This standard was chosen for the following reasons: A diagnosis made by a doctor following a careful medical history and clinical examination is an important criterion for a diagnosis of asthma. However, studies have shown that a diagnosis of asthma based on this approach results in considerable rates of misdiagnosis in children (3). Therefore, a doctor diagnosis had to be supported by at least one abnormal objective test. The TF agreed on the following comparator tests: Spirometry, BDR, FeNO, two-week PEFR variability test, direct and indirect bronchial challenge tests.

The TF agreed not to include "trial of treatment" and "allergy testing" as comparator tests but to evaluate the usefulness of a "trial of treatment" and "allergy testing" to diagnose asthma in children as separate PICO questions instead.

We have addressed important aspects relating to asthma diagnosis such as hierarchy and timing of objective tests, cut off points of objective tests and confounders. Because we did not formally assess the evidence for these aspects, we present the results based on the Delphi process and discussions using the Evidence to Decision (EtD) tables without making formal recommendations.

Quality of evidence and strength of recommendations

We used the GRADE approach through the entire process, from grading the quality of the evidence, to determining the strength of the recommendations. GRADE represents a rigorous methodology to evaluate the quality of evidence and is considered the gold standard for grading the strength of evidence-based recommendations in health care due to its structured approach and transparency. In keeping with the GRADE approach, we formulated from the outset clear clinical PICO questions. TF members assessed the quality of the evidence by evaluating risk of bias, indirectness, inconsistency, imprecision, and other factors (22-26).

The TF based recommendations for the asthma diagnostic algorithm on the strength of the evidence, test availability and factors such as sensitivity and specificity of the index test. Using the EtD framework (27) the TF considered additional factors such as test availability, feasibility and patient and caregiver acceptability and access to specialist tests. The GRADE and EtD tables for all the PICO questions are shown in the online supplement.

Patient and caregiver important perspectives

The GRADE approach emphasises the importance of recommendations based on the impact on patient-important outcomes (25). The patient representatives of the TF fully endorsed that an accurate diagnosis was an important outcome, because it leads to a better recognition of their child's problems by physicians. Patient representatives stated that this would lead to treatment that is more effective, would reduce overtreatment in some children and generally improve health and quality of life. However, diagnostic accuracy studies do not provide direct evidence for the improvement of patient-important outcomes; consequently, the confidence in results of test accuracy studies can be judged, at best, as moderate.

Development of recommendations and the diagnostic algorithm

The TF used the EtD framework (27) as well as an informal consensus development method (28) to agree each recommendation and to build the diagnostic algorithm. This involved a face-to-face meeting where the whole TF discussed and agreed the recommendations and the tests

recommended to support a diagnosis of asthma in children, based on the literature searches, the 'GRADEing' of the evidence and the EtD framework.

Once the provisional recommendations and the building blocks of the diagnostic algorithm were agreed, the TF used free discussion to reach consensus and agree a provisional hierarchy of tests and a prototype diagnostic algorithm.

In order to obtain the most reliable consensus of opinion of our expert group we employed a modified Delphi process using repeated iterative online voting (29). All the recommendation statements and all the steps of the diagnostic algorithm that had been developed and discussed at the face-to-face meeting were listed in an online questionnaire and circulated to the whole TF. In each round, panel members were asked to mark "agree" or "disagree" beside each statement, and provide comments. Recommendation statements and the diagnostic algorithm were modified after each round. The whole TF finally approved the final version after three rounds of online voting. Responses were not anonymous and the TF defined consensus *a priori* as agreement by 75% or more of the participants.

Results

Results of literature reviews and TF recommendations

Definition of asthma: Several definitions exist. (18,30,31) The TF agreed on the following definition of asthma: Asthma is a disease that includes the symptoms of wheeze, cough and breathing difficulty together with reversible airways obstruction, airway inflammation and bronchial hyper-responsiveness. However, asthma is a heterogeneous and variable condition and frequently not all of the above are present in each individual patient at the same time.
The TF emphasizes that the words to describe asthma symptoms vary considerably depending on language, culture, education and age of the patient. In addition, young children may describe pain in the abdomen due to difficulty pinpointing the lungs. The results of the evidence assessment gave rise to the recommendations listed in table 2.

Table 2: Evidence-based recommendations for the use of each of the tests considered for asthma diagnosis in children aged 5-16 years in primary, secondary or tertiary care.

PICO 1: *In children aged 5-16 years under investigation for asthma, should the presence of the symptoms wheeze, cough and breathing difficulty be used to diagnose asthma?* • The TF recommends against diagnosing asthma based on symptoms alone (strong recommendation against the intervention, moderate quality of evidence) Remarks: 1. Recurrent wheeze, cough and breathing difficulty are key symptoms of asthma. The TF considers a history of recurrent reported wheeze or wheeze on auscultation as the most important symptom of asthma 2. Children with chronic cough (i.e. cough for more than 4 weeks) as the only symptom are unlikely to have asthma and should be investigated according to the ERS guidelines for chronic cough in children (32) and a referral for further investigations to exclude differential diagnoses should be considered
PICO 2: *In children aged 5-16 years under investigation for asthma, should an improvement in symptoms following a trial of preventer medication be used to diagnose asthma?* • The TF recommends against using an improvement in symptoms after a trial of preventer medication alone to diagnose asthma (conditional recommendation against the intervention,

based on clinical experience)

Remarks:

1. The TF did not find any evidence for or against a trial of preventer medication to diagnose asthma in children aged 5 to 16 years
2. Despite the lack of evidence, based on clinical experience, the TF members agreed that a trial of preventer medication can be considered; but only in symptomatic children with abnormal spirometry and negative bronchodilatator response. In such cases, the objective tests spirometry and, if indicated, BDR should be repeated after 4 to 8 weeks

PICO 3: *In children aged 5-16 years under investigation for asthma, should spirometry testing be used to diagnose asthma?*

- The TF recommends to perform spirometry as part of the diagnostic work-up of children aged 5-16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence)

Remarks:

1. An FEV_1/FVC < lower limit of normal (LLN) or < 80%, or an FEV_1 < LLN, or < 80% predicted should be considered supportive of an asthma diagnosis. It is important to be aware that not all children are able to perform a sufficient FVC manoeuvre resulting in a false normal FEV_1/FVC ratio
2. A normal spirometry result does not exclude asthma

PICO 4: *In children aged 5-16 years under investigation for asthma, should bronchodilator reversibility (BDR) testing be used to diagnose asthma?*

- The TF recommends BDR testing in all children with FEV_1 < LLN or < 80% predicted and/or FEV_1/FVC < LLN or < 80% predicted (strong recommendation for the intervention, based on clinical experience)

Remarks:

1. Consider an increase in FEV_1 ≥ 12% and/or 200 ml following inhalation of 400 micrograms of a short acting beta2-agonist as diagnostic of asthma
2. A BDR < 12% does not exclude asthma
3. Most TF members consider BDR testing when baseline spirometry is normal if the clinical

history is strongly suggestive of asthma

PICO 5: *In children aged 5-16 years under investigation for asthma, should FeNO testing be used to diagnose asthma?*

- The TF recommends to measure FeNO as part of the diagnostic work-up of children aged 5 to 16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence)

Remarks:

1. A FeNO value ≥ 25ppb in a child with asthma symptoms should be considered as supportive of a diagnosis of asthma
2. A FeNO value < 25ppb does not exclude asthma

PICO 6: *In children aged 5-16 years under investigation for asthma, should peak expiratory flow rate (PEFR) variability be used to diagnose asthma?*

- The TF recommends against PEFR variability testing as the primary objective test on its own to diagnose asthma in children aged 5-16 years (conditional recommendation against the intervention, moderate quality of evidence)

Remarks:

1. Other objective tests are preferred but a PEFR variability test can be considered in healthcare settings lacking other objective tests
2. If a PEFR variability test is used the result should be based on two weeks of measurements, ideally using electronic peak flow meters
3. A cut-off of ≥ 12% in PEFR variability should be considered a positive test
4. A PEFR variability of <12% does not exclude asthma

PICO 7: *In children aged 5-16 years under investigation for asthma, should allergy testing be used to diagnose asthma?*

- The TF recommends against the use skin prick tests to aeroallergens as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence)
- The TF recommends against the use of serum total and specific IgE tests as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence)

PICO 8: *In children aged 5-16 years under investigation for asthma, should direct bronchial challenge testing including methacholine and histamine be used to diagnose asthma?*

- The TF recommends a direct bronchial challenge test using methacholine in children aged 5-16 years under investigation for asthma where asthma diagnosis could not be confirmed with first line objective tests. (conditional recommendation for the intervention, low quality evidence)

Remarks:

1. A provocative concentration of methacholine that results in a 20% drop in FEV_1 (PC_{20}) value of 8 mg/ml or less should be considered as a positive test
2. The TF found no evidence for or against performing histamine challenge tests in children under investigation for asthma

PICO 9: *In children aged 5-16 years under investigation for asthma, should indirect bronchial challenge testing including exercise and mannitol be used to diagnose asthma?*

- The TF recommends an indirect bronchial challenge test using a treadmill or a bicycle in children aged 5-16 years under investigation for asthma with exercise related symptoms where asthma diagnosis could not be confirmed with first line objective tests. (conditional recommendation for the intervention, moderate quality evidence)

Remarks:

1. A fall in FEV_1 of > 10% from baseline should be taken as a positive test
2. A mannitol challenge can be considered as an alternative to exercise challenge. However due to its limited availability in most countries, and the fact that children often find the test unpleasant, mannitol challenge should be best avoided in favour of other challenge tests

Results of the literature reviews and TF recommendations for PICO 1 to 9

PICO 1 - *In children aged 5-16 years under investigation for asthma, should the presence of the symptoms wheeze, cough and breathing difficulty be used to diagnose asthma?*

Recommendation

- The TF recommends against diagnosing asthma based on symptoms alone (strong recommendation against the intervention, moderate quality of evidence)

Remarks

1. Recurrent wheeze, cough and breathing difficulty are key symptoms of asthma. The TF considers a history of recurrent reported wheeze or wheeze on auscultation as the most important symptom of asthma
2. Children with chronic cough (i.e. cough for more than 4 weeks) as the only symptom are unlikely to have asthma and should be investigated according to the ERS guidelines for chronic cough in children (32) and a referral for further investigations to exclude differential diagnoses should be considered

Background

Asthma symptoms vary over time and may respond to bronchodilator treatment. Wheeze is a key feature of asthma but the term is poorly understood by clinicians and patients (33). Wheeze is a soft polyphonic noise or whistling sound heard mainly during expiration and is caused by turbulent airflow occurring simultaneously in many airways of different calibre. Parents often describe stridor and rattles as wheeze. Moreover, the word wheeze does not have an equivalent in many languages (34). Other symptoms that caregivers often report are cough and breathing difficulty with or without exercise. Most asthma definitions include the presence of respiratory symptoms such as wheeze, cough, breathing difficulty and others.

Review of evidence directly addressing PICO 1

We included four observational published studies (from Switzerland, Inner Mongolia, Netherlands and Brazil) that fulfilled inclusion criteria (supplementary table 2). All four reported the relationship between reported wheeze and subsequent asthma diagnosis (table 3). (35-38). Wheeze, cough and breathing difficulty was by parental/caregiver report in all four studies. Any prior ICS treatment was withheld for three days before lung function testing in one study (35), ≥ one month in a second

study (36) and not mentioned in the remaining two. Overall, the sensitivity of wheeze to correctly identify a child with asthma ranged between 0.55 and 0.86 and the specificity between 0.64 and 0.90 (supplementary table 3 and 5). Cough and breathing difficulty were much less specific for asthma ranging from very low to low depending on the study. Results for breathing difficulty were variable and this symptom generally was very non-specific.

Justification of the recommendation

Overall, the sensitivity of wheeze to correctly identify a child with asthma ranged between 0.55 and 0.86 and the specificity between 0.64 and 0.90. Using the presence of the symptoms wheeze, cough and breathing difficulty alone results in misdiagnosis in a considerable number of children. The Task Force agreed that sensitivity and specificity of wheeze was not strong enough to confirm a diagnosis of asthma on its own.

Cough and breathing difficulty are non-specific symptoms and should not be used to diagnose asthma (supplementary table 4 and 5).

Key unanswered questions and future research needs

Further studies are needed that combine symptoms with other predictors of asthma such as the presence of other atopic features, family history etc. to test whether this increases the sensitivity and /or specificity of symptoms to diagnose asthma. Further studies are also needed investigating the diagnostic accuracy of wheeze heard by a medical doctor and video recordings of wheezing children made by parents or carers.

PICO 2 – In children aged 5-16 years under investigation for asthma, should an improvement in symptoms following a trial of preventer medication be used to diagnose asthma?

Recommendation

- The TF recommends against using an improvement in symptoms after a trial of preventer medication alone to diagnose asthma (conditional recommendation against the intervention, based on clinical experience)

Remarks

1. The TF did not find any evidence for or against a trial of preventer medication to diagnose asthma in children aged 5 to 16 years
2. Despite the lack of evidence, based on clinical experience, the TF members agreed that a trial of preventer medication can be considered; but only in symptomatic children with abnormal

spirometry and negative bronchodilatator response. In such cases, the objective tests spirometry and, if indicated, BDR should be repeated after 4 to 8 weeks

Background

A trial of preventer medication with inhaled corticosteroids (ICS), either alone or in combination with a long-acting beta-2 agonist (LABA), or leukotriene receptor antagonist (LTRA) is widely used by clinical practitioners to evaluate the response in children with suspected asthma. The treatment trial consists of starting ICS or LTRA treatment empirically in a child presenting with symptoms of asthma, without performing additional objective tests. The child is reviewed after a period of 4 to 8 weeks and the diagnosis of asthma is then often made based on symptom improvement alone at clinical review.

Review of evidence directly addressing PICO 2

We found no study where children with asthma symptoms but no confirmed diagnosis received a trial of treatment and investigation with at least one objective test. Most studies did not meet the inclusion criteria because they investigated the effectiveness of the trial medication in children already diagnosed with asthma.

Justification of the recommendation

Despite the lack of evidence to support a recommendation, the TF members are well aware that a trial of preventer medication is widely employed by clinicians to evaluate the response in children with symptoms of asthma. The main reason for this is remaining diagnostic uncertainty and because spirometry and FeNO confirm asthma only in a minority of children seen during routine clinical reviews in children (39-41). The TF discussed and agreed that a trial of treatment with ICS can be considered, but only in steroid-naïve or non-adherent children with asthma symptoms in whom initial tests have not been able to confirm the diagnosis. Objective tests should be repeated after 4 to 8 weeks. (18,42-44)

The difference in our diagnostic approach is that the TF does not recommend to diagnose asthma on the basis of improvements in reported symptoms alone following the treatment trial but to base the diagnosis on a significant improvement in lung function and symptoms after completion of the trial of treatment. This recommendation is supported by the GINA 2020 strategy document. (18) GINA in addition proposes a supervised stepping down of preventer medication in conjunction with lung function tests to confirm or refute the presence of (active) asthma (supplementary table 6).

Key unanswered questions and future research needs

There is a need for validation studies investigating the diagnostic accuracy and limitations of preventer medication treatment trials in preventer naïve school-age children. Studies need to assess the type, dosage and the length of the treatment trial period, taking into account factors such as proper inhaler technique, adherence to medication and the season during which the trial is conducted.

PICO 3 - In children aged 5-16 years under investigation for asthma, should spirometry testing be used to diagnose asthma?

Recommendation

- The TF recommends to perform spirometry as part of the diagnostic work-up of children aged 5-16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence)

Remarks

1. An FEV_1/FVC < LLN or < 80%, or an FEV_1 < LLN or < 80% predicted should be considered supportive of an asthma diagnosis. It is important to be aware that not all children are able to perform a sufficient FVC manoeuvre resulting in a false normal FEV_1/FVC ratio
2. A normal spirometry result does not exclude asthma

Background

Spirometry is a non-invasive physiological test, which measures the volume and flow rate of air during inhalation and exhalation. The most commonly reported parameters are FEV_1 (forced expiratory volume in 1 second) and FVC (forced vital capacity) and the ratio of FEV_1 to FVC (FEV_1/FVC). The FEV_1 represents the volume of air (litres) expired in the first second and the FVC (litres) is the total volume of air expired from the start of the manoeuvre to the end. A reduced FEV_1 to FVC ratio indicates airway obstruction.

A standardised procedure for performing spirometry has been published jointly by the European Respiratory Society (ERS) and American Thoracic Society (ATS) (45).

Cut-offs: The TF strongly recommends the use of LLN to define abnormal spirometry but the panel agreed to accept a fixed cut-off for FEV_1/FVC and FEV_1 < 80% where LLN is not available because this

cut-off reasonably closely approximates LLN. In a large recent UK study using a fixed cut-off of 80% for FEV_1/FVC and FEV_1 % predicted, airflow obstruction was falsely identified in 6.4% of children aged 5 to 16 years (41) compared to using LLN.

Review of evidence directly addressing PICO 3

Our search strategy was designed to identify studies addressing the diagnostic accuracy of spirometry using the lower limit of normal (LLN) or a fixed cut-off for FEV_1 and/or FEV_1/FVC to diagnose asthma in children aged 5-16 years. Three studies fulfilled the inclusion criteria (supplementary table 7) (35,46,47). All were observational, cross-sectional studies comparing the diagnostic accuracy of spirometry in school-aged children against a second objective test.
Studies using a fixed cut-off for FEV_1 % predicted of < 80% or FEV_1/FVC < 80% to diagnose asthma in children showed low sensitivity (0.12 to 0.52) and moderate to high specificity (0.72 to 0.93) (35,46,47) (supplementary tables 8 and 9). Only one study utilised Global Lung Function Initiative (GLI) reference equations to determine predicted values (35). This study reported the diagnostic accuracy of FEV_1 z-score ≤ 0.8 with a sensitivity of 0.44 and specificity of 0.77

Justification of recommendation

Good quality spirometry can detect airway obstruction, the hallmark of asthma. Obstructed spirometry with positive BDR confirms the diagnosis. Spirometry testing is fairly quick and non-invasive and an experienced operator can obtain good quality data from the majority of children ≥ 5 years (41,48). The equipment is portable and the test is widely available, however availability in primary care is variable. It is important to emphasise that spirometry as a one-off measurement has a low sensitivity and is therefore poor at ruling out asthma. Because of the variable nature of the condition, when the asthma is controlled, spirometry is frequently normal (40,41). Serial measurements may be required to confirm the diagnosis (19). Abnormal spirometry has good specificity for asthma (supplementary table 9).

Key unanswered questions and future research needs

There is an urgent need for studies in children assessing the ideal timing and the frequency of spirometry measurements to improve the sensitivity of the test.

PICO 4 – In children aged 5-16 years under investigation for asthma, should bronchodilator reversibility (BDR) testing be used to diagnose asthma?

Recommendation

- The TF recommends BDR testing in all children with FEV_1 < LLN or < 80% predicted and/or FEV_1/FVC < LLN or < 80% predicted (strong recommendation for the intervention, based on clinical experience)

Remarks

1. Consider an increase in FEV_1 ≥ 12% and/or 200 ml following inhalation of 400 micrograms of a short acting beta2-agonist as diagnostic of asthma
2. A BDR < 12% does not exclude asthma
3. Most TF members consider BDR testing when baseline spirometry is normal if the clinical history is strongly suggestive of asthma

Background

The bronchodilator reversibility (BDR) test measures changes in lung function following inhalation of a short acting bronchodilator. BDR is a test of bronchial lability, the hallmark of asthma. ERS/ATS test procedure and interpretation of results have been published (45,49).

Review of evidence directly addressing PICO 4

We found no studies directly addressing the diagnostic accuracy of BDR testing in school-aged children using a second objective test, which were the inclusion criteria. However, variable airflow limitation is the hallmark of asthma and the presence of variable airflow limitation demonstrated by BDR testing is part of the definition of asthma stated in all major international asthma guidelines such as GINA and BTS/SIGN. (18-20,30,31) The literature searches revealed that most studies, including most of those included in these clinical practice guidelines, used the presence of BDR as evidence to confirm the diagnosis of asthma. (35,36,46,47,50).

Additional evidence: The main uncertainty about BDR relates to its low sensitivity, and in children there is no direct evidence to support a robust cut-off for BDR. A change in FEV_1 (L) of ≥ 12% and/or 200 ml is the widely used cut-off in children to define the presence of BDR. This cut-off is however derived from adult studies. Paediatric studies reported the mean change in FEV_1 (L) post-bronchodilator to be 2.2-2.7% from baseline in healthy children (51,52) compared with 8.6-10.7% in those with a history of asthma. The reported values for sensitivity and specificity using a 12% cut-off in children is 0.35-0.36 and 0.90-0.98 respectively (52,53). Despite providing important information,

we excluded these studies from the evidence synthesis because they did not fulfil inclusion criteria, namely a second objective test within the reference standard.

Justification of recommendation

Even though we did not find any studies investigating the diagnostic accuracy of BDR testing we recommend BDR testing in all children with abnormal spirometry. Variable airflow limitation is a defining feature of asthma as stated in major international asthma guidelines such as GINA and BTS/SIGN and a positive BDR in conjunction with obstructed spirometry has a high accuracy at confirming the diagnosis in children with relevant clinical signs and symptoms. Most studies included in these guidelines use a positive BDR test as the reference standard to support the diagnosis of asthma. In a child with relevant clinical symptoms, abnormal spirometry and positive BDR test treatment can be started immediately. Importantly, a child with abnormal spirometry and no evidence of BDR could have a restrictive lung disease or fixed airways obstruction and referral should be considered to specialist care for further investigations. The TF agreed with the cut-off for BDR of 12% in children, in agreement with previous studies in children (52,53) and existing international asthma guidance (18-20,49). The TF acknowledges that BDR testing has low sensitivity especially at the 12% threshold but good specificity for a diagnosis of asthma in children (52). The TF acknowledges that there are resource implications, but based on the high specificity of the test, its non-invasive nature and its availability, the TF recommends BDR testing in children with obstructed spirometry and/or low FEV_1 (supplementary table 10).

The TF considered that BDR testing is a non-invasive procedure and usable results are obtained in the majority of children. Spirometry and BDR can be performed in any health care setting and the results are immediately available. Equipment and consumables costs are moderate but the test is time consuming and there are training requirements. Reversible airflow obstruction is the hallmark of asthma and it would make little sense to perform spirometry but not BDR in cases where spirometry is abnormal/obstructed.

Key unanswered questions and future research needs

We need validation studies in children to investigate the diagnostic accuracy and limitations of BDR testing in asthma using different cut-offs, compared with an appropriate reference standard, which includes a second objective test. Different studies need to assess the type and dosage of short acting bronchodilator used, and when to perform BDR testing (i.e. for all children, or only when FEV_1 or FEV_1/FVC is < LLN).

PICO 5 – In children aged 5-16 years under investigation for asthma, should FeNO testing be used to diagnose asthma?

Recommendation

- The TF recommends to measure FeNO as part of the diagnostic work-up of children aged 5 to 16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence)

Remarks

1. A FeNO value ≥ 25ppb in a child with asthma symptoms should be considered as supportive of a diagnosis of asthma
2. A FeNO value < 25ppb does not exclude asthma

Background

FeNO was first measured in exhaled air by Gustafsson *et al.* in 1991 (54), and subsequently has been shown to be increased in asthma and regarded as an indirect marker of eosinophilic airway inflammation (55). Measurement is non-invasive, can be obtained in most children ≥ 5 years and results are available in a few minutes using portable, desktop equipment. Success in the routine clinical setting is variable in children aged 5 to 7 years (48).

International guidelines describe a standardized methodology and provide clinical interpretation of FeNO measurements (55). FeNO has been recommended as a useful test to support a diagnosis of asthma in adults and children. (20)

Multiple factors have been reported to influence the measurement (55) including subject related factors, such as age, height and ethnicity, lifestyle factors, such as smoking, diet and exercise, and environmental exposures such as to pollen (55). Atopy is associated with elevated FeNO, independent of asthma (55). Asthma treatments including ICS (56) and LTRA reduce FeNO by between 25% and 50% (57).

Review of evidence directly addressing the question

Four recent systematic reviews investigated the accuracy of FeNO in the diagnosis of asthma in children (58-61). Four observational studies in children fulfilled the inclusion criteria (35,46,47,50). Unpublished data were provided by the authors of a fifth study (36). A summary of this published evidence on FeNO is shown in table 5.

The overall diagnostic accuracy of the test is moderate since conclusions are based on non-weighted average FeNO values without 95% confidence intervals. FeNO values of 19 parts per billion (ppb) and

25 ppb showed the equal highest Youden's index (sensitivity+specificity-100) shown in supplementary table 13.

The influence of inhaled corticosteroid (ICS) treatment on the results was considered; participants in the study reported by Brouwer et al (36) had withheld any ICS for four weeks. In contrast, in the study reported by Sivan et al, one third of cases finally categorized as asthma were using ICS at the time of testing (46). Woo et al (50) included only steroid naïve children and finally, in the study by Grzelewski et al, 11% and in the study by de Jong et al, 19% of children were on controller medication at the time of FeNO measurement (35,47).

The TF explored whether there might be sub-groups of children where FeNO may be particularly suited to diagnosing/excluding asthma and one study showed that children with allergy show better accuracy for FeNO testing (50).

The five studies fulfilling the criteria for inclusion (35,36,46,47,50) reported sensitivity and specificity results for different cut-points for FeNO. These are shown in supplementary table 11.

Justification of recommendation

Although the diagnostic accuracy of FeNO is moderate the results of our review show that evidence exists to support FeNO as a useful test to diagnose asthma in children (supplementary table 14). FeNO testing is a relatively simple, non-invasive test that is highly acceptable to children and their caregivers. There are equipment and consumables costs that need to be considered. The TF panel agreed that a single recommended cut-off value was essential. The panel agreed that 25 ppb was the best cut-off value based on the mean sensitivity (0.57) and specificity (0.81) values (supplementary tables 12 and 13) at this cut-point. To reach this decision the panel considered the harm from over-treatment arising from false positive results and the remit of the TF, which was to provide recommendations on diagnosing asthma and not on excluding asthma. The TF acknowledges that any cut-off relating to continuous variables such as FeNO are to some extent arbitrary and confidence into the result increases with greater distance from the cut-off value. The TF also emphasises the importance of interpreting FeNO as part of a wider clinical assessment.

Key unanswered questions and future research needs

We need studies investigating the sensitivity and specificity of FeNO in ICS naïve child populations presenting with symptoms of asthma and studies, which further explore the role of FeNO in non-atopic children with asthma symptoms. Studies are also required to establish the "wash out" time after cessation of ICS or LTRA before FeNO can be used for diagnostic testing. We also need better technology to routinely test FeNO in children ≤ 5 years.

PICO 6 - In children aged 5-16 years under investigation for asthma, should peak expiratory flow rate (PEFR) variability be used to diagnose asthma?

Recommendation

- The TF recommends against PEFR variability testing as the primary objective test on its own to diagnose asthma in children aged 5-16 years (conditional recommendation against the intervention, moderate quality of evidence)

Remarks

1. Other objective tests are preferred but a PEFR variability test can be considered in healthcare settings lacking other objective tests
2. If a PEFR variability test is used the result should be based on two weeks of measurements, ideally using electronic peak flow meters
3. A cut-off of ≥ 12% in PEFR variability should be considered a positive test
4. A PEFR variability of <12% does not exclude asthma

Background

PEFR is a physiological measurement of the largest flow of exhalation that can be achieved from maximal inspiration, expressed in L/min. PEF should be recorded as the best of three forced expiratory blows immediately after a full inspiration with the patient either standing or sitting. The PEF variability is calculated as the difference between the highest and lowest PEF expressed as a percentage of the average PEF. PEF variability as a diagnostic test is supported by the BTS/SIGN and the UK NICE guidelines and the GINA 2020 asthma strategy document. (18-20)

Review of evidence directly addressing PICO 6

One study met our inclusion criteria (supplementary table 15). Brouwer et al. studied the usefulness of home spirometry and PEFR variability in diagnosing asthma in children consecutively referred to secondary care with nonspecific respiratory symptoms (36). Children performed home spirometry and peak flow measurements using an electronic device, twice daily for two weeks. Using a pre-defined cut-off of 12.3% (based on above 95% confidence interval of normal values in children) the sensitivity and specificity of PEFR variability was 0.5 and 0.72 respectively (supplementary tables 16 and 17).

Justification of recommendation

PEFR variability has been included as an optional test in the diagnostic algorithm however spirometry (with BDR where appropriate) and FeNO are preferred first line diagnostic tests. There is limited evidence to support PEFR variability as an asthma diagnostic tool (supplementary table 17). The only evidence to support its use is as a PEFR diary with twice-daily measurements for at least two weeks. More frequent testing may have greater sensitivity (62) but is offset by decreasing adherence to the test by children and their families (63). The use of electronic meters and diaries may help to overcome some of the adherence issues (64).

Key unanswered questions and future research needs

We need more studies to assess the diagnostic use and accuracy of PEFR variability in children. Future research should involve larger numbers of treatment naïve children referred with asthma symptoms who are investigated by means of PEFR variability and other objective tests.

PICO 7 – In children aged 5-16 years under investigation for asthma, should allergy testing be used to diagnose asthma?

Recommendations

- The TF recommends against the use skin prick tests to aeroallergens as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence)
- The TF recommends against the use of serum total and specific IgE tests as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence)

Background

Allergic sensitisation to aeroallergens is common among all children and even more common among children with asthma. Aeroallergens are common triggers of asthma symptoms. Common aeroallergens are house dust mites, animal dander, pollens and moulds. Allergic sensitisation to aeroallergens can be measured in several ways, but the most commonly used are skin prick test, or specific IgE measurement.

Skin prick tests

Skin prick tests (SPT) use the presence and degree of cutaneous reactivity as a marker for allergic sensitisation. A wheal size of ≥ 3 mm compared to negative control is considered a positive test (65).

SPT is not practical in patients who have extensive eczema, dermographism, urticaria, or who are taking antihistamines or other medications, which interfere with the proper interpretation of the test results (65,66).

Allergen-specific IgE tests

The allergen specific IgE can be detected by a Radio-Allergo-Sorbent Tests (RAST) or by an Enzyme-Linked Immuno-Sorbent Assays (ELISA). (67) Different systems can measure allergen specific IgE. The cut-off for a positive test to diagnose allergic sensitisation in children is commonly defined as <0.35 kU/l.

Review of evidence directly addressing PICO 7

Four observational studies met our inclusion criteria (supplementary table 18) (35,36,47,50). However, only one study directly assessed allergy tests as an index test (35), even though it was possible to calculate the diagnostic accuracy of allergy tests from the other three studies as well. Most studies were excluded because they assessed prevalence and patterns of allergic sensitization in children with a prior asthma diagnosis or in healthy populations. Skin prick test had a sensitivity of 0.77-0.90 and specificity of 0.23-0.40 for one positive test and sensitivity of 0.79 and specificity of 0.53 for two positive tests (supplementary tables 19 and 21). Specific IgE measurements had a sensitivity of 0.58-0.90 and a low specificity of 0.56-0.65 (supplementary tables 20 and 21).

Justification of recommendation

Evidence from the available studies suggests that skin prick tests and specific IgE measurements have a limited value to diagnose asthma. The low specificity is likely to lead to an over-diagnosis of asthma, particularly in children with other atopic diseases. Non-allergic asthma, in contrast, will be under-diagnosed if physicians rely on allergy tests for asthma diagnosis.

However, after diagnosis, allergy tests can be useful for asthma management, in particular to describe the phenotype and to plan individualised prevention measures.

Considering the low specificity, the TF recommends against allergy testing as a diagnostic test for asthma in children (supplementary table 21).

Key unanswered questions and future research needs

Allergy tests are useful in patients already diagnosed with asthma, to determine measures of tertiary prevention, i.e. avoidance of clinically relevant allergens that trigger asthma attacks or maintain chronic symptoms. Carefully designed clinical studies in children with suspected asthma are essential

to provide more evidence on their role in diagnosing asthma.

PICO 8 – In children aged 5-16 years under investigation for asthma, should direct bronchial challenge testing including methacholine and histamine be used to diagnose asthma?

Recommendation

- The TF recommends a direct bronchial challenge test using methacholine in children aged 5-16 years under investigation for asthma where asthma diagnosis could not be confirmed with first line objective tests (conditional recommendation for the intervention, low quality evidence).

Remarks

1. A PC_{20} value of 8 mg/ml or less should be considered as a positive test
2. The TF found no evidence for or against performing histamine challenge tests in children under investigation for asthma

Background

One of the hallmarks of asthma is airway hyperresponsiveness (AHR), which is characterized by an increased sensitivity and exagerated response to stimuli resulting in airway obstruction (68). Direct bronchial challenge testing is performed with different chemical substances to test non-specific bronchial responsiveness to a variety of stimuli such as meatacholine (a neurotransmitter substance) or histamine (a mediator substance) directly interacting with receptors on airway smooth muscle. In individuals with asthma the response occurs at a lower dose and to a greater degree compared to children without AHR. An ERS TF recently revised the recommendations for methacholine bronchial challenge tests (69). The results are based on the concentration (PC_{20}) causing a 20% fall in FEV_1 or the delivered dose of methacholine resulting in a 20% fall in FEV_1 (provocative dose (PD_{20})). As results are comparable between different protocols and devices, the latter is the preferred method (69). No studies using histamine challenge fulfilling inclusion criteria were identified by the literature searches.

Some parents/carers and patients have concerns about challenge tests due to the risk of creating a potentially severe asthma response. Health professionals should be mindful of these concerns when explaining the risks and benefits of challenge testing.

Review of evidence directly addressing PICO 8

Three studies directly addressed the PICO question and were included in the quantitative analysis (supplementary table 22) (35,70,71). Histamine for bronchial challenge was not tested in any of the studies fulfilling inclusion criteria.

We were unable to pool the accuracy data for these studies because sensitivity and specificity differed too much between studies, and therefore calculated the absolute effects of tests using the range of results. Sensitivity and specificity ranged from 0.66 to 0.91 and from 0.63 to 0.82 respectively (supplementary table 23).

Justification of recommendation

Direct bronchial testing is time consuming, requires a specialist setting and tests can be unpleasant for children. Children referred for direct bronchial challenge testing therefore require careful selection. However, the TF agreed that direct bronchial challenge testing should be offered to children where diagnostic uncertainty remains after repeated first line tests have not confirmed the diagnosis, the child remains symptomatic and other diagnoses have been considered. (supplementary table 24). The TF emphasises the importance of interpreting direct challenge testing as part of a wider clinical assessment. A positive challenge test may be present in the absence of asthma.

Key unanswered questions and future research needs

We need clinical studies to answer the question as to which children benefit most from direct bronchial challenge testing in order to make recommendations on the most appropriate referrals.

PICO 9 – In children aged 5-16 years under investigation for asthma, should indirect bronchial challenge testing including exercise and mannitol be used to diagnose asthma?

Recommendation

- The TF recommends an indirect bronchial challenge test using a treadmill or a bicycle in children aged 5-16 years under investigation for asthma with exercise related symptoms where asthma diagnosis could not be confirmed with first line objective tests. (conditional recommendation for the intervention, moderate quality evidence)

Remarks

1. A fall in FEV_1 of > 10% from baseline should be taken as a positive test
2. A mannitol challenge can be considered as an alternative to exercise challenge. However due to its limited availability in most countries, and the fact that children often find the test unpleasant, mannitol challenge should be best avoided in favour of other challenge tests

Background

Indirect bronchial challenge tests trigger airway obstruction via endogenous pathways that are involved in the pathophysiology of asthma (72). Therefore, they are considered to be more specific for asthma compared to direct challenge tests but may be less sensitive at detecting AHR. Several methods exist for indirect bronchial challenge testing including exercise, eucapnic voluntary hyperpnoea, cold air challenge and the inhalation of osmotic substances such as hypertonic saline, mannitol or adenosine monophosphate. An ERS TF recently revised the recommendations for indirect bronchial challenge testing (73).

Exercise testing using a cycle ergometer or a motorized treadmill is the preferred test (73,74). Exercise induced bronchoconstriction is defined as a decrease in $FEV_1 \geq 10\%$ from baseline, but some studies use the criterion of 15%, which results in a higher specificity (73,75).

The mannitol challenge test is performed with the alcohol sugar mannitol, an osmotic agent, using a dry powder inhaler device. Increasing doses of mannitol are inhaled and FEV_1 is measured repeatedly between the inhalation steps (76).The test is considered positive if there is a fall of 15% or more in FEV_1 from baseline in response to the cumulative total dose or a 10% decrease between two consecutive doses of mannitol (77).

As above, some parents/carers and patients have concerns around challenge testing and potential

adverse events.

Review of evidence directly addressing the question

We only found studies using either exercise challenge test or the mannitol challenge test that fulfilled our inclusion criteria. Three studies directly answered the review question and were included in the quantitative analysis (supplementary table 25) (35,70,71). All three studies provided accuracy data for indirect bronchial challenge tests using either exercise or mannitol.

Anderson et al. provided data for mannitol inhalation in children as a subsample of a larger study in adults (70). Zaczeniuk et al. reported the diagnostic accuracy of exercise testing by treadmill (71) as did De Jong et al. who also included bicycle (35). We were not able to pool the accuracy data of these studies because of the range of the results. Zaczeniuk et al. defined a positive test by a ≥10% decrease in FEV_1 and reported a sensitivity of 0.77 and a specificity of 0.68 with de Jong et al. reporting sensitivity and specificity data for ≥10% and ≥12% FEV_1 cut-off. Sensitivity was 0.47 and 0.37 respectively and specificity was 0.77 for both cut-offs (supplementary table 26).

We were unable to pool the mannitol challenge test data due to the range of values. For mannitol challenge testing, Anderson et al. reported a sensitivity of 0.63 and specificity of 0.81, and de Jong et al. reported a sensitivity and specificity of 0.39 and 0.97 respectively (supplementary table 27).

Justification of recommendation

Indirect bronchial testing is time consuming and formal tests require a specialist setting. Children referred for indirect direct bronchial challenge testing require careful selection. A positive indirect bronchial challenge test however confirms the diagnosis of asthma with a moderate sensitivity and high specificity. Based on the evidence (supplementary table 28), the TF agreed that indirect challenge testing during the diagnostic work-up with treadmill or bicycle is recommended in children where the diagnosis could not be confirmed using first line diagnostic tests and particularly for children with exercise induced symptoms.

The TF emphasises the importance of interpreting indirect challenge testing as part of a wider clinical assessment. A positive challenge test may be present in the absence of asthma.

Key unanswered questions and future research needs

There is uncertainty regarding the best approach with respect to challenge testing in children and it is unclear whether indirect or direct challenge tests should be prioritized in the asthma diagnostic

pathway. Younger children especially were under-represented in the selected studies and should be included in future studies.

Development of the diagnostic algorithm

The TF agreed on the recommended diagnostic tests and a draft diagnostic algorithm during a meeting of the whole TF based on the results of the literature reviews, the recommendations for each PICO question and the EtD framework.
The TF used a modified Delphi process to decide on the hierarchy of the diagnostic tests.
Using the Delphi process described in the methods' section, the TF members agreed that no single test on its own is currently sufficient to confirm the diagnosis of asthma. The TF agreed that two positive, evidence-based tests, are required to confirm the diagnosis in children aged 5-16 years. Spirometry, BDR testing and FeNO are the most widely available objective tests performed in patients under investigation for asthma. Major international asthma guidelines variously recommended these as first line tests. In addition, the tests are non-invasive, the equipment is portable, feasible in all healthcare settings, and have high acceptability by children and families (41). The evidence supporting the proposed objective tests was frequently sparse and in some places relied on a single research publication fulfilling inclusion criteria. In addition there is no study that tested a hierarchy of tests to diagnose asthma in children, or adults. No test was recommended for which there was no evidence. This means that a 'trial of preventer medication' is not included as a diagnostic test. Whilst it has been included as a step in the algorithm, the diagnosis of asthma depends entirely on a significant improvement in lung function after the trial of treatment. No studies were found investigating BDR as a test for asthma. However, there is substantial indirect evidence. Variable airflow obstruction is universally accepted as the key feature of asthma and most studies included in this TF report used the presence of BDR as a reference standard to measure other tests against. This approach is pragmatic and there is no evidence underpinning it. The diagnostic algorithm is shown in the figure.

Application of the algorithm
This algorithm applies to all children and adolescents presenting with symptoms of asthma irrespective of whether they are treatment naïve or had a prior diagnosis of asthma and are currently on treatment including ICS.

Where children are symptomatic despite ICS treatment, the algorithm can also be applied because in children with current symptoms but normal lung function and a normal FeNO value alternative diagnoses should be considered. Asymptomatic children on ICS should be reviewed at regular intervals (6 to 12 monthly) and treatment stepped down. If symptoms recur, the algorithm should be applied to confirm the diagnosis of asthma.

The algorithm is valid across the paediatric age group of 5 to 16 years. We did not conduct separate reviews for children 5 to 11 years and adolescents (12-16 years) because most included studies had recruited children across school age and adolescence and did not stratify their analyses by age. The whole Task Force agreed that the algorithm applies to children from age 5 to 16 years. Future studies could test whether the algorithm can be refined by adapting it to different age-groups, although every diversification will have to be gauged against the increasing complexity of its use in clinical practice.

Discussion

This document presents the first European evidence-based clinical practice guidelines for the diagnosis of asthma in children. We reviewed the literature for the last 40 years and found adequate evidence to support our recommendations in some areas but limited or no data in others.
Key recommendations: The TF recommends to diagnose asthma in children only when at least two objective test results are abnormal. The TF recommends that spirometry, BDR and FeNO are first line tests in the asthma diagnostic pathway. The TF also recommends against trials of treatment where an improvement of symptoms alone after a period of empiric asthma preventer medication is used to confirm the diagnosis.

We are not aware of any national or international guidelines that focus entirely on the diagnosis of asthma in children. The most widely cited asthma guidelines make statements or recommendations for diagnosis whilst focussing on the management of asthma, and cover children and adults in one document. The guideline development is different between all major asthma guidelines resulting in considerable variability of recommendations. These are summarised in table 3.

Table 3: Summary of the key recommendations for the diagnosis of asthma in children from three frequently cited current asthma guidelines

Major asthma guidelines	**Diagnostic recommendations for children**
The Global Initiative for Asthma (GINA) 2020 strategy document (18)	Recommends Spirometry and Bronchodilator reversibility (BDR) testing or two weeks of twice-daily PEFR variability measurements to investigate for asthma.
British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guideline 2019 (19)	States that asthma is a clinical diagnosis. Lung function tests influence the probability of an asthma diagnosis and BTS/SIGN recommend comparing the results of lung function tests undertaken whilst a patient is asymptomatic with that undertaken when the patient is symptomatic to detect variation over time to aid diagnosis.
UK National Institute for Health and Care Excellence guideline 2017 (20)	The guideline stipulates that two positive objective tests are required in children aged 5-16 years to confirm the diagnosis of asthma. Spirometry (and BDR if spirometry is obstructed) and FeNO are recommended as 1st line tests.

Our guidelines differ from the GINA strategy document and the BTS/SIGN guidelines in that neither proposes a clear diagnostic pathway for either a sequence or timing of investigations. The BTS/SIGN

guideline (19) does not recommend any tests for the routine diagnosis of asthma. Neither guideline recommends FeNO testing to diagnose asthma. The UK National Institute for Health and Care Excellence (NICE) recently developed asthma guidelines using GRADE methodology and systematic literature searches similar to our approach. (20) These guidelines included a diagnostic algorithm for children aged 5-16 years presenting with symptoms of asthma. Key differences between this and the UK NICE guideline include a) downgrading of the use of PEFR variability testing because the evidence to support this test in children is not strong. The cut-off for PEFR variability testing is also different based on the available evidence (12% vs 20%), b) the FeNO cut-off is lower (25ppb vs 35ppb) based on recent evidence that was not available to NICE, c) challenge testing in children was not recommended by NICE based on insufficient evidence. The TF recommends challenge testing in children as part of the diagnostic algorithm due to new evidence not available to NICE (35) and two studies not identified by the NICE searches. (71,76)

The TF strongly recommends the use of lower limits of normal (LLN) derived from the Global Lung Function Initiative (GLI) (78) as the reference standard for spirometry cut-off values. We have included fixed cut-offs only as a close approximation to be used in exceptional circumstances where LLN are not available either due to the spirometry equipment not displaying LLN values or where there is no GLI data due to the ethnicity of the patient.

We have included fixed cut-off values for other tests including BDR, FeNO, PEFR variability and challenge testing. These cut-offs are based on the evidence available to the TF and the research papers included in the quantitative analysis for each PICO. We used the Youden's index for pooled data where more than one research paper was available. The TF is aware that these cut-offs represent arbitrary thresholds and that the likelihood that a child has asthma increases with decreasing FEV_1, increasing BDR, increasing PEFR variability, increasing FeNO, and greater BHR.

We did not include children <5 years in these guidelines, because diagnostic tests for asthma on young children are rarely performed and there is insufficient evidence to support an evidence based diagnostic algorithm. We recognise that many children <5 years are treated for asthma-like symtpoms and families can't understand why asthma can't be diagnosed sooner but their child has to take asthma treatment. We refer the interested reader to a recent ERS TF report on the management of children with preschool wheeze (79).

There are no randomised controlled trials, which used diagnostic tests to diagnose asthma and the proposed diagnostic algorithm is based on pragmatic decisions including access to test equipment, clinicians' familiarity with the tests and acceptability by children and families. All these factors and decisions are clearly documented in the EtDs in the supplementary material. In addition, we have not undertaken a health economic analysis because this was beyond the scope of this TF. Because of this lack of evidence to support a diagnostic sequence every diagnostic algorithm will be open to criticism. A recent study from Switzerland confirms the limited use of individual tests and applying the NICE and GINA algorithm retrospectively to a series of diagnostic tests showed variable sensitivity and specificity between the NICE and GINA algorithms (80). The TF is aware that diagnostic algorithms involving multiple tests are challenging especially in the primary care setting. Moreover, spirometry is frequently normal in patients with asthma during stable disease (40,41). Where this is the case and if the child is relatively asymptomatic a 'watchful waiting approach' can be considered. Repeat spirometry testing should then be performed with comparison of test results over time. Spirometry testing is likely to be most useful when the child is symptomatic, especially when wheezing is present, and a comparison is made with spirometry obtained during disease stability as suggested by the BTS/SIGN asthma guidelines (19).

We have highlighted areas of research need in the individual PICO sections. Future studies require careful planning with respect to study designs to improve the evidence base of paediatric asthma diagnosis and focus on affordable and scalable tests to diagnose asthma. Better strategies to diagnose childhood asthma in primary care are of particular importance in order to avoid large numbers of secondary and tertiary care referrals for asthma diagnostic tests, in particular challenge tests. More research is urgently needed in this area.

Invariably, regional differences exist in Europe in relation to asthma incidence and severity, availability of tests and the approach to asthma diagnosis. Given the resources and timeframe of this clinical practice guideline it was not possible to evaluate all the tests described in the literature for the diagnosis of asthma but instead to focus on the most commonly used tests and approaches. The ERS TF clinical practice guidelines closely align to other major international asthma guidelines. (18-20) All recommend some form of spirometry testing in patients with suspected asthma, usually from five years of age. Where this guideline differs is in the recommendation of a diagnostic algorithm that should ultimately allow us to diagnose or refute the diagnosis of asthma in all children presenting with relevant respiratory symptoms.

In summary: We present the first European guidelines for the diagnosis of asthma in children aged 5-16 years. The TF recommends spirometry, BDR and FeNO as first line tests to diagnose asthma in children and to diagnose asthma only when two test results are abnormal.

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Figure: Asthma diagnostic algorithm for children and young people aged 5 to 16 years presenting in primary, secondary and tertiary care.

Figure caption:

This algorithm is based on the recommendations stemming from the PICO questions; the hierarchy of the recommendations was decided using a Delphi-process. There is no gold standard test to confirm the diagnosis of asthma and no single abnormal test by itself is sufficient to make the diagnosis. If initial tests (spirometry, BDR and FeNO) fail to confirm the diagnosis, watchful waiting can be considered in children with normal spirometry with repeat testing especially at a time when the child presents with symptoms of asthma. Reported wheeze has better sensitivity and specificity for the diagnosis of asthma compared to the other symptoms cough and breathing difficulty, which are rather non-specific.

[1] Spirometry normal: FEV_1 and FEV_1/FVC ≥ LLN and/or ≥ 80% predicted. Normal spirometry in a child presenting with symptoms of asthma does not exclude a diagnosis of asthma.

[2] Spirometry abnormal: FEV_1, or FEV_1/FVC < LLN and/or < 80% predicted. Abnormal spirometry in a child presenting with symptoms of asthma does not confirm a diagnosis of asthma.

[3] BDR testing can be considered if there is a strong clinical suspicion of asthma despite normal spirometry.

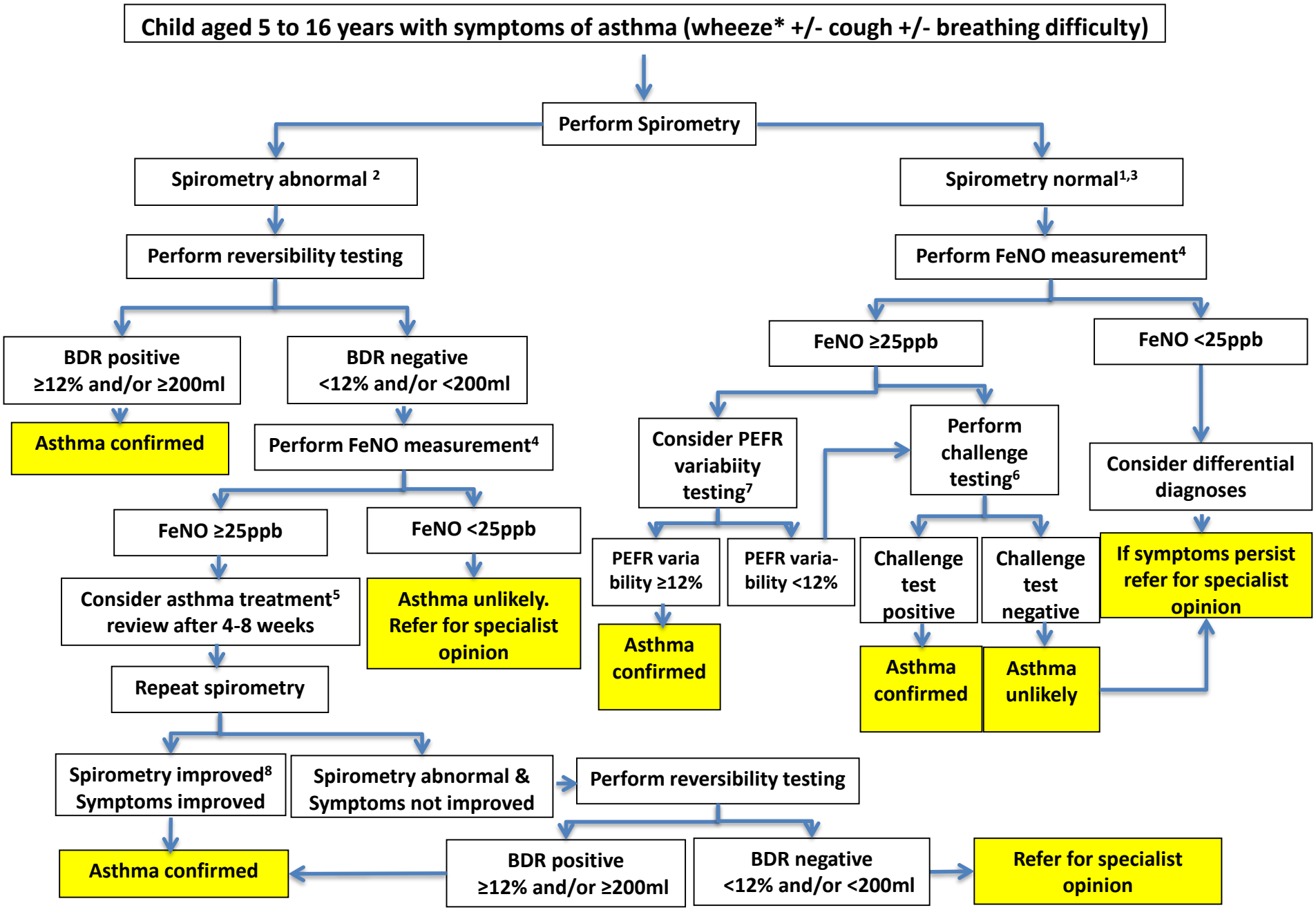
[4] The task force is aware that FeNO should ideally be performed before spirometry and in many clinics both tests are performed together.

[5] Asthma treatment using anti-inflammatory therapy with inhaled corticosteroids according to current national and international guidelines. Depending on the severity of symptoms therapy should be started at GINA step 2 or 3. If starting treatment, please demonstrate and check inhaler technique and prescribe age-appropriate spacer devices unless breath activated devices are prescribed age-appropriately.

[6] Direct bronchial challenge testing with methacholine or indirect bronchial challenge testing using treadmill or bicycle or both (direct and indirect bronchial challenge testing) should be performed in children where asthma diagnosis could not be confirmed with other objective tests.

[7] PEF variability could be used instead of challenge testing in healthcare settings where challenge testing is unavailable but this would be an inferior choice..

[8] Task Force recommendation based on clinical experience, no direct but indirect evidence that an improvement in FEV_1 > 7% may be considered significant (43). Please reduce treatment after 6-, to 12-month periods of disease stability as suggested by GINA 2020 (18).


Child aged 5 to 16 years with symptoms of asthma (wheeze* +/- cough +/- breathing difficulty)
Perform Spirometry
Spirometry abnormal [2]
Spirometry normal[1,3]
Perform reversibility testing
Perform FeNO measurement[4]
BDR positive ≥12% and/or ≥200ml
BDR negative <12% and/or <200ml
FeNO ≥25ppb
FeNO <25ppb
Asthma confirmed
Perform FeNO measurement[4]
Consider PEFR variabiity testing[7]
Perform challenge testing[6]
Consider differential diagnoses
FeNO ≥25ppb
FeNO <25ppb
PEFR varia bility ≥12%
PEFR varia-bility <12%
Challenge test positive
Challenge test negative
If symptoms persist refer for specialist opinion
Consider asthma treatment[5] review after 4-8 weeks
Asthma unlikely. Refer for specialist opinion
Asthma confirmed
Asthma confirmed
Asthma unlikely
Repeat spirometry
Spirometry improved[8] Symptoms improved
Spirometry abnormal & Symptoms not improved
Perform reversibility testing
Asthma confirmed
BDR positive ≥12% and/or ≥200ml
BDR negative <12% and/or <200ml
Refer for specialist opinion

Title:

European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5 to 16 years

Supplementary material

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Methods

Task Force and Work Group Composition

The membership and roles of the Task Force (TF) panel are summarised in Supplementary Table 1. The task force chairs Erol Gaillard and Alexander Moeller took overall responsibility for the governance of the TF and the integrity of the work conducted and published. The chairs were directly supported by Claudia Kuehhni and Steve Turner. Junior ERS members supported this leadership group based at Leicester (UK), Zuerich (Switzerland), Bern (Switzerland) and Aberdeen (UK). The PICO group leaders were agreed at the first meeting of the task force. The four centres divided the PICOs between themselves and the other TF members divided themselves to form PICO subgroups with the four leading centres.
The whole Task force was involved in formulating the PICO questions, approved the search strategies, and screened full text manuscripts to decide on inclusion or exclusion to answer the PICO question. The whole Task Force was involved in monitoring progress. This leadership group also coordinated the writing of the practice guideline and oversaw the editing.

Two ERS methodologists (David Rigau and Thomy Tonia) provided training online and during meetings of the TF on GRADE methodology. Following this training, the lead centres supported by the ERS methodologists worked with a librarian (Sarah Sutton) experienced with systematic reviews, based at University Hospitals Leicester, to design the search strategies for each PICO question. The respective PICO subgroups approved the search strategy. Junior TF members screened all the titles and abstracts identified and selected manuscripts for full text screening. All this information was shared with the TF subgroup who also screened the full text manuscripts and approved the manuscripts included in the recommendations. In difficult cases where the TF subgroup did not reach a consensus on the inclusion or exclusion of a manuscript, this was discussed at a meeting of the whole TF, where the final decision on inclusion/exclusion was taken. Once the included manuscripts for each PICO were agreed, the junior ERS members extracted the data, graded the evidence using the GRADE approach and calculated sensitivity and specificity data supported by the ERS methodologists. All this information was shared with the PICO subgroups who cross-checked the quality of the included manuscripts.

Supplementary Table 1: TF and PICO group composition, presented in alphabetical order. All were members of the TF panel for the duration of the work. Additionally, David Rigau, Blin Nagavci and Thomy Tonia are ERS methodologists who supported the project.

TASK FORCE MEMBER	SPECIALTY/EXPERTISE	ROLE/PICO GROUP MEMBERSHIP
Coleman, Courtney (UK)	European Lung Foundation	Coordination of lay members contributing to this Task Force
De Jong, Carmen (Netherlands)	Paediatrics, Epidemiology	Junior member and systematic reviewer of PICO 1, 5, and 7
Gaillard, Erol (UK)	Paediatric Respiratory Medicine	Chair of Task Force, leadership team, WG leader PICO 3 and 4
Goutaki, Myrofora (Switzerland)	Paediatrics, Epidemiology	WG leader of PICO 2 (trial medication), reviewer PICO 7
Holden, Karl (UK)	Junior member	Junior member and systematic reviewer of PICO 6
Johnson, Barbara (UK)	European Lung Foundation	Coordination of lay members contributing to this Task Force
Kuehni, Claudia (Switzerland)	Paediatric Respiratory Medicine	Leadership team, WG leader of PICO 7, also contributed to PICO 2
Lex, Christiane (Germany)	Paediatric Respiratory Medicine	Subgroup member for PICO 5, 8 and 9
Lo, David (UK)	Paediatric Respiratory Medicine	Junior member and systematic reviewer of PICO 3 and 4
Lucas, Jane (UK)	Paediatric Respiratory Medicine	Subgroup member for PICO 7 and 8
Lycett, Kelly	Parent/Patient representative	Parent/Patient representative
Midulla, Fabio (Italy)	Paediatric Respiratory Medicine	Subgroup member for PICO 1 and 2
Moeller, Alexander (Switzerland)	Paediatric Respiratory Medicine	Co-chair of Task Force, leadership team, WG leader PICO 8 and 9
Mozun, Rebeca (Switzerland)	Paediatrics, Epidemiology	Junior member and systematic reviewer of PICO 2
Piacentini, Giorgio (Italy)	Paediatric Respiratory Medicine	Subgroup member for PICO 5 and 9
Ross, Emma (UK)	Junior member	Junior member and systematic

		reviewer of PICO 1 and 5
Rottier, Bart (Netherlands)	Paediatric Respiratory Medicine	Subgroup member for PICO 1 and 2
Supple, Alex	Patient representative	Patient representative
Supple, David (UK)	Parent/Patient representative	Parent/Patient representative
Thomas, Mike (UK)	Primary Care Medicine	Subgroup member for PICO 1 and 5
Turner, Steve (UK)	Paediatric Respiratory Medicine	Leadership team, WG leader PICO 1 and 5
Usemann, Jakob (Switzerland)	Junior member	Junior member and systematic reviewer of PICO 8 and 9 and supporting PICO 5
Yilmaz, Ozge (Turkey)	Paediatric Respiratory Medicine	Subgroup member for PICO 3, 4, 7 and 8
Zacharasiewicz, Angela (Austria)	Paediatric Respiratory Medicine	Subgroup member for PICO 3, 4 and 6

Conflicts of interest disclosures

Panel members provided conflict of interest statements at the beginning of the Task Force and again prior to publication of the final manuscript in keeping with ERS policy. The statements were reviewed by Erol Gaillard and Alexander Moeller and following this review the chairs concluded that all panel member could be included in all the PICOs, all the votes and the modified Delphi process to establish the diagnostic algorithm.

The ERS provided meeting facilities during their annual conference to allow the whole Task Force to meet in 2018 and 2019. The ERS Task Force budget provided funding for two additional two-day meetings in Zuerich 2018 and Leicester 2019. The interests or views of the ERS had no bearing on the final PICO recommendations or the diagnostic algorithm.

Development of the diagnostic algorithm

PICO searches were complete in the summer of 2019. Based on the results from the manuscripts identified for each PICO question the whole TF agreed on the tests for inclusion in the diagnostic algorithm. The TF drafted the first version of the diagnostic algorithm including a hierarchy of tests based on discussions and consensus during the face-to-face meeting of the whole TF during the Leicester (UK) meeting on 21st and 22nd March 2019. We refined this algorithm using a modified Delphi process with repeated iterative online voting (1). After each round, all TF members received the results of the surveys, including comments made by panel members. A consensus was reached when ≥ 75% of participants agreed with aparticular step in the algorithm. Full consensus on the diagnostic algorithm was reached after three rounds of voting.

GRADE methodology

The TF employed GRADE methodology to identify relevant evidence for each PICO question, assess the quality of the evidence, extract the data and interpret the results. This ensured that panel members were able to make fully informed decisions on the inclusion/exclusion of manuscripts, the recommendations and the diagnostic algorithm.
Internationally cited asthma guidelines such as the GINA strategy document (2), The BTS/SIGN guidelines (3) and NICE UK (4) recommend tests to diagnose asthma in children. Recommendations differ from guideline to guideline and recommendations are usually broad and do not specify who should be tested when and what tests should be used. The UK NICE asthma guideline is the only one using the GRADE approach to formulate recommendations for diagnostic tests and a diagnostic algorithm.

Based on the tests recommended in these guidelines, the TF initially formulated eight PICO questions using the following format: “In children aged 5-16 years under investigation for asthma, should the presence of symptoms (wheeze, cough, breathing difficulty) or should tests (spirometry, BDR, FeNO, allergy, direct and indirect bronchial challenge tests) be used to diagnose asthma?” The whole TF reviewed and discussed these PICO questions during the first telephone conference, discussed further over email and agreed a final list of nine PICO questions during the first face-to-face TF meeting early 2018.

Literature review

Search strategies were modified from the ones published by NICE. (4) All final search strategies were approved by the PICO subgroups. A librarian (Sarah Sutton) based at University Hospitals Leicester (UK) performed all the searches in the Medline, Embase and Cochrane databases from 1980 to August 2019 with no language limitations. We excluded conference proceedings, review articles and manuscripts written in a non-European language.

Junior members of the PICO subgroup screened titles and abstracts identified by the searches. A senior member of the subgroup independently reviewed a subset of titles and abstracts for quality control. The whole TF screened the full-text papers of selected studies and agreed the final list of manuscripts to be included for analysis for each PICO question.

There is no gold standard test to diagnose asthma in children. In addition, asthma is a variable condition and tests are frequently normal when performed at a time when patients are well. In many health care settings, the diagnosis of asthma is made based on the clinical history without tests (3) but this is often inaccurate. (5-7) The TF therefore agreed to evaluate the sensitivity and specificity of objective tests against a reference standard that included a doctor diagnosis of asthma supported by at least one other positive objective test.

A PRISMA flow diagram was created for each PICO to summarise the number of papers included and excluded at each stage of the review process (supplementary figure 1). We also included a table with all the studies that were excluded after full manuscript screening with reasons for exclusion for each PICO. To reduce the risk of missing relevant studies, the reference lists of all the included research articles and/or recent reviews, in particular Cochrane reviews, were checked and panel members were asked whether they were aware of relevant studies that were not included in the final selection.

We used Quadas-2 tool (Quality Assessment of Diagnostic Accuracy Studies-2) (8), to assess the risk of bias in the selected studies of diagnostic test accuracy and assign low and high quality. This is one factor we considerd when we assessed the overall quality of the evidence for each PICO.

The TF then used the Evidence to Decision (EtD) frameworks to inform decisions for each PICO question in a structured and transparent way and to issue recommendations based on the research evidence and additional considerations. (9). There is no universally accepted system to grade sensitivity and specificity and we acknowledge that this is subjective and much depends on context. We pragmatically describe sensitivity and specificity in the following way: < 0.50, very low; 0.50 to 0.69, low; 0.70 to 0.89, moderate and 0.90 to 1.0 as good. We have given the actual numbers in the

EtD tables so that the reader can make up their own mind. The TF made all the final recommendations including the strength of the recommendations based on a modified Delphi process. (1)

Results

The PRISMA flowcharts (10) for the outcomes of the literature searches for PICO questions one to nine are shown in the supplementary figure 1A to I.

PICO 1: In children aged 5-16 years under investigation for asthma, should the presence of the symptoms wheeze, cough and breathing difficulty be used to diagnose asthma?

Supplementary material

The titles and abstracts of 1314 research papers were screened (supplementary figure 1A) and four studies were included in the quantitative and qualitative analysis (supplementary table 2) (11-14). Excluded studies after full-text review are shown in supplementary table 29, the GRADE table for included studies in supplementary table 3 and 4 and the evidence to decision table for PICO 1 in supplementary table 5.

Supplementary table 2. Details of included studies for PICO 1: classical symptoms including wheeze, cough and breathing difficulty					
Study	Study Population	Definition of asthma	Index Test and Cut-Off	Diagnostic Accuracy of Index Test	
				Sensitivity	Specificity
Brouwer 2010 Netherland (12)	• 61 children (aged 6-16y) referred to hospital due to chronic respiratory symptoms • ICS and LABA withheld for four weeks • Semi-structured medical history, spirometry, bronchodilator response, and FeNO at baseline • FEV1 and peak flow variability twice daily for 14 days • FeNO and methacholine challenge after 14 days • Asthma diagnosed in 21 (34%)	Based on the history, physical examination and lung function data on the second visit (including spirometry, bronchodilator response and methacholine challenge but not including variability data).	Wheeze*	0.86 (0.63, 0.97)	0.73 (0.56, 0.85)
			Cough*	0.71 (0.48, 0.89)	0.45 (0.29, 0.62)
			Breathlessness*	1.00 (0.84, 1.00)	0 (0, 0.09)
Santos 2005 Brasil (13)	• 211 children (aged 5-15y) presenting to emergency department with acute asthma symptoms completed a four-question questionnaire. Spirometry and bronchodilator response were measured. • Asthma diagnosed in 47 (22%)	≥12% increased in FEV1 after short acting beta agonist	Wheeze†	0.75 (0.61, 0.85)	0.64 (0.56, 0.71)
			Cough lasting >10 days	0.45 (0.31, 0.59)	0.59 (0.52, 0.66)
			Night waking due to cough†	0.34 (0.22, 0.48)	0.76 (0.69, 0.82)
			Exertional symptoms†	0.23 (0.14, 0.37)	0.76 (0.69, 0.82)
Ma 2017 Mongolia (14)	• 391 children (aged 6-18y) presenting to respiratory outpatients with respiratory symptoms during the pollen season completed a questionnaire and had spirometry, bronchodilator response and skin prick testing assessed. • Asthma diagnosed in 132 (34%)	GINA 2014 criteria, i.e. variable respiratory symptoms and variable airflow limitation (i.e. >12% BDR)	Wheeze‡	0.55	0.90
			Cough‡	0.89	0.27
			Breathlessness‡	0.37	0.80
			Chest tightness‡	0.42	0.75
			Night time waking‡	0.33	0.84
De Jong 2019 Switzerland (11)	• 111 children (aged 6-16y) referred to one of two hospitals due to suspected asthma • Questionnaire, spirometry, bronchodilator response,	One clinician made a diagnosis on the first assessment based on symptoms, skin prick tests, FeNO	Wheeze†	0.80 (0.70, 0.88)	0.48 (0.30, 0.67)

	FeNO, airway challenges (exercise and methacholine) and skin prick testing. Within a week of the first tests, a mannitol challenge and second FeNO measurement were performed. • Asthma diagnosed in 80 (72%)	and spirometry. The same clinician revisited the diagnosis on the second visit based on all the data available. Asthma was defined as either "definite" or "probable" asthma.	>3 attacks of wheeze†	0.44 (0.33, 0.55)	0.90 (0.74, 0.98)
			Night time waking due to wheeze†	0.41 (0.30, 0.53)	0.90 (0.74, 0.98)
			Cough lasting >28 days †	0.14 (0.07, 0.24)	0.68 (0.49, 0.83)
			Exertional wheeze†	0.68 (0.56, 0.78)	0.48 (0.30, 0.67)

*symptoms for at least three months reported as partly relieved by bronchodilator

†any episode in the previous twelve months

‡on a month-to-month basis over the last twelve months. No confidence intervals presented for sensitivity and specificity.

Supplementary table 3: GRADE table forPICO 1: Should the presence of wheeze be used to diagnose asthma in children?

Sensitivity	0.55 to 0.86
Specificity	0.48 to 0.90

Prevalence	30%*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30% *	
True positives (patients with [asthma])	4 studies 774 patients 4 studies . (11-14)	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious	not serious	none	165 to 258	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having [asthma])								42 to 135	

Explanations: *Pretest probability was pragmatically estimated at 30% because the prevalence of asthma in children is around 5 to 15% and children presenting for investigation with symptoms are likely to have a higher pre-test probability.

[a] Unclear if reference standard results were interpreted without knowledge of the results of the index test

Supplementary table 4: GRADE table forPICO 1: Should the presence of cough be used to diagnose asthma in children?

Sensitivity	0.14 to 0.89
Specificity	0.27 to 0.68

Prevalence	30%*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
True positives (patients with [asthma])	4 studies 774 patients (11-14)	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious	not serious	none	42 to 267	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having [asthma])								33 to 258	
True negatives (patients without [asthma])	4 studies 774 patients (11-14)	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious	not serious	none	189 to 476	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having								224 to 511	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
[asthma])									

Explanations: *Pretest probability was pragmatically estimated at 30% because the prevalence of asthma in children is around 5 to 15% and children presenting for investigation with symptoms are likely to have a higher pre-test probability.

[a] Unclear if reference standard results were interpreted without knowledge of the results of the index test

Supplementary table 5: Evidence to decision table for PICO 1

PICO question

In children aged 5-16 years under investigation for asthma, should the presence of the symptoms wheeze, cough and breathing difficulty be used to diagnose asthma?	
POPULATION:	Children aged 5-16 under investigation for asthma
INTERVENTION:	Using the report of the symptoms wheeze, cough and breathing difficulty to diagnose asthma

ASSESSMENT

Test accuracy How accurate is the presence of the symptoms wheeze, cough and breathing difficulty to diagnose asthma?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ **Inaccurate** ○ Accurate ○ Very accurate ○ Varies ○ Don't know	Reported wheeze had better sensitivity and specificity for the diagnosis of asthma compared to the other symptoms cough and breathing difficulty, which are rather non-specific. The sensitivity and specificity of wheeze for a diagnosis of asthma varied between 0.55-0.86 (Low to moderate) and 0.48-0.90 (very low to good) respectively. The ranges in sensitivity and specificity of cough for asthma were respectively 0.14-0.71 (very low to moderate) and 0.27-0.68 (very low to low); note that different definitions of cough were used across studies. Results for breathing difficulty were variable and this symptom generally was non-specific (11-14).	

Desirable Effects How substantial are the desirable anticipated effects of using the presence of the symptoms wheeze, cough and breathing difficulty to diagnose asthma?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ **Moderate** ○ Large ○ Varies	Wheeze heard by a health care professional has the best specificity (0.48-0.90) for the diagnosis of asthma of the classical symptoms wheeze, cough and breathing	A detailed clinical history and examination are important in the diagnostic work-up for asthma. Clinical symptoms are relatively easy to assess and wheeze heard by a clinician is an

○ Don't know	difficulty.	important sign of asthma. Wheeze reported by the child or the caregiver is less reliable. In cases where cough is the predominant symptom, asthma is less likely.
Undesirable Effects How substantial are the undesirable anticipated effects of using the presence of the symptoms wheeze, cough and breathing difficulty to diagnose asthma?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Large** ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	There is evidence that using a history of symptoms including wheeze, cough and breathing difficulty alone results in misdiagnosis in a considerable number of children.	The presence of wheeze is an important sign of asthma. However, by itself the sensitivity and specificity of a history of wheeze is too low for this to be diagnostic by itself. Wheeze is usually absent when the patient is well.
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of of using the presence of the symptoms wheeze, cough and breathing difficulty to diagnose asthma?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ **Moderate** ○ High ○ No included studies	The certainty of the evidence of test accuracy is moderate.	
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the presence of the symptoms wheeze, cough and breathing difficulty?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ **Moderate** ○ High ○ No included studies	Not reviewed as part of this TF.	Much depends on the timing of the assessment and the reporting of symptoms is subjective. Variable sensitivity carries the risks of misdiagnosis and this can adversely affect health outcomes. Management

		decisions based on the presence or absence of asthma signs and symptoms are likely to be variable and depend on the health care setting and resources.
Certainty of the evidence of test result/management How certain is the link between the presence of the symptoms wheeze, cough and breathing difficulty and management decisions?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ **Low** ○ Moderate ○ High ○ No included studies	Not reviewed as part of this TF.	Management decisions based on the presence or absence of asthma signs and symptoms are likely to be variable and depend on the health care setting and resources.
Balance of effects Does the balance between desirable and undesirable effects favor the use of presence of the symptoms wheeze, cough and breathing difficulty for diagnosis or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ **Probably favors the comparison** ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The sensitivity of wheeze for asthma ranged from very low to moderate (0.55-0.86) and specificity varied from very low to good (0.48-0.90). The ranges in sensitivity and specificity of cough and breathing difficulty for asthma were very wide and as low as 0.14.	Clinical symptoms are relatively easy to assess and wheeze heard by a clinician is an important sign of asthma. However, by itself the sensitivity and specificity of a history of wheeze is too low for this to be diagnostic by itself and wheeze is usually absent when the patient is well. This raises the risk of misdiagnosis leading to either over-treatment or under-treatment of asthma and the risk of missing the correct diagnosis.

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ **Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Not reviewed as part of this TF.	The health care practitioner obtains the clinical history of asthma signs and symptoms during the medical consultation. There are no additional costs.
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ **Probably reduced** ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Not reviewed as part of this TF.	Not reviewed as part of this TF. but members are aware that language is important when describing symptoms and the word wheeze does not exist in all the languages. Description of symptoms is subjective. Unequal access to additional tests may result in less health equity in relevant populations. However using symptoms alone will result result in a delay in appropriate asthma treatment or in over-treatment and potentially missing the correct diagnosis in a considerable number of children.
Acceptability Is the use of the presence of the symptoms wheeze, cough and breathing difficulty for diagnosis acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ **Probably no** ○ Probably yes ○ Yes ○ Varies ○ Don't know	Not reviewed as part of this TF.	This intervention is not invasive or painful, but has the potential to result in significant misdiagnosis, mostly overdiagnosis but underdiagnosis is also possible. Parents and lay members of the TF expressed concern about the rate of misdiagnosis. They also raised concern about diagnosing asthma based on the

		presence or absence of symptoms alone.
Feasibility Is the the use of presence of the symptoms wheeze, cough and breathing difficulty for the diagnosis of asthma feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	Not reviewed as part of this TF.	Evaluation of symptoms is part of every asthma consultation.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

Conclusions

Recommendation

- The TF recommends against diagnosing asthma based on symptoms alone (strong recommendation against the intervention, moderate quality of evidence)

Remarks:

1. Recurrent wheeze, cough and breathing difficulty are key symptoms of asthma. The TF considers a history of recurrent reported wheeze or wheeze on auscultation as the most important symptom of asthma
2. Children with chronic cough (i.e. cough for more than 4 weeks) as the only symptom are unlikely to have asthma and should be investigated according to the ERS guidelines for chronic cough in children (15) and a referral for further investigations to exclude differential diagnoses should be considered

Justification

Overall, the sensitivity of wheeze to correctly identify a child with asthma ranged between 0.55 and 0.86 and the specificity between 0.64 and 0.90. Using the presence of the symptoms wheeze, cough and breathing difficulty alone results in misdiagnosis in a considerable number of children. The TF agreed that sensitivity and specificity of wheeze was not strong enough to confirm a diagnosis of asthma on its own.

Subgroup considerations

none

Implementation considerations

none in addition to the above

Monitoring and evaluation

not applicable

Research priorities

We need studies investigating the sensitivity and specificity of symptoms in combination with other respiratory symptoms.

PICO 2: In children aged 5-16 years under investigation for asthma, should an improvement in symptoms following a trial of preventer medication be used to diagnose asthma?

Supplementary material

We wanted to include studies investigating the diagnostic accuracy of a trial of preventer medication with inhaled corticosteroids (ICS, alone or in combination with long acting beta agonists) and/or leukotriene receptor antagonists (LTRA) in children aged 5 to 15 years under investigation for asthma. Of the 2835 papers identified through the database searches and two papers identified through reference lists, we excluded 766 duplicated papers, 2031 papers based on title and abstract screening, and 40 papers after the full-text eligibility assessment (supplementary figure 1B). The exclusion reasons in the full-text screening (supplementary table 30) were not original article (n = 9), age < 5 years or median age > 20 years (n = 12), inclusion criteria not patients suspected for asthma (n = 11), and non-diagnostic studies (n = 8).

Most studies did not meet the inclusion criteria because they investigated the role of treatment trial in assessing effectiveness of treatment in children already diagnosed with asthma rather than its diagnostic accuracy in children suspected for asthma. For instance, Baxter-Jones et al assessed symptom response in a six-month treatment trial (16). They randomized 86 British children aged six months to 16 years with history suggestive of asthma and/or recurrent wheeze, naïve to preventer medication, to either SABA or SABA plus ICS treatment. There were no significant differences in the number of symptom-free days between treatment groups after three- and six-months follow-up. More than half of the children had more days free of symptoms at three months of follow-up in both the SABA group and the ICS group (56% vs. 58% respectively), about a third had fewer symptom-free days (31 vs. 34%) and the rest experienced no change (13% vs. 8%). In a randomized crossover trial including children aged 6-17 years with mild to moderate asthma, Szefler et al studied whether the children's responses to ICSs and LTRAs were concordant (17). After an 8-week course of each medication, response was assessed as improvement in FEV1 of 7.5% or greater. Out of 126 children completing both treatment arms, 17% responded similarly to both treatments while 55% did not respond to either. 23% of children responded to fluticasone and 5% to montelukast alone. The EtD table for PICO 2 is shown in supplementary table 6.

Supplementary table 6: Evidence to decision table for PICO 2

PICO question

In children aged 5-16 years under investigation for asthma, should an improvement in symptoms following a trial of preventer medication be used to diagnose asthma?	
POPULATION:	Children aged 5-16 years under investigation for asthma
INTERVENTION:	Conducting a trial of preventer medication with inhaled corticosteroids and/or leukotriene receptor antagonists to diagnose asthma

ASSESSMENT

Test accuracy How accurate is a trial of preventer medication?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ **Inaccurate** ○ Accurate ○ Very accurate ○ Varies ○ Don't know	No studies identified that fulfilled the inclusion criteria.	We found no studies to determine the diagnostic accuracy of a trial of preventer medication in children in children under investigation for asthma. A proportion of children diagnosed with asthma may not see an improvement in symptoms despite a trial of preventer medication based on clinical experience and on treatment efficacy studies (16,17). Asthma symptoms can be influenced also by inhaler technique, adherence, seasonal changes and exposure to trigger factors. Therefore, an improvement in symptoms after a trial of preventer medication in children suspected for asthma would probably be an inaccurate test to diagnose asthma.
Desirable Effects How substantial are the desirable anticipated effects of a trial of preventer medication?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large	No studies identified that fulfilled the inclusion criteria.	The test on its own has no physical effect on the children. Children correctly diagnosed with asthma may experience an improvement in their symptoms after

○ Varies ○ **Don't know**		a trial of preventer medication based on clinical experience and on treatment efficacy studies. (16,17)
Undesirable Effects How substantial are the undesirable anticipated effects of a trial of preventer medication?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ **Moderate** ○ Small ○ Trivial ○ Varies ○ Don't know	No studies identified that fulfilled the inclusion criteria.	The test on its own has no physical effect on the children because when it is being done it is only for a short period of time. There is a risk of over-treatment in children misdiagnosed with asthma.
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of a trial of preventer medication test accuracy?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Very low** ○ Low ○ Moderate ○ High ○ No included studies	No studies identified that fulfilled the inclusion criteria.	We have very low certainty for the accuracy of using an improvement in symptoms after a trial of preventer medication to diagnose asthma in children, since we found no evidence.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the a trial of preventer medication result?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Very low** ○ Low ○ Moderate ○ High ○ No included studies	Not reviewed as part of this TF.	Asthma management guided by an improvement in symptoms after a trial of preventer medication may result in overtreatment due to misdiagnosis, but our certainty is very low based on the lack of research evidence.
Certainty of the evidence of test result/management How certain is the link between a trial of preventer medication test result and management decisions?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ **Very low** ○ Low ○ Moderate ○ High	Not reviewed as part of this TF.	In clinical practice, some physicians take into account symptom improvement after a trial of preventer medication to stablish an asthma diagnosis, but never

○ No included studies		base the final diagnosis solely on this test.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ **Does not favor either the intervention or the comparison** ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	No studies identified that fulfilled the inclusion criteria.	A trial of preventer medication is not an invasive or costly intervention, but carries the potential risk of misdiagnosis, resulting in unnecessary treatment of children misdiagnosed with asthma and potentially a delay in establishing the correct diagnosis.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Not reviewed as part of this TF.	A trial of preventer medication is not an expensive intervention based on clinical experience.
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	Not reviewed as part of this TF.	A trial of preventer medication is probably accessible though prescription to any subgroup of the population if indicated based on clinical experience. However, in low income countries the cost of the required medication might be too high.

Acceptability Is a trial of preventer medication acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ **Probably no** ○ Probably yes ○ Yes ○ Varies ○ Don't know	Not reviewed as part of this TF.	This intervention is not invasive or painful, but is likely to result in significant misdiagnosis, mostly overdiagnosis but underdiagnosis is also possible. Parents and key stakeholders have expressed concern about the rate of misdiagnosis.
Feasibility **Is a trial of preventer medication feasible to implement?**		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	Not reviewed as part of this TF.	A trial of preventer medication is feasible to implement based on clinical experience. However this approach likely results in significant misdiagnosis.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

- The TF recommends against using an improvement in symptoms after a trial of preventer medication alone to diagnose asthma (conditional recommendation against the intervention, based on clinical experience)

Remarks:

1. The TF did not find any evidence for or against a trial of preventer medication to diagnose asthma in children aged 5 to 16 years

2. Despite the lack of evidence, based on clinical experience, the TF members agreed that a trial of preventer medication can be considered; but only in symptomatic children with abnormal spirometry and negative bronchodilatator response. In such cases, the objective tests spirometry and, if indicated, BDR should be repeated after 4 to 8 weeks

Justification

Despite the lack of evidence to support a recommendation, the TF members are well aware that a trial of preventer medication is widely employed by clinicians to evaluate the response in children with symptoms of asthma. The main reason for this is remaining diagnostic uncertainty and because spirometry and FeNO confirm asthma only in a minority of children seen during routine clinical reviews in children (18-20). The TF discussed and agreed that a trial of treatment with ICS can be considered, but only in steroid-naïve or non-adherent children with asthma symptoms in whom initial tests have not been able to confirm the diagnosis. Objective tests should be repeated after 4 to 8 weeks. (2,17,21,22)

The difference in our diagnostic approach is that the TF does not recommend to diagnose asthma on the basis of improvements in reported symptoms alone following the treatment trial but to base the diagnosis on a significant improvement in lung function and symptoms after completion of the trial of treatment. This recommendation is supported by the GINA 2020 strategy document. (2) GINA in addition proposes a supervised stepping down of preventer medication in conjunction with lung function tests to confirm or refute the presence of (active) asthma.

Subgroup considerations

Implementation considerations

Monitoring and evaluation

Research priorities

There is a need for validation studies investigating the diagnostic accuracy and limitations of preventer medication treatment trials in preventer naïve school-age children. Studies need to assess the type, dosage and the length of the treatment trial period, taking into account factors such as proper inhaler technique, adherence to medication and the season during which the trial is conducted. Careful consideration is needed to define a positive response.

PICO 3: In children aged 5-16 years under investigation for asthma, should spirometry testing be used to diagnose asthma?

Supplementary material

PICO question 3 sought to investigate the diagnostic accuracy of spirometry testing in children aged 5-16 years under investigation for asthma. We performed the searches for PICO questions 3 and 4 together as both diagnostic tests involved the use of a spirometer and measurement of the same spirometric parameters i.e. FEV_1. Of the 2548 papers we identified 3 (supplementary table 7) through database searches, we excluded 664 duplicates, 1851 papers based on title and abstract screening, and 30 papers after the full-text eligibility assessment (supplementary figure 1C). The reasons for exclusion of the papers following full text screening are shown in supplementary table 31. We show the GRADE table for PICO 3 in the supplementary table 8; effect sizes are presented for a range of different pre-test probabilities to reflect the difference in prevalence of asthma in children cared for in different healthcare settings. The EtD table for PICO 3 is presented in supplementary table 9.

Supplementary table 7: Details of included studies for PICO 3: Spirometry testing					
Study	Study Population	Reference Standard	Index Test and cut-off	Diagnostic Accuracy of Index Test	
				Sensitivity	Specificity
Sivan 2009 Israel (23)	• 150 children (age 5-18y) referred to hospital clinic for evaluation of possible asthma • 69 were steroid naïve • Questionnaire, spirometry, FeNO and sputum eosinophilia Asthma diagnosed in 106 (71%)	A diagnosis of asthma was made during an 18-months follow up period, based on a history of two or more clinical exacerbations, dyspnoea or cough relieved by bronchodilators, documented variability in $FEV_1 \geq 15\%$ in response to bronchodilators, or documented variability of $FEV_1 \geq 15\%$ over time with or without controller medications.	$FEV_1 < 80\%$ predicted	0.52 (0.40-0.64)	0.72 (0.57-0.85)
Grzelewski 2014 Poland (24)	• Retrospective analysis case notes of 3612 children (age 6-18y) years attending an allergy clinic with symptoms suggestive of asthma and who had at least two year's follow up • Questionnaire, spirometry, Rint, sRaw, specific IgE • Asthma diagnosed in 2178 (60%)	According to GINA 2012 symptoms plus BDR ≥ 12%	FEV_1 / FVC < 80%	0.12 (0.10-0.13)	0.91 (0.89-0.93)
De Jong 2019 Switzerland (11)	• 111 children (aged 6-16y) referred to one of two hospitals due to suspected asthma • Questionnaire, spirometry, bronchodilator response, FeNO, airway challenges (exercise and methacholine) and skin prick testing. Within a week of the first tests, a mannitol challenge and second FeNO measurement were performed. • Asthma diagnosed in 80 (72%)	One clinician made a diagnosis on the first assessment based on symptoms, skin prick tests, FeNO and spirometry. The same clinician revisited the diagnosis on the second visit based on all the data available. Asthma was defined as either "definite" or "probable" asthma.	FEV_1 / FVC < 80%	0.46 (0.35-0.58)	0.93 (0.78-0.99)
			FEV_1 z-score $\leq$ -0.8	0.44 (0.33-0.56)	0.77 (0.59-0.90)

Supplementary table 8: GRADE table forPICO 3: Should spirometry be used to diagnose asthma in children?

Sensitivity	0.12 to 0.52
Specificity	0.72 to 0.93

Prevalence	30%*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
True positives (patients with Asthma)	3 studies 3873 patients	cross-sectional (cohort type accuracy study)	serious [1,2,3,a]	not serious	not serious	not serious	none	36 to 156	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having Asthma)								144 to 264	
True negatives (patients without Asthma)	3 studies 3873 patients	cross-sectional (cohort type accuracy study)	serious 1,2,3[a]	not serious	not serious	not serious	none	504 to 651	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having								49 to 196	

Asthma)									

Explanations: *Pretest probability was pragmatically estimated at 30% because the prevalence of asthma in children is around 5 to 15% and children presenting for investigation with symptoms are likely to have a higher pre-test probability.

[a]Unclear if reference standard results were interpreted without knowledge of the results of the index test

Supplementary table 9: Evidence to decision table for PICO 3.

PICO question

In children aged 5-16 years under investigation for asthma, should spirometry testing be used to diagnose asthma?	
POPULATION:	Children 5 to 16 years under investigation for asthma
INTERVENTION:	Performing spirometry testing to diagnose asthma

Assesment

Test accuracy How accurate is spirometry testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very inaccurate o Inaccurate o Accurate o Very accurate o **Varies** o Don't know	Spirometry has very low to low sensitivity (0.12 to 0.52) but moderate to good specificity (0.72 to 0.93) for the diagnosis of asthma.	Asthma is a variable condition and lung function is frequently normal when the patient is well. This means that a normal spirometry result does not rule out the diagnosis. In contrast, abnormal spirometry makes the diagnosis more likely.
Desirable Effects How substantial are the desirable anticipated effects of spirometry testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small o **Moderate** o Large o Varies o Don't know	Abnormal spirometry has a moderate to good specificity (0.72 to 0.93) as a diagnostic test for asthma in children.	Spirometry testing is a non-invasive procedure. Abnormal spirometry and a positive reversibility test confirm the diagnosis.

Undesirable Effects How substantial are the undesirable anticipated effects of spirometry testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ **Small** ○ Trivial ○ Varies ○ Don't know	There is evidence that the sensitivity of spirometry on its own is very low or low (0.12 to 0.52) as a diagnostic test for asthma.	Spirometry and BDR testing are well tolerated but time-consuming away from specialist services (20). The test is generally well tolerated however a small number of children report light-headedness especially after repeated forced expiratory manoeuvres. In some children the repeated forced expiratory manoeuvres themselves can cause progressive airway obstruction and the number of manoeuvres should be limited in those children and a bronchodilator administered. Asthma is an episodic condition and spirometry is frequently normal when the child's asthma is well controlled or the child is asymptomatic
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of spirometry test accuracy?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ **Moderate** ○ High ○ No included studies	The certainty of the evidence of test accuracy is moderate.	Accuracy of the test itself depends on operator training and child cooperation. Evidence of test accuracy is moderate however, timing of the test is important. The certainty of asthma diagnosis is high where abnormal spirometry and positive BDR have been demonstrated.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the spirometry test result?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ **Moderate** ○ High	Not reviewed as part of this TF.	Low sensitivity risks delaying making the correct diagnosis and this can adversely impact health outcomes. The TF is aware that spirometry is frequently normal in

○ No included studies		children with asthma especially if measured during stable disease as asthma is a variable condition. Where spirometry is abnormal the test has good specificity as a diagnostic test for asthma in children. An abnormal spirometry test result is likely to guide management.
Certainty of the evidence of spirometry test result/management How certain is the link between spirometry test results and management decisions?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	Not reviewed as part of this TF.	Spirometry by itself has low sensitivity and a normal spirometry does not rule out asthma. An abnormal spirometry test result is likely to guide management.
Balance of effects Does the balance between desirable and undesirable effects favor spirometry testing or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	Spirometry testing provides moderate to good specificity for diagnosing asthma. Normal spirometry does not rule out asthma.	The test is non-invasive and abnormal spirometry with positive BDR confirms the diagnosis.

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Not reviewed as part of this TF.	Moderate cost for equipment and maintenance and training issues. Spirometry alone takes approximately 5 minutes, spirometry with BDR testing approximately 30 minutes of operator time (20). There is also training required to interpret the results.
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ **Don't know**	Not reviewed as part of this TF.	Not providing spirometry may delay the diagnosis in relevant populations. This may result in a delay in appropriate asthma treatment. This would have a negative impact on health equity.
Acceptability Is spirometry testing acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Not reviewed as part of this TF.	The intervention was judged acceptable to the lay members of the TF. In fact the lay members preferred to have objective evidence for asthma ascertained by healthcare professionals. Acceptance may vary depending on resources, healthcare settings and travel times.

Feasibility Is spirometry testing feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Not reviewed as part of this TF.	There are equipment and maintenance costs and costs for consumables. There are training costs to perform the test and interpret the test results.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	○

CONCLUSIONS

Recommendation

- The TF recommends to perform spirometry as part of the diagnostic work-up of children aged 5-16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence)

Remarks:

1. An FEV_1/FVC < LLN or < 80%, or an FEV_1 < LLN, or < 80% predicted should be considered supportive of an asthma diagnosis. It is important to be aware that not all children are able to perform a sufficient FVC manoeuvre resulting in a false normal FEV_1/FVC ratio
2. A normal spirometry result does not exclude asthma

Justification

Good quality spirometry can detect airway obstruction, the hallmark of asthma. Obstructed spirometry with positive BDR confirms the diagnosis. Spirometry testing is fairly quick and non-invasive and an experienced operator can obtain good quality data from the majority of children ≥ 5 years (20,25). The equipment is portable and the test is widely available, however availability in primary care is variable. It is important to emphasise that spirometry as a one-off measurement has

a low sensitivity and is therefore poor at ruling out asthma. Because of the variable nature of the condition, when the asthma is controlled, spirometry is frequently normal (19,20). Serial measurements may be required to confirm the diagnosis (26). Abnormal spirometry has good specificity for asthma.

Subgroup considerations

none

Implementation considerations

Equipment and maintenance costs and costs for consumables.
Training costs to perform the test and interpret the test results.

Monitoring and evaluation

not applicable

Research priorities

There is an urgent need for well-designed studies in children assessing the diagnostic accuracy of spirometry using GLI LLN.

PICO 4: In children aged 5-16 years under investigation for asthma, should bronchodilator reversibility (BDR) testing be used to diagnose asthma?

Supplementary material

PICO question 4 aimed to investigate the diagnostic accuracy of BDR testing in children aged 5-16 years under investigation for asthma. We identified 2548 papers through database searches, excluded 664 duplicates, 1851 papers based on title and abstract screening, and 33 papers after the full-text eligibility assessment (supplementary figure 1D). The reasons for exclusion of the papers following full text screening are shown in table x. A positive BDR test, usually using the 12% and/or ≥ 200 ml threshold is generally taken as diagnostic for asthma. No study investigated the diagnostic accuracy of BDR as a diagnostic test for asthma for that reason. We show the evidence to decision table for PICO 4 in supplementary table 10.

Supplementary table 10: Evidence to decision table for PICO 4.

PICO question

In children aged 5-16 years under investigation for asthma, should bronchodilator reversibility (BDR) testing be used to diagnose asthma?	
POPULATION:	Children 5 to 16 years under investigation for asthma
INTERVENTION:	Performing BDR testing to diagnose asthma

Assesment

Test accuracy How accurate is the BDR test?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ **Varies** ○ Don't know	No studies identified that fulfilled the inclusion criteria.	Asthma is universally defined as a condition with variable airflow limitation (2,4,26-28) and abnormal spirometry with a positive BDR is generally taken as support for the diagnosis. Most studies included in this evidence-based clinical practice guideline have used BDR ≥ 12% as confirmtory test for asthma. There has been discussion about cut-offs (29) but the validity of a positive BDR test is not in question. A negative BDR does not rule out the diagnosis of asthma.
Desirable Effects How substantial are the desirable anticipated effects of BDR testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ **Moderate** ○ Large ○ Varies ○ Don't know	No studies identified that fulfilled the inclusion criteria.	Abnormal spirometry and a positive BDR confirm the diagnosis due to the high specificity of a positive BDR test. (29) BDR testing is a non-invasive procedure and usable results are obtained in the majority of children from age 5 years (30). Spirometry and BDR can be performed in any health care setting and the results are immedaitely available. Equipment and consumables costs are moderate. Given that reversible airflow obstruction is the hallmark of asthma it would make little sense to perform spirometry and not BDR in cases where spirometry is abnormal/obstructed. Importantly, a child with abnormal spirometry and no evidence of BDR should be referred to specialist care because the child could have either a restrictive lung disease or fixed airways obstruction, both of which require further investigations.

Undesirable Effects How substantial are the undesirable anticipated effects of BDR testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ **Small** ○ Trivial ○ Varies ○ Don't know	No studies identified that fulfilled the inclusion criteria.	BDR testing is time-consuming (20,25) and away from specialist services this is an important consideration. In addition, the test relies on the performance of spirometry and this requires training to perform the test and training to interpret the results. None of the studies included in this TF report that used BDR testing in children reported any side effect relating to the test. Minor side effects in the experience of the TF members are fleeting light-headedness following SABA administration and repeated forced expiratory manoeuvres. This however rarely results in the test not being performed as planned. One solution is for those children with light-headedness is to sit down for a few minutes and to perform the test with the child sitting rather than standingDue to moderate staff, equipment and training costs and low sensitivity the test is frequently not done in low resource and in primary care settings.
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of BDR test accuracy?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ **Varies** ○ No included studies	No studies identified that fulfilled the inclusion criteria.	The hallmark of asthma is variable airflow obstruction. Therefore the certainty of an asthma diagnosis is high in children presenting with symptoms of asthma who have abnormal spirometry and a positive BDR test. Accuracy of the test itself depends on operator training and child cooperation and timing of the test is important. Uncertainty exists with the proposed cut-off of ≥ 12% (29). This cut-off is usually used in children although there is no direct evidence for its validity in children. This cut-off has poor sensitivity but good specificity for the diagnosis of asthma.

Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the BDR test results?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	Not reviewed as part of this TF.	Abnormal spirometry with positive BDR confirms the diagnosis and appropriate treatment is usually started.
Certainty of the evidence of test result/management How certain is the link between BDR test results and management decisions?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	Not reviewed as part of this TF.	Abnormal spirometry with positive BDR confirms the diagnosis and appropriate treatment is usually started.
Balance of effects Does the balance between desirable and undesirable effects favor BDR testing or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	Not reviewed as part of this TF.	BDR testing using the 12% cut-off has poor sensitivity but good specificity. It is not a good test to rule out asthma, the major weakness of this test. The BDR value is continuous and the 12% cut-off arbitrary. The higher the BDR the more likely it is that the patient has asthma. The test is non-invasive and abnormal spirometry with positive BDR confirms the diagnosis. Looking at the balance between desirable and undesirable effects the TF agreed that BDR testing should be offered to children with abnormal spirometry.

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Not reviewed as part of this TF.	Moderate cost for equipment, consumables, maintenance and training. Spirometry alone takes approximately 5 minutes, spirometry with BDR testing approximately 30 minutes of operator time (30). Cost-effectiveness has not been evaluated as part of this evidence synthesis.
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ **Don't know**	Not reviewed as part of this TF.	Not providing BDR testing may delay the diagnosis in relevant populations. This may result in a delay in appropriate asthma treatment. This would have a negative impact on health equity.
Acceptability Is BDR testing acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Not reviewed as part of this TF.	The intervention was judged acceptable to the patient and caregiver members of the TF. Patients and caregivers expressed that they would like asthma to be confirmed using objective tests rather than relying on clinical judgement alone. Acceptance by stakeholders will vary depending on resources and healthcare setting.

Feasibility Is BDR testing feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Not reviewed as part of this TF.	Implementation of the intervention per se is feasible in many if not all health care settings.There are equipment, consumables and maintenance costs. (20) The training requird to perform and implement BDR testing and the time taken to perform the test will be barriers in some health care settings. Implementation was Not reviewed as part of this TF.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	○

CONCLUSIONS

Recommendation

- The TF recommends BDR testing in all children with FEV_1 < LLN or < 80% predicted and/or FEV_1/FVC < LLN or < 80% predicted (strong recommendation for the intervention, based on clinical experience)

Remarks:

1. Consider an increase in FEV_1 ≥ 12% and/or 200 ml following inhalation of 400 micrograms of a short acting beta2-agonist as diagnostic of asthma
2. A BDR < 12% does not exclude asthma
3. Most TF members consider BDR testing when baseline spirometry is normal if the clinical history is strongly suggestive of asthma

Justification

Variable airflow limitation is a defining feature of asthma and a positive BDR in conjunction with obstructed spirometry has a high accuracy at confirming the diagnosis in children with relevant clinical signs and symptoms. Most studies included in these guidelines use a positive BDR test as the reference standard to support the diagnosis of asthma. The TF agreed with the cut-off for BDR of 12% in children, in agreement with previous studies in children (29,31) and existing international asthma guidance. (2,4,26,32). The TF acknowledges that BDR testing has low sensitivity especially at the 12% threshold but good specificity for a diagnosis of asthma in children (29). The TF acknowledges that there are resource implications, but based on the high specificity of the test, its non-invasive nature and its availability, the TF recommends BDR testing in children with obstructed spirometry and/or low FEV_1.

The TF considered that BDR testing is a non-invasive procedure and usable results are obtained in the majority of children. Spirometry and BDR can be performed in any health care setting and the results are immedaitely available. Equipment and consumables costs are moderate but the test is time consuming and there are training requirements. Reversible airflow obstruction is the hallmark of asthma and it would make little sense to perform spirometry but not BDR in cases where spirometry is abnormal/obstructed.

Subgroup considerations

The TF recommends BDR testing in children with abnormal spirometry. The TF is aware that in some setings BDR testing is also performed in children with normal spirometry as a small number of these children will have BDR ≥ 12% despite normal spirometry and with this a confirmation of the diagnosis.

Implementation considerations

Equipment and maintenance costs and costs for consumables.
Training costs to perform the test and interpret the test results.

Monitoring and evaluation

not applicable

Research priorities

There is an urgent need for well-designed studies in children assessing the best cut-off value for BDR testing in children.

PICO 5: In children aged 5-16 years under investigation for asthma, should FeNO testing be used to diagnose asthma?

Supplementary material

The references of 26 systematic reviews on the diagnostic accuracy of FeNO were screened and two research papers identified through other sources (supplementary figure 1D). Five studies were included in the quantitative and qualitative analysis (supplementary table 11). Excluded studies after full-text review are shown in supplementary table 33 and the GRADE table for included studies in supplementary table 12. Sensitivity and specificity analysis for different FeNO cut-offs obtained form the included studies are shown in table 13. The evidence to decision table for PICO 5 is shown in supplementary table 14.

Supplementary table 11: Details of included studies for PICO 5: FeNO testing					
Study	Study Population	Reference Standard	Index Test and cut-off	Diagnostic Accuracy of Index Test	
				Sensitivity	Specificity
Brouwer 2010 Netherlands (12)	• 61 children (aged 6-16 y) referred to hospital due to chronic respiratory symptoms • ICS and LABA withheld for four weeks • Semi-structured medical history, spirometry, bronchodilator response, and FeNO at baseline • FEV_1 and peak flow variability twice daily for 14 days • FeNO and methacholine challenge after 14 days • Asthma diagnosed in 21 (34%) • 56% (34) had IgE specific for inhaled allergens	Based on the history, physical examination and lung function data on the second visit (including spirometry, bronchodilator response and methacholine challenge but not including variability data).	>16ppb	0.68 (0.43. 0.87)	0.36 (0.21, 0.53)
Woo 2012 South Korea (33)	• 245 steroid naïve children (aged 8-16y) referred to hospital for evaluation of asthma • Questionnaire, spirometry, FeNO, methacholine challenge and skin prick testing • Asthma diagnosed in 167 (68%) • 77% (189) had at least one positive skin prick test	According to NAEPP guidelines, i.e. relevant symptom history and ≥12% BDR and/or methacholine PC_{20} ≤8mg/mL	>21ppb	0.57 (0.49, 0.65)	0.87 (0.78, 0.94)
Sivan 2009 Israel (23)	• 150 children (age 5-18y) referred to hospital clinic for evaluation of possible asthma • 69 were steroid naïve • Questionnaire, spirometry, FeNO and sputum eosinophilia • Asthma diagnosed in 106 (71%) • Allergy testing was not included in patient evaluation	A diagnosis of asthma was made during an 18-months follow up period, based on a history of two or more clinical exacerbations, dyspnoea or cough relieved by bronchodilators, documented variability in FEV_1 ≥ 15% in response to bronchodilators, or documented variability of FEV_1 ≥ 15% over time with or without controller medications.	>19ppb	0.86 (0.78-0.92)	0.89 (0.75-0.97)
Grzelewski 2014 Poland (24)	• Retrospective analysis case notes of 3612 children (age 6-18y) years attending an allergy clinic with symptoms suggestive of asthma and who had at least two year's	According to GINA 2012 symptoms plus FEV_1 ≥ 12%	>16 ppb	0.59 (0.56- 0.62)	0.47 (0.44, 0.51)

	follow up • Questionnaire, spirometry, Rint, sRaw, specific IgE • Asthma diagnosed in 2178 (60%) • 50% (863) were sensitised to at least one perennial allergen				
De Jong 2019 Switzerland (11)	• 111 children (aged 6-16y) referred to one of two hospitals due to suspected asthma • Questionnaire, spirometry, bronchodilator response, FeNO, airway challenges (exercise and methacholine) and skin prick testing. Within a week of the first tests, a mannitol challenge and second FeNO measurement were performed. • Asthma diagnosed in 80 (72%) • 62% (69) had at least one positive skin prick test	One clinician made a diagnosis on the first assessment based on symptoms, skin prick tests, FeNO and spirometry. The same clinician revisited the diagnosis on the second visit based on all the data available. Asthma was defined as either “definite” or “probable” asthma.	>20ppb	0.59 (0.47, 0.70)	0.87 (0.70, 0.96)

Supplementary table 12: GRADE table forPICO 5: Should FeNO be used to diagnose asthma in children?

Sensitivity	0.57 to 0.86
Specificity	0.36 to 0.89

Prevalence	30%*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
True positives (patients with [asthma])	5 studies 4179 patients (11,12,23,24,33)	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious	not serious	none	171 to 258	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having [asthma])								42 to 129	
True	5 studies	cross-	serious [a]	not serious	not serious	not serious	none	252 to 623	⨁⨁⨁◯

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
negatives (patients without [asthma])	4179 patients (11,12,23,24,33)	sectional (cohort type accuracy study)							MODERATE
False positives (patients incorrectly classified as having [asthma])								77 to 448	

Explanations: *Pretest probability was pragmatically estimated at 30% because the prevalence of asthma in children is around 5 to 15% and children presenting for investigation with symptoms are likely to have a higher pre-test probability.

[a]Unclear if reference standard results were interpreted without knowledge of the results of the index test

Supplementary table 13: Sensitivity and specificity results for different cut-points for FeNO based on five eligible studies.

Cut off	Single studies					All studies	
	Sivan 2009 (23) N=144	Brouwer 2010 (12) N=58	Woo 2012 (33) N=245	Grzelewski 2014 (24) N=1784	De Jong 2019 (11) N=111	Mean	Youdens Index (Sens + Spec - 100)
>15 ppb	Sens: 90 Spec: 70	Sens: 68 Spec: 33	Sens: 72 Spec: 67		Sens: 70 Spec: 74	Sens: 75 Spec: 61	36
>16 ppb		Sens: 68 Spec: 36		Sens: 59 Spec: 47	Sens: 68 Spec: 77	Sens: 65 Spec: 53	16
>17 ppb		Sens: 63 Spec: 36			Sens: 64 Spec: 77	Sens: 64 Spec: 57	19
>18 ppb		Sens: 58 Spec: 38			Sens: 61 Spec: 84	Sens: 60 Spec: 61	21
>19 ppb	Sens: 86 Spec: 89	Sens: 58 Spec: 38			Sens: 59 Spec: 84	Sens: 68 Spec: 70	38
>20 ppb		Sens: 53 Spec: 38	Sens: 61 Spec: 81		Sens: 59 Spec: 87	Sens: 58 Spec: 68	26
>21 ppb		Sens: 53 Spec: 41	Sens: 57 Spec: 87		Sens: 55 Spec: 87	Sens: 55 Spec: 72	27
>22 ppb		Sens: 53 Spec: 44	Sens: 54 Spec: 87		Sens: 53 Spec: 90	Sens: 53 Spec: 74	27
>23 ppb		Sens: 53 Spec: 44	Sens: 52 Spec: 91		Sens: 50 Spec: 90	Sens: 52 Spec: 78	30
>24 ppb		Sens: 53 Spec: 49	Sens: 50 Spec: 91		Sens: 50 Spec: 94	Sens: 51 Spec: 78	29
>25 ppb	Sens: 75 Spec: 89	Sens: 53 Spec: 49	Sens: 50 Spec: 92		Sens: 48 Spec: 94	Sens: 57 Spec: 81	38
>30 ppb		Sens: 47 Spec: 49	Sens: 43 Spec: 95		Sens: 43 Spec: 94	Sens: 44 Spec: 79	21
>35 ppb		Sens: 37 Spec: 51	Sens: 32 Spec: 99		Sens: 38 Spec: 94	Sens: 36 Spec: 81	27

Supplementary table 14: Evidence to decision table for PICO 5.

PICO question

In children aged 5-16 years under investigation for asthma, should FeNO testing be used to diagnose asthma?	
POPULATION:	Children aged 5-16 under investigation for asthma
INTERVENTION:	Performing a FeNO measurement to diagnose asthma

ASSESSMENT

Test accuracy How accurate is the FeNO test?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ○ **Accurate** ○ Very accurate ○ Varies ○ Don't know	Identified studies reported sensitivity and specificity results for for an asthma diagnosis in children at different cut-points for FeNO. FeNO values of 25 ppb had a low mean sensitivity of 0.57 and a moderate mean specificity of 0.81.	To reach this decision the panel considered the harm from over-treatment arising from false positive results and the remit of the TF, which was to provide recommendations on diagnosing asthma and not on excluding asthma. The TF panel recognises that any cut-point is arbitrary to some extent but the panel agreed that a single recommended cut off value is essential. Based on the Youden index the panel agreed that 25 ppb was the best cut-off value.
Desirable Effects How substantial are the desirable anticipated effects of FeNO testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ **Moderate** ○ Large ○ Varies ○ Don't know	A FeNO ≥ 25ppb has moderate specificity (moderate mean specificity 0.81) as a diagnostic test for asthma in children.	FeNO testing is a non-invasive procedure. The test is quick and easy to perform. Moderate specificity results for for an asthma diagnosis in children.
Undesirable Effects How substantial are the undesirable anticipated effects of FeNO testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ **Moderate** ○ Small ○ Trivial ○ Varies ○ Don't know	There is evidence that FeNO ≥ 25ppb has only low sensitivity as a diagnostic test for asthma in children depending on the population studied. This could lead to underdiagnosis due to false negatives. Equally, moderate specificity can result	FeNO is not a test for asthma. FeNO is raised in other atopic conditions such as eczema and allergic rhinitis. It is important to interpret FeNO in the context of the clinical picture. Normal FeNO values do not rule out a diagnosis of asthma.

	in overdiagnosis.	
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of FeNO test accuracy?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ **Moderate** ○ High ○ No included studies	The certainty of evidence for test accuracy is moderate.	Good quality studies have shown that FeNO has low sensitivity and moderate specificity to support an asthma diagnosis in children. FeNO is raised in other atopic conditions and the test needs to be interpreted in the context of the clinical presentation.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the FeNO test result?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ **Moderate** ○ High ○ No included studies	Not reviewed as part of this TF.	The TF agreed that a raised FeNO should not be used by itself to diagnose asthma in children.
Certainty of the evidence of test result/management How certain is the link between FeNO test results and management decisions?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	Not reviewed as part of this TF.	FeNO by itself has low sensitivity and moderate specificity and a raised FeNO alone does not confirm the diagnosis of asthma. Equally, a low FeNO does not rule out an asthma diagnosis.

Balance of effects Does the balance between desirable and undesirable effects favor the FeNO test or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	FeNO testing provides low sensitivity and modeate specificity to support an asthma diagnosis in children.	The test is non-invasive and easy to interpret. FeNO is raised in other atopic conditions.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Not reviewed as part of this TF.	Moderate cost for equipment and consumables. Relatively little training required to perform and interpret the test result.
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ **Probably increased** ○ Increased ○ Varies ○ Don't know	Not reviewed as part of this TF..	Unequal access to FeNO may delay the diagnosis in relevant populations. This may result in a delay in appropriate asthma treatment. This would have a negative impact on health equity.

Acceptability Is FeNO testing acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Not reviewed as part of this TF.	The intervention is non-invasive and lay members of TF found it acceptable. Acceptance by health care practitioners and commissioners may vary depending on resources and healthcare setting.
Feasibility Is FeNO testing feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	Not reviewed as part of this TF.	There are equipment and consumables costs. Provided these are acceptable, there are no major barriers to implementation.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	○

Conclusions

Recommendation

- The TF recommends to measure FeNO as part of the diagnostic work-up of children aged 5 to 16 years with suspected asthma (strong recommendation for the intervention, moderate quality of evidence)

Remarks:

1. A FeNO value ≥ 25ppb in a child with asthma symptoms should be considered as supportive of a

diagnosis of asthma

1. A FeNO value < 25ppb does not exclude asthma

Justification

Although the diagnostic accuracy of FeNO is moderate the results of our review show that evidence exists to support FeNO as a useful test to diagnose asthma in children. FeNO testing is a relatively simple, non-invasive test that is highly acceptable to children and their caregivers. There are equipment and consumables costs that need to be considered. The TF panel agreed that a single recommended cut-off value was essential. The panel agreed that 25 ppb was the best cut-off value based on the mean sensitivity (0.57) and specificity (0.81) values (supplementary table 13) at this cut-point. To reach this decision the panel considered the harm from over-treatment arising from false positive results and the remit of the TF, which was to provide recommendations on diagnosing asthma and not on excluding asthma. The TF acknowledges that any cut-off relating to continuous variables such as FeNO are to some extent arbitrary and confidence into the result increases with greater distance from the cut-off value. The TF also emphasises the importance of interpreting FeNO as part of a wider clinical assessment.

Subgroup considerations

none

Implementation considerations

Equipment and consumables costs

Monitoring and evaluation

not applicable

Research priorities

Studies are required that investigate the sensitivity and specificity of FeNO in ICS naïve child populations presenting with symptoms of asthma and studies which further explore the role of FeNO in non-atopic children with asthma symptoms. Studies are also required to establish the “wash out” time after cessation of ICS or LTRA before FeNO can be used for diagnostic testing. We also need better technology to routinely test FeNO in children < 8 years.

PICO 6: In children aged 5-16 years under investigation for asthma, should peak expiratory flow rate (PEFR) variability be used to diagnose asthma?

Supplementary material

Our database searches found 148 research papers (supplementary figure 1E). No additional papers were identified through other sources including reference screening. One research paper was included in the qualitative and quantitative analysis (supplementary table 15) (12). Excluded studies after full-text review are shown in supplementary table 34, the GRADE table for the included study in supplementary table 16 and the evidence to decision table for PICO 6 in supplementary table 17.

Supplementary table 15: Details of included studies for PICO 6: 2 weeks of peak expiratory flow rate monitoring					
Study	Study Population	Reference Standard	Index Test and cut-off	Diagnostic Accuracy of Index Test	
				Sensitivity	Specificity
Brouwer 2010 Netherlands (12)	• 61 children (aged 6-16 y) referred to hospital due to chronic respiratory symptoms • ICS and LABA withheld for four weeks • Semi-structured medical history, spirometry, bronchodilator response, and FeNO at baseline • FEV_1 and peak flow variability twice daily for 14 days • FeNO and methacholine challenge after 14 days Asthma diagnosed in 21 (34%)	Based on the history, physical examination and lung function data on the second visit (including spirometry, bronchodilator response and methacholine challenge but not including variability data).	12.3%	0.50 (0.30-0.70)	0.72 (0.56-0.86)

Supplementary table 16: GRADE table forPICO 6: Should peak expiratory flow variability be used to diagnose asthma in children?

Sensitivity	0.50 (95% CI: 0.30 to 0.70)
Specificity	0.72 (95% CI: 0.56 to 0.84)

Prevalence	30%*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
True positives (patients with asthma)	1 studies 59 patients (12)	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious	not serious	none	150 (90 to 210)	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having asthma)								150 (90 to 210)	
True negatives (patients without asthma)	1 studies 59 patients	cross-sectional (cohort type	serious [a]	not serious	not serious	not serious	none	504 (392 to 588)	⊕⊕⊕◯ MODERATE

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
False positives (patients incorrectly classified as having asthma)	(12)	accuracy study)						196 (112 to 308)	

Explanations: *Pretest probability was pragmatically estimated at 30% because the prevalence of asthma in children is around 5 to 15% and children presenting for investigation with symptoms are likely to have a higher pre-test probability.

[a]Unclear if reference standard results were interpreted without knowledge of the results of the index test

Supplementary table 17: Evidence to decision table for PICO 6.

PICO question

In children aged 5-16 years under investigation for asthma, should peak expiratory flow rate (PEFR) variability be used to diagnosed asthma?	
POPULATION:	Children aged 5-16 under investigation for asthma
INTERVENTION:	Performing PEFR variability testing to diagnose asthma

ASSESSMENT

Test accuracy How accurate is the test?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Very inaccurate o **Inaccurate** o Accurate o Very accurate o Varies o Don't know	PEFR variability testing over a two-week period in children referred for assessment for asthma yielded a low sensitivity of 0.50 and moderate specificity of 0.72 in the one study included.	The evidence is based on a single study that met inclusion criteria. From the experience of the panel it is felt that the test is not a very accurate way of diagnosing asthma in children as often children/caregivers do not complete PEFR diaries or results are fabricated which leads to inaccuracy. Accuracy is further reliant on the quality of instructions that are given to children/caregivers about how to perform the test.
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o **Small** o Moderate o Large o Varies o Don't know	The test only detected asthma in half of the cases in the one study included.	The test is non-invasive and quick to perform and should not cause harm. It is a widely available test as peak flow meters are easily obtainable and cheap, however the test is rarely used.

Undesirable Effects How substantial are the undesirable anticipated effects of PEFR variability testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ **Small** ○ Trivial ○ Varies ○ Don't know	Sensitivity is low (0.50) and a negative test does not rule out a diagnosis of asthma.	The test itself is well tolerated. Repeated forced blows can result in light-headedness in a small number of children. .
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of PEFR variability test accuracy?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ **Moderate** ○ High ○ No included studies	The certainty of the evidence of test accuracy is moderate.	Accuracy of the test itself depends on caregiver and child cooperation and the extent to which the procedure for recording PEFR measurements for two weeks is explained to the child and caregiver.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by PEFR variability?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ **Low** ○ Moderate ○ High ○ No included studies	Not reviewed as part of this TF.	There is evidence of low sensitivity and moderate specificity. There is a risk of misdiagnosis and this has the potential to adversely affect health outcomes.The test is rarely performed in secondary/tertiary care. There is little evidence on the use of the test in primary care and in low resource settings.
Certainty of the evidence of test result/management How certain is the link between PEFR variability test results and management decisions?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low	Not reviewed as part of this TF.	There is uncertainty of the link between PERF variability and management decisions in children

○ Moderate ○ High ○ **No included studies**		as the test is rarely performed.The TF is aware that PEFR variability testing is done occasionally in UK primary care. How often this influences management decisions is not clear.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	We only found one study for inclusion in this TF report. This study reported that PEFR variability testing over a two-week period had low sensitivity but moderate specificity for a diagnosis of asthma	. A negative test does not rule out asthma.The test is widely available, cheap and non-invasive. The evidence supporting its use however is weak, therefore confidence in the test result is not high. As a result, the test is not widely performed. As a result, we have only recommended that the test be used in conjunction with other objective tests and should be used if other objective tests are not available.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ **Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Not reviewed as part of this TF.	Whilst the test itself is cheap, the test results need to be reviewed and PEFR variability calculated. The staff time needed has resource implications
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased	Not reviewed as part of this TF.	In low resource settings, the test could improve health equity as this objective tests would improve diagnostic accuracy compared to no

○ Increased ○ **Varies** ○ Don't know		tests. In high resource settings, unequal access to other objective tests may delay the diagnosis in relevant populations. This may result in a delay in appropriate asthma treatment.
Acceptability Is PEFR variability testing acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Not reviewed as part of this TF.	The intervention was judged acceptable to the patients and parents' representatives of the TF. Acceptance may vary depending on whether the test result is judged reliable or not and the availability of other tests. Acceptability may also vary depending on the health care setting such as high or low resource and primary and secondary/tertiary care.
Feasibility Is PEFR variability testing feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know	Not reviewed as part of this TF.	The intervention would be relatively easy to implement, with the caveat that currently only < 50% of PEFR diaries are returned to the medical team. Factors that increase the return of PEFR diaries need more research.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

- The TF recommends against PEFR variability testing as the primary objective test on its own to diagnose asthma in children aged 5-16 years (conditional recommendation against the intervention, moderate quality of evidence)

Remarks:

1. Other objective tests are preferred but a PEFR variability test can be considered in healthcare settings lacking other objective tests
2. If a PEFR variability test is used the result should be based on two weeks of measurements, ideally using electronic peak flow meters
3. A cut-off of ≥ 12% in PEFR variability should be considered a positive test
4. A PEFR variability of <12% does not exclude asthma

Justification

PEFR variability has been included as an optional test in the diagnostic algorithm however spirometry (with BDR where appropriate) and FeNO are preferred first line diagnostic tests. There is limited evidence to support PEFR variability as an asthma diagnostic tool. The only evidence to support its use is as a PEFR diary with twice-daily measurements for at least two weeks. More frequent testing may have greater sensitivity (34) but is offset by decreasing adherence to the test by children and their families (35). The use of electronic meters and diaries may help to overcome some of the adherence issues (36).

Subgroup considerations

None

Implementation considerations

The test is cheap and peak flow meters are widely available and cheap to buy. The TF did not formally assess implementation.

Monitoring and evaluation

Research priorities

To further assess the accuracy of PEFR variability in diagnosing asthma in children, future research should include (ideally treatment naïve) children referred with respiratory symptoms for workup of asthma who are investigated by means of PEFR variability and other objective tests such as spirometry, bronchodilator reversibility and bronchial provocation tests.

PICO 7: In children aged 5-16 years under investigation for asthma, should allergy testing be used to diagnose asthma?

Supplementary material

The TF subgroup screened 3002 titles and abstracts identified by the literature searches and reviewed the full-text manuscripts of 49 research papers (supplementary figure 1F). Of these, four were included in the qualitative and quantitative evaluation (supplementary table 18) (11,12,24,33). We show excluded studies after full-text review in supplementary table 35, the GRADE tables for included studies in supplementary table 19 and 20 and the evidence to decision table for PICO 7 in supplementary table 21.

Supplementary table 18: Details of included studies for PICO 7: skin prick or specific IgE (RAST) testing for aeroallergens?					
Study	Study Population	Reference Standard	Index Test and Cut-Off	Diagnostic Accuracy of Index Test	
				Sensitivity	Specificity
De Jong 2019 Switzerland (11)	• 111 children (aged 6-16y) referred to one of two hospitals due to suspected asthma • Questionnaire, spirometry, bronchodilator response, FeNO, airway challenges (exercise and methacholine) and skin prick testing. Within a week of the first tests, a mannitol challenge and second FeNO measurement were performed. • Asthma diagnosed in 80 (72%) • 62% (69) had at least one positive skin prick test	Asthma was defined as either "definite" or "probable" asthma diagnosed by a paediatric pulmonologist based on medical history, clinical examination, and all test results (skin prick test, FeNO, spirometry, airway challenge tests and bronchodilator response).	One positive skin prick test to: birch, grass, mugwort, *Alternaria*, cat, and dust mite.	0.90 (0.81-0.95)	0.40 (0.23-0.59)
			More than one positive skin prick test to the allergens mentioned above.	0.79 (0.68-0.88)	0.53 (0.34-0.72)
Woo 2012 South Korea (33)	• 245 steroid naïve children (aged 8-16y) referred to hospital for evaluation of asthma • Questionnaire, spirometry, FeNO, methacholine challenge and skin prick testing • Asthma diagnosed in 167 (68%) • 77% (189) had at least one positive skin prick test	According to NAEPP guidelines, i.e. relevant symptom history and ≥12% BDR and/or methacholine PC_{20} ≤8mg/mL	Any positive skin prick tests for dust mites, *Alternaria, Cladosporium, Aspergillus, Mucor, Penicillium*, dog, cat, cockroach, mugwort, timothy, ragweed, birch, alder, hazel, plane tree, and oak	0.77 (0.70-0.83)	0.23 (0.14-0.34)
Brouwer 2010 Netherlands (12)	• 61 children (aged 6-16 y) referred to hospital due to chronic respiratory symptoms • ICS and LABA withheld for four weeks • Semi-structured medical history, spirometry, bronchodilator response, and FeNO at baseline • FEV_1 and peak flow variability twice daily for 14 days • FeNO and methacholine challenge after 14 days	Based on the history, physical examination and lung function data on the second visit (including spirometry, bronchodilator response and methacholine challenge but not including variability data).	Specific IgE for dust mites, tree pollen, grass pollen, cat and/or dog	0.90 (0.70-0.99)	0.58 (0.41-0.73)

	• Asthma diagnosed in 21 (34%) • 56% (34) had IgE specific for inhaled allergens				
Grzelewski 2014 Poland (24)	• Retrospective analysis case notes of 3612 children (age 6-18y) years attending an allergy clinic with symptoms suggestive of asthma and who had at least two year's follow up • Questionnaire, spirometry, Rint, sRaw, specific IgE • Asthma diagnosed in 2178 (60%) • 50% (863) were sensitised to at least one perennial allergen	According to GINA 2012 symptoms plus $FEV_1 \geq 12\%$	Specific IgE ≥0.35kU/L for dust mites, moulds, cat and/or dog	0.58 (0.54-0.62)	0.65 (0.61-0.69)
			Specific IgE ≥0.35kU/L for tree pollen and/or grass pollen	0.63 (0.59-0.67)	0.56 (0.52-0.61)

Supplementary table 19: GRADE table forPICO 7: Should skin prick tests be used to diagnose asthma in children?

Sensitivity	0.77 to 0.90
Specificity	0.23 to 0.40

Prevalence	30%*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
True positives (patients with [asthma])	2 studies 356 patients (11,33)	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious	not serious	none	231 to 270	⨁⨁⨁◯ MODERATE
False negatives (patients incorrectly classified as not having [asthma])								30 to 69	
True negatives (patients without [asthma])	2 studies 356 patients (11,33)	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious	not serious	none	161 to 280	⨁⨁⨁◯ MODERATE
False positives								420 to 539	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
(patients incorrectly classified as having [asthma])									

Explanations: *Pretest probability was pragmatically estimated at 30% because the prevalence of asthma in children is around 5 to 15% and children presenting for investigation with symptoms are likely to have a higher pre-test probability.

[a] Unclear if reference standard results were interpreted without knowledge of the results of the index test

Supplementary table 20: GRADE table forPICO 7: Should specific IgE testing be used to diagnose asthma in children?

Sensitivity	0.58 to 0.90
Specificity	0.56 to 0.58

Prevalence	30%*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
True positives (patients with [asthma])	2 studies 3673 patients (12,24)	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious	not serious	none	174 to 270	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having [asthma])								30 to 126	
True negatives (patients without [asthma])	2 studies 3673 patients (12,24)	cross-sectional (cohort type accuracy study)	serious [a]	not serious	not serious	not serious	none	392 to 406	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly classified as having								294 to 308	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
[asthma])									

Explanations: *Pretest probability was pragmatically estimated at 30% because the prevalence of asthma in children is around 5 to 15% and children presenting for investigation with symptoms are likely to have a higher pre-test probability.

[a] Unclear if reference standard results were interpreted without knowledge of the results of the index test

Supplementary table 21: Evidence to decision table for PICO 7.

PICO question

In children aged 5-16 years under investigation for asthma, should allergy testing be used to diagnose asthma in children	
POPULATION:	Children aged 5-16 under investigation for asthma
INTERVENTION:	Performing allergy testing to diagnose asthma

ASSESSMENT

Test accuracy How accurate is allergy testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ **Inaccurate** ○ Accurate ○ Very accurate ○ Varies ○ Don't know	4 studies were included to answer PICO question 7. Two studies assessed skin prick tests, 2 studies assessed specific IgE. Skin prick tests showed moderate to good sensitivity (0.77 to 0.90) but low to very low specificity (0.23 to 0.53) for a diagnosis of asthma. Specific IgE also showed low to good sensitivity (0.58 to 0.90) but low specificity from (0.56 to 0.65) for a diagnosis of asthma. For 2 or more positive allergy tests sensitivity was low to moderate (0.58 to 0.76) and specificity was moderate (0.73) (11,12,24,33)	Both for SPT and IgE, sensitivity and specificity were dependent on the cut-off chosen (number of positive tests). Sensitivity and specificity are likely to vary by the age of the children, the presence or absence of other atopic disease (hayfever, eczema), the type of test used and the number of positive tests. In contrast to other measuremenents, allergy tests have less temporal variation. There is a slight seasonsal variation, but that is not strong, and there is no diurnal variation. This is an advantage and explains partly the high sensitivity. All these aspects were not covered in the few publicaions identified by the search and need to be considered in future research.

Desirable Effects How substantial are the desirable anticipated effects of allergy testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ **Moderate** ○ Large ○ Varies ○ Don't know	There is evidence that positive allergy tests have moderate to good sensitivity but low specificity for the diagnosis of asthma. The taskforce decided that the low specificity outweighs the desirable effect (high sensitivity) because this results in overdiagnosis of asthma.	Allergy tests are not useful to make a diagnosis of asthma, but for further phenotyping and management in order to identify triggers of poor asthma control or exacerbations, to distinguish between asthma phenotypes, to predict prognosis, to plan individualised prevention measures (e.g. mattress covers) and to decide on tools to monitor asthma control such as FeNO.
Undesirable Effects How substantial are the undesirable anticipated effects of allergy testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ **Moderate** ○ Small ○ Trivial ○ Varies ○ Don't know	There is evidence that positive allergy tests have low specificity for the diagnosis of asthma. Reliance on allergy tests to diagnose asthma leads to a risk of asthma overdiagnosis, particularly in children with allergic rhinitis. There is also a risk of underdiagnosis of non-allergic asthma.	Skin-prick testing (SPT) is time consuming and limited to relatively small numbers of allergens. Blood RAST testing is semi-invasive and incurs moderate costs for the analysis. Both skin prick tests and taking blood are slightly disagreeable to children, but not associated with relevant side effects.

Certainty of the evidence of test accuracy What is the overall certainty of the evidence of accuracy of allergy tests?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ **Moderate** ○ High ○ No included studies	The certainty of the evidence of test accuracy is moderate.	Test accuracy for both skin prick testing and specific IgE testing is good.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by allergy test results?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	Not reviewed as part of this TF.	None of the major asthma guidelines recommends allergy testing to support a diagnosis of asthma. Information on allergies however is often helpful for further management, such as prediction prognosis, deciding on personalized prevention measures (e.g. mattress covers) and reducing attacks by avoiding relevant trigger factors.
Certainty of the evidence of test result/management How certain is the link between allergy test results and management decisions?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	Not reviewed as part of this TF.	Positive allergy tests have low specificity and a positive test does not confirm the diagnosis of asthma.

Balance of effects Does the balance between desirable and undesirable effects favor allergy tests or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ **Probably favors the comparison** ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Overall the taskforce found the negative aspects (caused by the low specificity) to prevail, so that it does not recommend to use allergy tests for diagnosing asthma. Allergy tests have, however, a role in asthma management after the diagnosis is made, for instance for choosing tertiary prevention.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Not reviewed as part of this TF.	SPT are time-consuming and there is a cost for consumables and the individual allergens. IgE tests are relatively costly, depending on the number of tests done.
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	Not reviewed as part of this TF.	Unequal access to allergy testing is unlikely to influence the ability to diagnose asthma. It could however affect personalized management after diagnosis.

Acceptability Is allergy testing acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ **Probably no** ○ Probably yes ○ Yes ○ Varies ○ Don't know	Not reviewed as part of this TF.	Acceptance is likely to vary but low specificity of a positive test does not make this a useful test to support a diagnosis of asthma. In addition, there is the cost to perform the test and analyse the test results. Blood testing is semi-invasive. Patients and parents usually accept allergy tests if recommended. Discomfort when taking blood can be reduced by application of anaesthetic creams. For physicians blood tests are part of the usual routine, so acceptable. Skin prick tests need special training and storage of ingredients, so may be less acceptable.
Feasibility Is allergy testing feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Not reviewed as part of this TF.	Both types of tests can be implemented in all care settings. Skin prick tests need experienced examiners (training) and adequate storage of ingredients (in fridge, timely replacements)

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendations

- The TF recommends against the use skin prick tests to aeroallergens as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence)
- The TF recommends against the use of serum total and specific IgE tests as diagnostic tests for asthma (strong recommendation against the intervention, moderate quality of evidence)

Justification

Evidence from the available studies suggests that skin prick tests and specific IgE measurements have a limited value to diagnose asthma. The low specificity is likely to lead to an over-diagnosis of asthma, particularly in children with other atopic diseases. Non-allergic asthma, in contrast, will be under-diagnosed if physicians rely on allergy tests for asthma diagnosis. Sensitivity is moderate to high, but may have been artificially boosted by the fact that research studies tend to include mainly children with allergic asthma, so biasing the sensitivity upwards.

However, after diagnosis, allergy tests can be useful for asthma management, in particular to describe the phenotype and to plan individualised prevention measures.

Considering the low specificity, the TF recommends against allergy testing as a diagnostic test for asthma in children

Subgroup considerations

None

Implementation considerations

Moderate cost for RAST testing also requiring access to relevant laboratory facilities. SPT is time consuming and limited to a relatively small number of allergens.

Monitoring and evaluation

Not applicable

Research priorities

Allergy tests are useful in patients already diagnosed with asthma, to determine measures of tertiary prevention, i.e. avoidance of clinically relevant allergens that trigger asthma attacks or maintain chronic symptoms. Carefully designed clinical studies in children with suspected asthma are essential to provide more evidence on their role in diagnosing asthma.

PICO 8: In children aged 5-16 years under investigation for asthma, should direct bronchial challenge testing including methacholine and histamine be used to diagnose asthma?

Supplementary material

We wanted to include studies investigating the diagnostic accuracy of direct bronchial challenge testing using histamine or methacholine in children aged 5 to 15 years under investigation for asthma.

For the question direct bronchial challenge testing, 973 papers were identified through the database searches, and one paper identified through another source. We excluded 213 duplicated papers, 725 papers based on title and abstract screening, and 33 papers after the full-text eligibility assessment (supplementary figure 1H). The exclusion criteria for title and abstract screening were; no full text available (n = 10), non-diagnostic studies (n = 106), inclusion criteria not patients suspected for asthma or asthma definition not according to TF criteria (n = 161). Others were excluded based on study design or because they were not original articles (n = 212), the sample size was < 20 participants (n = 67), the age was <5 years or the median age was >20 years (n = 9) or studies did not include direct bronchial challenge testing (n = 160). Data from three papers were included in the

final report (supplementary table 22). (11,37,38) Excluded studies after full-text review are shown in supplementary table 36, the GRADE table for included studies in supplementary table 23 and the evidence to decision table for PICO 8 in supplementary table 24. We found no studies to assess the diagnostic accuracy of histamine challenge testing in children under investigation for asthma.

Supplementary table 22: Details of Included studies for PICO 8 :a. direct bronchial challenge testing (histamine, methacholine)					
Study	Study Population	Reference Standard	Index Test and Cut-Off	Diagnostic Accuracy of Index Test	
				Sensitivity	Specificity
Anderson 2009, USA (37)	1. 115 children (age 6-17) referred to several centres with an equivocal diagnosis of asthma. All had signs and symptoms suggestive of asthma according to National Institute of Health questionnaire. 2. Five visits 1. Questionnaire, spirometry, BDR, skin prick reactivity 2. +1-4 days, exercise test 3. +1-4 days, exercise test 4. Mannitol or methacholine challenge 5. Challenge not done at visit 4 • Asthma diagnosed in 240 (64%) of all individuals (data not provided for <18 year olds)	One blinded clinician in each centre made the diagnosis at assessment 5 based on history and spirometry, BDR, skin prick testing and exercise test results. Mannitol and methacholine testing were not part of the diagnostic pathway.	Methacholine PC_{20} ≤16mg/mL	0.66 (0.55-0.77)	0.63 (0.45-0.79)
Zaczeniuket 2015, Poland (38)	• 101 children (aged 10-18) with post exercise symptoms referred to hospital clinic • Questionnaire, spirometry, BDR and exercise test were done and one week later a methacholine challenge was also done. • Asthma diagnosed in 44 (44%)	According to GINA 2012	Methacholine PD_{20} ≤0.72 mg	0.82 (0.67-0.91)	0.82 (0.70-0.91)
De Jong 2019, Switzerland (11)	• 111 children (aged 6-16y) referred to one of two hospitals due to suspected asthma • Questionnaire, spirometry, bronchodilator response, FeNO, airway challenges (exercise and methacholine) and skin prick testing. Within a week of the first tests, a mannitol challenge and second FeNO measurement were performed. • Asthma diagnosed in 80 (72%)	One clinician made a diagnosis on the first assessment based on symptoms, skin prick tests, FeNO and spirometry. The same clinician revisited the diagnosis on the second visit based on all the data available. Asthma was defined as either “definite” or “probable” asthma.	Methacholine PD_{20} <0.7 mg	0.83 (0.72-0.90)	0.72 (0.79-0.87)
			Methacholine PD_{20} <1.0 mg	0.85 (0.75-0.92)	0.69 (0.49-0.85)

Supplementary table 23: GRADE table forPICO 8: Should a direct bronchial challenge test with methacholine be performed to diagnose asthma in children?

Sensitivity	0.66 to 0.85
Specificity	0.63 to 0.82

Prevalence	30%*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
True positives (patients with asthma)	3 studies 295 patients (11,37,38)	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious [a]	serious [b]	none	198 to 255	⊕⊕⊕◯ MODERATE
False negatives (patients incorrectly classified as not having asthma)								45 to 102	
True negatives (patients without asthma)	3 studies 295 patients (11,37,38)	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious [a]	serious [b]	none	441 to 574	⊕⊕⊕◯ MODERATE
False positives (patients incorrectly								126 to 259	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
classified as having asthma)									

Explanations: *Pretest probability was pragmatically estimated at 30% because the prevalence of asthma in children is around 5 to 15% and children presenting for investigation with symptoms are likely to have a higher pre-test probability.

[a]No statistical approach used, point estimates and 95%CI overlap

[b]It has not been possible to pool accuracy data, 95%CIs are not known and absolute results represent central point estimates.

Supplementary table 24: Evidence to decision table for PICO 8

PICO question

In children aged 5-16 years under investigation for asthma, should direct bronchial challenge testing including methacholine and histamine be used to diagnose asthma?	
POPULATION:	Children 5 to 16 years under investigation for asthma
INTERVENTION:	Perform direct bronchial challenge testing using methacholine or histamine

Assesment

Test accuracy How accurate is the test?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ○ **Accurate** ○ Very accurate ○ Varies ○ Don't know	3 Studies are included to answer PICO question 8. All 3 studies reported methacholine challenge testing. Methacholine challenge testing showed moderate sensitivity (0.66 to 0.85) and low to moderate specificity (0.63 to 0.82) for a diagnosis of asthma (11,37,38).	No studies were identified to assess the diagnostic accuracy of histamine challenge testing in children under investigation for asthma.

Desirable Effects How substantial are the desirable anticipated effects of direct bronchial challenge testing using methacholine?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ **Moderate** ○ Large ○ Varies	There is evidence that a positive direct bronchial challenge test has moderate sensitivity and specificity to confirm the diagnosis of asthma in children.	Direct bronchial challenge testing is a non-invasive procedure. Bronchial hyper-reactivity is a cornerstone of asthma pathophysiology. Patient representatives agreed that direct bronchial challenge

○ Don't know		testing should be offered to children where diagnostic uncertainty remains after repeated first line tests have not confirmed the diagnosis, the child remains symptomatic and other diagnoses have been considered
Undesirable Effects How substantial are the undesirable anticipated effects of direct bronchial challenge testing using methacholine?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ **Moderate** ○ Small ○ Trivial ○ Varies ○ Don't know	Despite moderate sensitivity and specificity of direct bronchial challenge tests, there are significant numbers of chidren returning false positive or false negative tests.	Direct bronchial challenge tests are time consuming and require a specialist setting. Therefore, children need to be referred to a specialist setting if bronchial challenge tests are not available. This can be bothersome for children and families. The tests can be uncomfortable for children
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of direct bronchial challenge test accuracy?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ **Moderate** ○ High ○ No included studies	The certainty of the evidence of test accuracy is moderate based on the 3 studies included.	Good quality studies have shown that direct bronchial challenge tests have a moderate sensitivity and specificity to support an asthma diagnosis in children. Accuracy of the test itself depends on operator training and child cooperation The certainty of an asthma diagnosis is high with a positive direct bronchial challenge test.

Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by direct bronchial challenge test results?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ **Moderate** ○ High ○ No included studies	Not reviewed as part of this TF.	The TF is aware that children need to be referred to a specialist setting for bronchial challenge tests and these may not be available in low resource settings. The burden of tests to be performed in specialist laboratories is not known.
Certainty of the evidence of test result/management How certain is the link between direct bronchial challenge testing test results and management decisions?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	Not reviewed as part of this TF.	Once the diagnosis is confirmed the child can be treated appropriately.
Balance of effects Does the balance between desirable and undesirable effects favor direct bronchial challenge testing with methacholine or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ **Probably favors the intervention**	Direct bronchial challenge testing provides moderate sensitivity (0.66 to 0.85) and specificity (0.63 to 0.82) for an asthma diagnosis in children.	The test is non-invasive and a positive test confirms the diagnosis of asthma. However, the test is time consuming and requires a specialist setting and hence, children may be referred to such a centre. However, the TF agreed that direct bronchial challenge testing should be offered to children where diagnostic uncertainty remains after repeated first line tests have not confirmed the diagnosis, the child remains

○ Favors the intervention ○ Varies ○ Don't know		symptomatic and other diagnoses have been considered.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Not reviewed as part of this TF.	Moderate cost for equipment, consumables, and maintenance and training issues. A direct bronchial challenge test requires approximately 30-45 minutes of time for patients and operators.
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ **Probably increased** ○ Increased ○ Varies ○ Don't know	Not reviewed as part of this TF.	Unequal access to direct bronchial challenge testing may delay the diagnosis in relevant populations. This may be compounded by the lack of access in low resource settings or the need for long travel to a specialist centre. This may result in diagnostic delay for children affected.

Acceptability Is direct bronchial challenge testing with methacholine acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Not reviewed as part of this TF.	The intervention is non-invasive and lay members of the TF found it acceptable. Acceptance by health care practitioners and commissioners may vary depending on resources and healthcare setting. If not available in the health care setting, patients have to be referred to a specialist laboratory.
Feasibility Is direct bronchial challenge testing with methacholine feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Not reviewed as part of this TF.	Lay members of TF found this acceptable in carefully selected children. There are equipment and consumables costs. There are training costs to perform the test and interpret the test results. Lay members of TF found this acceptable in carefully selected children A barrier for implementation may be the need for referral to a specialist laboratory especially if this laboratory is a long distance away.

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

- The TF recommends a direct bronchial challenge test using methacholine in children aged 5-16 years under investigation for asthma where asthma diagnosis could not be confirmed with first line objective tests. (conditional recommendation for the intervention, low quality evidence)

Remarks:

1. A PC20 value of 8 mg/ml or less should be considered as a positive test
2. The TF found no evidence for or against performing histamine challenge tests in children under investigation for asthma

Justification

Direct bronchial testing is time consuming, requires a specialist setting and tests can be unpleasant for children. Children referred for direct bronchial challenge testing therefore require careful selection. However, the TF agreed that direct bronchial challenge testing should be offered to children where diagnostic uncertainty remains after repeated first line tests have not confirmed the diagnosis, the child remains symptomatic and other diagnoses have been considered .

The TF emphasises the importance of interpreting direct challenge testing as part of a wider clinical assessment.

Subgroup considerations

Direct bronchial challenge testing with methacholine should be researved for patients where the diagnosis was not confirmed with first line objective tests.

Implementation considerations

Equipment and maintenance costs and costs for consumables. Training costs to perform the test and interpret the test results. A barrier for implementation may be the need for referral to specialist setting if bronchial challenge testing is not available at the setting. The TF and lay members of TF found this acceptable in carefully selected children where asthma diagnosis could not be confirmed

with first line objective tests.

Monitoring and evaluation

Not applicable

Research priorities

Clinical studies are needed to answer the question as to which children benefit most from direct bronchial challenge testing in order to make recommendations on the most appropriate referrals.

PICO 9: In children aged 5-16 years under investigation for asthma, should indirect bronchial challenge testing including exercise and mannitol be used to diagnose asthma?

Supplementary material

We wanted to include studies investigating the diagnostic accuracy of indirect bronchial challenge testing using mannitol or exercise testing in children aged 5 to 15 years under investigation for asthma.

For the question indirect bronchial challenge testing, of the 309 papers identified, we excluded 65 duplicated papers, 210 papers based on title and abstract screening, and 31 papers after the full-text eligibility assessment (supplementary figure 1l). The exclusion reasons for the title and abstract screening were; non-diagnostic studies (n =54), inclusion criteria not patients suspected for asthma or asthma definition not according to TF criteria (n = 31), study design or not original articles (n = 99), sample size < 20 participants (n = 7) or no indirect bronchial challenge testing (n = 19). We assessed 34 full text articles of which 31 were excluded. The specific reason for exclusion are given in supplementary table 37. Data from three papers were included in the final report (supplementary table 25) (11,37,38). We show the GRADE tables for included studies in supplementary table 26 and 27 and the evidence to decision table for PICO 9 in supplementary table 28.

Supplementary table 25: Details of included studies for PICO 9: b Indirect bronchial challenge (mannitol and exercise testing)					
Study	Study Population	Reference Standard	Index Test and cut-off	Diagnostic Accuracy of Index Test	
				Sensitivity	Specificity
Anderson 2009 USA (37)	• 115 children (age 6-17y) among 375 patients aged 6-50y referred to several centres with an equivocal diagnosis of asthma. All had signs and symptoms suggestive of asthma according to National Institute of Health questionnaire. • Five visits 1. Questionnaire, spirometry, BDR, skin prick reactivity 2. +1-4 days, exercise test 3. +1-4 days, exercise test 4. Mannitol or methacholine challenge 5. Challenge not done at visit 4 • Asthma diagnosed in 240 (64%) of all individuals (data not provided for <18 year olds)	One blinded clinician in each centre made the diagnosis at assessment 5 based on history and spirometry, BDR, skin prick testing and exercise test results. Mannitol and methacholine testing were not part of the diagnostic pathway.	Mannitol PD_{15} ≤ 635mg	0.63 (0.52-0.74)	0.81 (0.66-0.93)
De Jong 2019 Switzerland (11)	• 111 children (aged 6-16y) referred to one of two hospitals due to suspected asthma • Questionnaire, spirometry, bronchodilator response, FeNO, airway challenges (exercise and methacholine) and skin prick testing. Within a week of the first tests, a mannitol challenge and second FeNO measurement were performed. • Asthma diagnosed in 80 (72%)	One clinician made a diagnosis on the first assessment based on symptoms, skin prick tests, FeNO and spirometry. The same clinician revisited the diagnosis on the second visit based on all the data available. Asthma was defined as either “definite” or “probable” asthma.	Mannitol PD_{15} ≤ 635mg	0.39 (0.28-0.50)	0.97 (0.83-0.99)
De Jong 2019 Switzerland (11)	• 111 children (aged 6-16y) referred to one of two hospitals due to suspected asthma • Questionnaire, spirometry, bronchodilator response, FeNO, airway challenges (exercise and methacholine) and skin prick testing. Within a week of the first tests, a mannitol challenge and second FeNO measurement were performed. • Asthma diagnosed in 80 (72%)	One clinician made a diagnosis on the first assessment based on symptoms, skin prick tests, FeNO and spirometry. The same clinician revisited the diagnosis on the second visit based on all the data available. Asthma was defined as either “definite” or “probable” asthma.	≥10% FEV_1 fall	0.52 (0.40-0.64)	0.83 (0.63-0.95)
			≥12% FEV_1 fall	0.44 (0.33-0.56)	0.92 (0.73-0.99)

Zaczeniuket 2015 Poland (38)	• 101 children (aged 10-18) with post exercise symptoms referred to hospital clinic • Questionnaire, spirometry, BDR and exercise test were done and one week later a methacholine challenge was also done. • Asthma diagnosed in 44 (44%)	According to GINA 2012	≥10% FEV_1 fall	0.77 (0.62-0.89)	0.68 (0.55-0.80)

Supplementary table 26: GRADE table forPICO 9: Should an indirect bronchial challenge test with exercise be used to diagnose asthma in children?

Sensitivity	0.37 to 0.77
Specificity	0.68 to 0.77

Prevalence	30%*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30% *	
True positives (patients with asthma)	2 studies 200 patients (11,38)	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	serious [b]	none	111 to 231	⨁⨁◯◯ LOW
False negatives (patients incorrectly classified as not having asthma)								69 to 189	
True negatives (patients without asthma)	2 studies 200 patients (11,38)	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	serious [b]	none	476 to 539	⨁⨁◯◯ LOW
False positives (patients incorrectly classified as having								161 to 224	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30% *	
asthma)									

Explanations: *Pretest probability was pragmatically estimated at 30% because the prevalence of asthma in children is around 5 to 15% and children presenting for investigation with symptoms are likely to have a higher pre-test probability.

[a]Accuracy values represent range of point estimates and 95%CI are not available, however range of results varies broadly.

[b]It has not been possible to pool accuracy data, 95%CI are not known and absolute results represent central point estimates.

Supplementary table 27: GRADE table forPICO 9: Should indirect bronchial challenge test with mannitol be used to diagnose asthma in children?

Sensitivity	0.39 to 0.63
Specificity	0.81 to 0.97

Prevalence	30%*

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
True positives (patients with asthma)	2 studies 207 patients (11,37)	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	serious [b]	none	117 to 189	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having asthma)								111 to 183 to	
True negatives (patients without asthma)	2 studies 207 patients (11,37)	cross-sectional (cohort type accuracy study)	not serious	not serious	serious [a]	serious [b]	none	567 to 873	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having								133 to 171	

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1000 patients tested	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 30%*	
asthma)									

Explanations: *Pretest probability was pragmatically estimated at 30% because the prevalence of asthma in children is around 5 to 15% and children presenting for investigation with symptoms are likely to have a higher pre-test probability.

[a]Accuracy values represent range of point estimates and 95%CI are not available, however range of results varies broadly.

[b]It has not been possible to pool accuracy data, 95%CI are not known and absolute results represent central point estimates.

Supplementary table 28: Evidence to decision table for PICO 9

PICO question

In children aged 5-16 years under investigation for asthma, should indirect bronchial challenge testing including exercise and mannitol be used to diagnose asthma?	
POPULATION:	Children 5 to 16 years under investigation for asthma
INTERVENTION:	Performing indirect bronchial challenge testing using exercise or mannitol

Assesment

Test accuracy How accurate is indirect bronchial challenge testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very inaccurate ○ Inaccurate ○ **Accurate** ○ Very accurate ○ Varies ○ Don't know	3 studies are included to answer PICO question 9. 2 data sets reported treadmill exercise testing and 2 data sets reported mannitol challenge testing. Treadmill exercise challenge testing at the 10% cut-off showed low to moderate sensitivity (0.52 to 0.77) and low to moderate specificity (0.68 to 0.72) for a diagnosis of asthma (11,38) Mannitol challenge testing showed very low to low sensitivity (0.39 to 0.63) and moderate to good specificity (0.81 to 0.97) for a diagnosis of asthma (11,37)	Sensitivity was very low (0.44) at the 12% cut-off (11) but specificity was good (0.92).

Desirable Effects How substantial are the desirable anticipated effects of indirect bronchial challenge testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ **Moderate** ○ Large ○ Varies ○ Don't know	Sensitivity of indirect bronchial challenge testing is very low to moderate depending on the test used but specificity is moderate to good making this a good test to confirm the diagnosis.	Indirect bronchial challenge testing, particulary the treadmill exercise test is a non-invasive procedure. Bronchial hyper-reactivity is a cornerstone of asthma pathophysiology. The TF agreed that indirect challenge testing during the diagnostic work-up with treadmill or bicycle is recommended in children where first line tests have failed to confirm or refute the diagnosis of asthma and treadmill exercise testing is especially recommended in children with exercise-induced symptoms.
Undesirable Effects How substantial are the undesirable anticipated effects of indirect bronchial challenge testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ **Moderate** ○ Small ○ Trivial ○ Varies ○ Don't know	Indirect bronchial challenge tests have only low to moderate sensitivity in diagnosing asthma in children.	Indirect bronchial challenge tests are time consuming and require a specialist setting. Therefore, children may need to be referred to a specialist laboratory. Exercise tests are tiring and can be considered bothersome by some children. As a result some children do not complete the test. Children often find the mannitol challenge test unpleasant. Patient representatives agreed that indirect bronchial challenge testing should be offered to children where diagnostic uncertainty remains after repeated first line tests have not confirmed the diagnosis, the child remains symptomatic and other diagnoses have been considered

Certainty of the evidence of test accuracy What is the overall certainty of the evidence of indirect bronchial challenge test accuracy?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ **Low** ○ Moderate ○ High ○ No included studies	The certainty of the evidence of test accuracy is low.	Good quality studies have shown that indirect bronchial challenge tests have a very low to moderate sensitivity and low to good specificity depending on the test to support asthma diagnosis in children. Accuracy of the test itself depends on operator training and child cooperation The certainty of an asthma diagnosis is high with a positive indirect bronchial challenge test.
Certainty of the evidence of management's effects What is the overall certainty of the evidence of effects of the management that is guided by the indirect bronchial challenge test results?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ **Moderate** ○ High ○ No included studies	Not reviewed as part of this TF.	A positive indirect bronchial challenge test makes the diagnosis of asthma very likely and the child can be treated accordingly.
Certainty of the evidence of test result/management How certain is the link between indirect bronchial challenge test results and management decisions?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ **No included studies**	Not reviewed as part of this TF.	A positive indirect bronchial challenge test makes the diagnosis of asthma very likely and the child can be treated accordingly.

Balance of effects Does the balance between desirable and undesirable effects favor indirect bronchial challenge testing or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	Indirect bronchial challenge testing provides very low to moderate sensitivity but low to good specificity, depending on the test employed, for the diagnosis of asthma in children.	The test is non-invasive and a positive test confirms the diagnosis of asthma. However, the test is time consuming and requires a specialist setting and hence, children may not be referred to such a centre. However, the TF agreed that indirect bronchial challenge testing should be offered to children where diagnostic uncertainty remains after repeated first line tests have not confirmed the diagnosis, the child remains symptomatic and other diagnoses have been considered. The TF considered that indirect bronchial challenge test using a treadmill or a bicycle should be offered to children with exercise related symptoms
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Not reviewed as part of this TF.	Moderate cost for equipment, consumables, and maintenance and training issues. An indirect bronchial challenge test requires approximately 30-45 minutes of time for patients and operators. There is limited availability for mannitol in most countries.

Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ **Varies** ○ Don't know	Not reviewed as part of this TF.	Unequal access to indirect bronchial challenge testing may delay the diagnosis in relevant populations. This may be compounded by the lack of access in low resource settings or the need for long travel to a specialist centre. This may result in diagnostic delay for children affected.
Acceptability Is indirect bronchial challenge testing acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ **Varies** ○ Don't know	Not reviewed as part of this TF.	The intervention is non-invasive and lay members of TF found it acceptable. In view of the fact that children often find mannitol challenge testing unpleasant, this test should be best avoided in favour of other challenge tests Acceptance by health care practitioners and commissioners may vary depending on resources and healthcare setting. If not available at the setting, patients have to be referred to a specialist laboratory.
Feasibility Is indirect bronchial challenge testing feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ **Probably yes**	Not reviewed as part of this TF.	There are equipment and consumables costs. There are training costs to perform the test

○ Yes ○ Varies ○ Don't know		and interpret the test results. A barrier for implementation may be the need for referral to a specialist centre or laboratory. Lay members of TF found the tests acceptable in selected children

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

- The TF recommends an indirect bronchial challenge test using a treadmill or a bicycle in children aged 5-16 years under investigation for asthma with exercise related symptoms where asthma diagnosis could not be confirmed with first line objective tests. (conditional recommendation for the intervention, moderate quality evidence)

Remarks:

1. A fall in FEV_1 of > 10% from baseline should be taken as a positive test
2. A mannitol challenge can be considered as an alternative to exercise challenge. However due to its limited availability in most countries, and the fact that children often find the test unpleasant, mannitol challenge should be best avoided in favour of other challenge tests

Justification

Indirect bronchial testing is time consuming and formal tests require a specialist setting. Children referred for indirect direct bronchial challenge testing require careful selection. A positive indirect bronchial challenge test however confirms the diagnosis of asthma with a moderate sensitivity and high specificity. Based on the evidence the TF agreed that indirect challenge testing during the diagnostic work-up with treadmill or bicycle is recommended in children where the diagnosis could not be confirmed using first line diagnostic tests and particularly for children with exercise induced symptoms.

The TF emphasises the importance of interpreting indirect challenge testing as part of a wider clinical assessment.

Subgroup considerations

Indirect bronchial challenge testing should be researved for patients where the diagnosis was not confirmed with first line objective tests.

Implementation considerations

Equipment and maintenance costs and costs for consumables. Training costs to perform the test and interpret the test results. A barrier for implementation may be the need for referral to specialist setting if bronchial challenge testing is not available at the setting. The TF and lay members of TF found this acceptable in carefully selected children where asthma diagnosis could not be confirmed with first line objective tests.

A mannitol challenge can be considered as an alternative to exercise challenge. However due to its limited availability in most countries, and the fact that children often find the test unpleasant, mannitol challenge should be best avoided in favour of other challenge tests

Monitoring and evaluation

not applicable

Research priorities

There is uncertainty regarding the best approach with respect to challenge testing in children and it is unclear whether indirect or direct challenge tests should be prioritised in the asthma diagnostic pathway. Younger children especially were under-represented in the selected studies and should be included in future studies.

Excludes Studies for PICO 1 to 9.

Supplementary table 29. Excluded studies following full text screen for PICO 1 (symptoms)

	Reference	Study Design	Reason for Exclusion
1	Ater 2018 (39)	Cohort study of children with suspected asthma. Outcome bronchial hyperresponsivness and not asthma.	Inappropriate outcome
2	Bailly 2011 (40)	Cohort study of children with suspected asthma. Outcome bronchial hyperresponsivness and not asthma.	Inappropriate outcome
3	Boccaccino 2007 (41)	Cohort study of children with suspected asthma. Outcome bronchial hyperresponsivness and not asthma.	Inappropriate outcome
4	Buchele 2007 (42)	Case control study of children with and without diagnosed asthma	Inappropriate study design
5	Demissie 1998 (43)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
6	Dundas 2005 (31)	Case control study of children with and without wheeze	Inappropriate study design
7	Fitzgerald 1996 (44)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
8	Fouzas 2012 (45)	Cohort study to find predictors for asthma at school age.	Inappropriate population
9	Godfrey 2004 (46)	Cohort study of pre-school aged children with suspected asthma.	Inappropriate population.
10	Goldberg 2005 (47)	Cohort study of 17-year-old teenagers with suspected asthma	Inappropriate population
11	Goldstein 2001 (48)	Cohort study of children with suspected asthma. Outcome bronchial hyperresponsivness and not asthma.	Inappropriate outcome
12	Gudelj 2012 (49)	Cohort study of children with suspected asthma. Asthma diagnosis based on peak-flow measurement.	Inappropriate study design/reference standard
13	Hansen 2015 (50)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
14	Hensley 2003 (51)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population

15	Ivkovic-Jurekovic 2017 (52)	Cohort study of children with suspected asthma. Outcome bronchial hyperresponsivness and not asthma.	Inappropriate outcome
16	Johnston 1995 (53)	Cohort study of children with suspected asthma. Outcome number of episodes with reduced peak expiratory flow and not asthma.	Inappropriate outcome
17	Joseph-Bowen 2004 (54)	Cohort study of children with suspected asthma. Outcome bronchial hyperresponsivness and not asthma.	Inappropriate outcome
18	Kannisto 1999 (55)	Cohort study of children with suspected asthma. Outcome exercise induced bronchospasm and not asthma.	Inappropriate outcome
19	Kannisto 1999 (55)	Cohort study of children with suspected asthma. Outcome exercise induced bronchospasm and not asthma.	Inappropriate outcome
20	Kim 1997 (56)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
21	Lang 2009 (57)	Cohort study of children with asthma	Inappropriate population
22	Lee 2015 (58)	Cohort study of children with suspected asthma. Outcome airway-hyperresponsivness and not asthma.	Inappropriate outcome
23	Lee 2020 (59)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
24	Mai 2002 (60)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
25	Malmberg 2009 (61)	Cohort study of children with suspected asthma. Outcome exercise induced bronchoconstriction and not asthma.	Inappropriate outcome
26	Mata Fernandez 2005 (62)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
27	Mitra 2002 (63)	Cohort study of children with asthma	Inappropriate population
28	Ponsonby 1996 (64)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
29	Riedler 1994 (65)	Cohort study of children with suspected asthma. Outcome bronchial	Inappropriate

		hyperresponsiveness and not asthma.	outcome
30	Sanchez-Garcia 2012 (66)	Cohort study of children with suspected asthma. Outcome bronchial hyperresponsiveness and not asthma.	Inappropriate outcome
31	Saraclar 2003 (67)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
32	Seear 2005 (68)	Cohort study of children with exercised induced asthma	Inappropriate population
33	Shapiro 1982 (69)	Cohort study of children with suspected asthma. Outcome bronchial hyperresponsiveness and not asthma.	Inappropriate outcome
34	Sheikh 2013 (70)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
35	Skylogianni 2015 (71)	Cohort study of 4-5 year old children with wheeze	Inappropriate population
36	Sockrider 2001 (72)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
37	Stensballe 2017 (73)	Population based study in children to detect asthma with an algorithm.	Inappropriate population
38	Timonen 2002 (74)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
39	Timonen 1995 (75)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
40	Timonen 1997 (76)	Cohort study of children with suspected asthma. Outcome peak flow variability and not asthma.	Inappropriate outcome
41	Vieira 2012 (77)	Cohort study of children with suspected asthma. Outcome bronchial hyperresponsiveness and not asthma.	Inappropriate outcome
42	Wang 2014 (78)	Birth cohort study to find predictors for asthma at school age.	Inappropriate population
43	Wegienka 2009 (79)	Birth cohort study to find predictors for asthma at school age.	Inappropriate population
44	Yang 2011 (80)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
45	Yeh 2010 (81)	Population based study in children to detect	Inappropriate

		asthma with a questionnaire.	population
46	Yu 2004 (82)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
47	Yunus 2003 (83)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population
48	Zejda 2002 (84)	Population based study in children to detect asthma with a questionnaire.	Inappropriate population

Supplementary table 30: Excluded studies following full text screen for PICO 2 (trial of preventer treatment).

	Reference	Study design	Reason for exclusion
1	Abrams et al, 2016 (85)	Systematic-review on the effect of asthma therapies on the natural course of asthma	Not patients suspected for asthma Non-diagnostic study
2	Bacharier et al, 2012 (86)	Non-systematic review on the diagnosis and management of early asthma in preschool children	Not original article Preschool children
3	Baxter-Jones et al, 2000 (16)	Randomized pragmatic longitudinal trial studying early treatment with ICS in children with early asthma	Not patients suspected for asthma Non-diagnostic study
4	Beigelman et al, 2015 (87)	Non-systematic review on the utility of corticosteroids in acute pediatric respiratory disorders	Not original article
5	Beigelman et al, 2017 (88)	Non-systematic review on the management of preschool recurrent wheezing and asthma	Not original article Preschool children
6	Bossley et al, 2009 (89)	Cross-sectional study describing corticosteroid responsiveness in childhood difficult asthma	Not patients suspected for asthma
7	Brand et al, 2011 (90)	Randomized double-blind study of inhaled ciclosonide vs placebo in preschool children	Preschool children Non-diagnostic study
8	Brodlie et al, 2015 (91)	Systematic review of LRTA as maintenance or intermittent treatment in preschool children with episodic viral wheeze	Preschool children Non-diagnostic study
9	Chang et al, 1998 (92)	Randomized placebo-controlled study of inhaled salbutamol and beclomethasone for recurrent cough	Non-diagnostic study

10	Chang et al, 2006 (93)	Systematic review and meta-analysis of randomized controlled trials evaluating the effectiveness of LTRA for prolonged non-specific cough in children	Non-diagnostic study
11	Chong et al, 2015 (94)	Systematic review and meta-analysis of randomized controlled trials evaluating the efficacy of intermittent ICS vs placebo for persistent asthma in children and adults	Not patients suspected for asthma
12	Clemmer et al, 2015 (95)	Cross-sectional study measuring the corticosteroid responsiveness endotype in asthma	Not patients suspected for asthma
13	Dahl et al, 2010 (96)	Randomized double-blind 2-arm parallel group study comparing the efficacy of low-dose ciclesonide and fluticasone propionate in asthma	Not patients suspected for asthma
14	Ducharme et al, 2010 (97)	Systematic review and meta-analysis of randomized controlled trials evaluating the efficacy of the addition of LABA to ICS in adult patients with chronic asthma insufficiently controlled with ICS alone.	Adults Not patients suspected for asthma Non-diagnostic study
15	Ebisawa et al, 2015 (98)	Randomized double-blind placebo-controlled parallel-group study evaluating the efficacy of pranlukast to improve control in wheezing small children.	Preschool children Non-diagnostic study
16	Edmonds et al, 2012 (99)	Systematic review and meta-analysis of randomized controlled trials evaluating the efficacy of ICS for the treatment of patients with acute asthma in the emergency department	Non-diagnostic study
17	Galant et al, 2014 (100)	Cohort study investigating the bronchodilator response as a predictor of ICS responsiveness in asthmatic children	Not patients suspected for asthma

18	Hirst et al, 2010 (101)	Systematic review and meta-analysis of observational studies comparing frequency of asthma exacerbations in children treated with fluticasone propionate/salmeterol vs ICS or ICS plus montelukast	Not original article
19	Hussein et al, 2017 (102)	Systematic review and meta-analysis of randomized controlled trials evaluating the efficacy of montelukast vs placebo in preschool children with recurrent wheeze	Preschool children Non-diagnostic study
20	Ismaila et al, 2014 (103)	Cost-utility study of LABA plus ICS treatment vs continuing on current ICS dose or increasing ICS dose in patients with uncontrolled asthma	Not patients suspected for asthma
21	Jehan et al, 2014 (104)	Randomized control trial evaluating the efficacy of ICS vs montelukast in reducing exacerbations in uncontrolled asthma in preschool children	Preschool children Non-diagnostic study
22	Kaiser et al, 2016 (105)	Systematic review and meta-analysis of randomized controlled trials evaluating the efficacy of several medication regimens including ICS / LTRA for the prevention of exacerbations in preschool children with recurrent wheeze	Preschool children Non-diagnostic study
23	Klug et al, 1999 (106)	Cohort study evaluating lung function in young asthmatic children treated with SABA alone or ICS	Preschool children Not patients suspected for asthma
24	Koster et al, 2011 (107)	Cohort study of children using ICS evaluating the agreement between current and long-term asthma control.	Non-diagnostic study
25	McKean et al, 2000	Systematic review and meta-analysis of randomized controlled trials evaluating the efficacy ICS	Non-diagnostic study

	(108)	in children with episodic viral wheeze	
26	Miller et al, 2008 (109)	Economic evaluation of budesonide/formeterol as maintenance and reliever treatment compared to fixed dose combination strategies	Non-diagnostic study
27	Murray et al, 2006 (110)	Randomized double-blind controlled study comparing the prevalence of asthma and lung function after treatment with ICS vs placebo in infants with wheeze.	Preschool children
28	Nwokoro et al, 2015 (111)	Randomized double-blind placebo-controlled parallel-group study of Montelukast vs placebo in preschool children with wheeze episodes	Preschool children
29	Reijonen et al, 2000 (112)	Randomized controlled study of ICS vs cromolyn sodium vs no treatment in children aged 2 years with infection associated wheezing and clinical asthma diagnosis at follow-up 3 years later.	Preschool children
30	Sekerel et al, 2005 (113)	Randomized double-blind placebo-controlled parallel-group trial evaluating the effect of a 5-day nebulized budesonide treatment in children with asthma exacerbation	Non-diagnostic study
31	Spahn et al, 2007 (114)	Non-systematic review of steroid therapy for asthma in children	Not original article
32	Szefler et al, 2005 (17)	Randomized crossover trial of ICS and LTRA in children with mild to moderate persistent asthma	Not patients suspected for asthma
33	Tomerak et al, 2005 (115)	Systematic review of randomized controlled trials evaluating the efficacy of ICS for non-specific cough in children	Non-diagnostic study
34	Vasilopoulou et al, 2014	Cross-sectional study assessing asthma diagnosis in children referred for clinical suspicion of	Not original article

	(116)	asthma	
35	Wasfi et al, 2011 (117)	Randomized double-blind 2-period cross-over study evaluating protective effect of 1 dose of montelukast vs placebo against exercise-induced bronchoconstriction in children	Not original article
36	Watts et al, 2012 (118)	Systematic review and meta-analysis of randomized controlled trials evaluating the additional beneficial effect of adding LTRA in children and adults with acute asthma currently receiving ICS and systemic corticosteroids	Not patients suspected for asthma
37	Wolthers et al, 2011 (119)	Cross-sectional study assessing the diagnostic outcome of children consecutively referred to a secondary clinic for primary care doctor diagnosis of difficult to treat asthma	Not original article
38	Young et al, 2002 (120)	Intervention study in adolescents with asthma	Not patients suspected for asthma
39	Zielen et al, 2010 (121)	Randomized study evaluating the response to fluticasone vs montelukast in young children with episodic asthma	Preschool children Not patients suspected for asthma
40	NCT01687296, 2012	Protocol of a randomized double-blind controlled trial evaluating the efficacy of ICS vs oral prednisolone in children with an acute exacerbation of asthma	Not original article Not patients suspected for asthma

Supplementary table 31: Excluded studies following full text screen for PICO 3 (spirometry).

	Reference	Study Design	Reason for Exclusion
1	Anderson 2010 (122)	Conference abstract only. Cohort study of children with suspected asthma using challenge tests.	No original article Inappropriate index test
2	Andregnette 2011 (123)	Conference abstract only. Cohort study of children with suspected asthma using challenge tests.	No original article Inappropriate index test
3	Bibi 1991 (124)	Cohort study of children with normal baseline spirometry. Non diagnostic study.	Inappropriate outcome
4	Brouwer 2010 (12)	Prospective cohort study of peak flow or FEV_1 variability of two weeks.	Inappropriate index test
5	Brozek 2016 (125)	Abstract only. Cross-sectional study. Unclear reference standard.	No original article Inappropriate reference standard
6	Ciprandi 2012 (126)	Cohort study of children with diagnosed asthma to establish cut-off values for FEF_{25-75}	Inappropriate population
7	Del Rio-Navarro 2004 (127)	Population based study. No second objective test used to confirm diagnosis.	Inappropriate reference standard
8	Denboba 2008 (128)	Case control study using cohort from population study to investigate validity of asthma questionnaire. No second objective test to confirm asthma.	Inappropriate outcome
9	Dundas 2005 (31)	Case control study with no second objective test to diagnose asthma.	Inappropriate reference standard
10	Fang 2018 (129)	Retrospective study of children with existing diagnosis of asthma to establish cut-off values of FeNO in those with allergic sensitisation	Inappropriate index test
11	Francisco 2015 (130)	Retrospective analysis of spirometry results in children with diagnosed asthma to compare different parameters of airflow obstruction.	Inappropriate index test
12	Galant 2007 (131)	Case control study investigating BDR. No second objective test.	Inappropriate reference standard

13	Gerald 2004 (132)	Case finding population study. No consistent gold standard diagnostic criteria.	Inappropriate reference standard
14	Goldstein 2001 (48)	Cohort study of people with normal baseline spirometry comparing PEFR variability with methacholine challenge. Non diagnostic study.	Inappropriate index test
15	Grzelewski 2016 (133)	Retrospective cross sectional study looking at FeNO to spirometry ratio cut-offs in children with existing diagnosis of asthma.	Inappropriate index test
16	Hansen 2015 (50)	Case control study using questionnaire to identify children with asthma	Inappropriate index test
17	Jerzynska 2015 (134)	Prospective study exploring diagnostic accuracy of specific airway resistance	Inappropriate index test
18	Kannisto 1999 (135)	Prospective study of children with suspected asthma using exercise challenge testing and peak flow recordings	Inappropriate reference standard
19	Lang 2009 (57)	Observational study of association between raised body mass index and asthma misdiagnosis	Inappropriate index test
20	Lee 2015 (58)	Population based cross sectional study using questionnaires to identify children with wheeze	Inappropriate index test
21	Murray 2017 (19)	Analysis of birth cohort study data. Asthma diagnosis based on questionnaire data without further objective testing	Inappropriate reference standard
22	Pattemore 1990 (136)	Cross sectional study of primary school children using questionnaire data and bronchial challenge testing. No second objective test to confirm diagnosis.	Inappropriate reference standard
23	Ratageri 2001 (137)	Case control study of children with existing diagnosis of asthma versus controls.	Inappropriate reference standard
24	Rufo 2019 (138)	Cross sectional study investigating ability of exhaled VOCs to differentiate between children with or without an existing diagnosis of asthma	Inappropriate index test
25	Saada 2012 (139)	Abstract only. Adults and children. Cross sectional study using questionnaires to identify people with asthma.	No original article Inappropriate reference standard

26	Smith 2004 (140)	Adult study evaluating diagnostic accuracy of FeNO	Inappropriate population
27	Sumino 2012 (141)	Adult case control study investigating diagnostic utility of methacholine challenge testing	Inappropriate population
28	Tavakol 2013 (142)	Abstract only. All participants had pre-existing diagnosis of asthma already. Non-diagnostic study.	No original article Inappropriate reference standard
29	Tse 2013 (29)	Case control study using two birth cohorts to identify children with asthma and no asthma. No second objective test to confirm asthma.	Inappropriate reference standard
30	Vilozni 2016 (143)	Case control study. Non-diagnostic. Majority of children were below 5 years.	Inappropriate population

Supplementary table 32: Excluded studies following full text screen for PICO 4 (BDR testing).

	Reference	Study Design	Reason for Exclusion
1	Anderson 2010 (122)	Conference abstract only. Cohort study of children with suspected asthma using challenge tests.	No original article Inappropriate index test
2	Andregnette 2011 (123)	Conference abstract only. Cohort study of children with suspected asthma using challenge tests.	No original article Inappropriate index test
3	Bibi 1991 (124)	Cohort study of children with normal baseline spirometry. Non diagnostic study.	Inappropriate outcome
4	Brouwer 2010 (12)	Prospective cohort study of peak flow or FEV_1 variability of two weeks.	Inappropriate index test
5	Brozek 2016 (125)	Abstract only. Cross-sectional study. Unclear reference standard.	No original article Inappropriate reference standard
6	Ciprandi 2012 (126)	Cohort study of children with diagnosed asthma to establish cut-off values for FEF_{25-75}	Inappropriate population
7	De Jong 2019	Cohort study of children presenting with suspected asthma. Bronchodilator reversibility test was only performed after challenge testing	Inappropriate index test
8	Del Rio-Navarro 2004 (127)	Population based study. No second objective test used to confirm diagnosis.	Inappropriate reference standard
9	Denboba 2008 (128)	Case control study using cohort from population study to investigate validity of asthma questionnaire. No second objective test to confirm asthma.	Inappropriate outcome
10	Dundas 2005 (31)	Case control study with no second objective test to diagnose asthma.	Inappropriate reference standard
11	Fang 2018 (129)	Retrospective study of children with existing diagnosis of asthma to establish	Inappropriate index test

		cut-off values of FeNO in those with allergic sensitisation	
12	Francisco 2015 (130)	Retrospective analysis of spirometry results in children with diagnosed asthma to compare different parameters of airflow obstruction.	Inappropriate index test
13	Galant 2007 (131)	Case control study investigating BDR. No second objective test.	Inappropriate reference standard
14	Gerald 2004 (132)	Case finding population study. No consistent gold standard diagnostic criteria.	Inappropriate reference standard
15	Goldstein 2001 (48)	Cohort study of people with normal baseline spirometry comparing PEFR variability with methacholine challenge. Non diagnostic study.	Inappropriate index test
16	Grzelewski 2014	Retrospective analysis of children presenting to hospital for evaluation of suspected asthma	Inappropriate index test
17	Grzelewski 2016 (133)	Retrospective cross sectional study looking at FeNO to spirometry ratio cut-offs in children with existing diagnosis of asthma.	Inappropriate index test
18	Hansen 2015 (50)	Case control study using questionnaire to identify children with asthma	Inappropriate index test
19	Jerzynska 2015 (134)	Prospective study exploring diagnostic accuracy of specific airway resistance	Inappropriate index test
20	Kannisto 1999 (135)	Prospective study of children with suspected asthma using exercise challenge testing and peak flow recordings	Inappropriate reference standard
21	Lang 2009 (57)	Observational study of association between raised body mass index and asthma misdiagnosis	Inappropriate index test
22	Lee 2015 (58)	Population based cross sectional study using questionnaires to identify children with wheeze	Inappropriate index test

23	Murray 2017 (19)	Analysis of birth cohort study data. Asthma diagnosis based on questionnaire data without further objective testing	Inappropriate reference standard
24	Pattemore 1990 (136)	Cross sectional study of primary school children using questionnaire data and bronchial challenge testing. No second objective test to confirm diagnosis.	Inappropriate reference standard
25	Ratageri 2001 (137)	Case control study of children with existing diagnosis of asthma versus controls.	Inappropriate reference standard
26	Rufo 2019 (138)	Cross sectional study investigating ability of exhaled VOCs to differentiate between children with or without an existing diagnosis of asthma	Inappropriate index test
27	Saada 2012 (139)	Abstract only. Adults and children. Cross sectional study using questionnaires to identify people with asthma.	No original article Inappropriate reference standard
28	Sivan 2009	Paediatric study evaluating diagnostic accuracy of FeNO and spirometry	Inappropriate index test
29	Smith 2004 (140)	Adult study evaluating diagnostic accuracy of FeNO	Inappropriate population
30	Sumino 2012 (141)	Adult case control study investigating diagnostic utility of methacholine challenge testing	Inappropriate population
31	Tavakol 2013 (142)	Abstract only. All participants had pre-existing diagnosis of asthma already. Non-diagnostic study.	No original article Inappropriate reference standard
32	Tse 2013 (29)	Case control study using two birth cohorts to identify children with asthma and no asthma. No second objective test to confirm asthma.	Inappropriate reference standard
33	Vilozni 2016 (143)	Case control study. Non-diagnostic. Majority of children were below 5 years.	Inappropriate population

Supplementary table 33: Excluded studies following full text screen for PICO 5 (FeNO)

	Reference	Study Design	Reason for Exclusion
1	Jerzynska 2014 (144)	Cohort study of children with suspected asthma and/or allergic rhinitis	Inappropriate population
2	Linkosalo 2012 (145)	Cohort study of children with suspected asthma. Outcome exercise induced bronchospasm and not asthma.	Inappropriate outcome
3	Sachs-Olsen 2010 (146)	Case control study of children with and without diagnosed asthma	Inappropriate study design
4	Yao 2011 (147)	Case control study of children with and without diagnosed asthma	Inappropriate study design
5	Perez-Tarazona 2011 (148)	Case control study of children with and without diagnosed asthma	Inappropriate study design
6	Zhu 2019 (149)	Study of children with suspected asthma. Outcome is cough variant asthma.	Inappropriate outcome
7	An 2015 (150)	Study of 1-3 year old children with suspected asthma	Inappropriate population
8	Ramser 2008 (151)	Case control study of children with and without diagnosed asthma	Inappropriate study design
9	Avital 2001 (152)	Case control study of children with and without diagnosed asthma	Inappropriate study design

Supplementary table 34: Excluded studies following full text screen for PICO 6 (peak flow variability).

	Reference	Study design	Reason for Exclusion
1	Pattemore 1999, (153)	Cross sectional study of school aged children using questionnaire data and bronchial challenge testing. No second objective test to confirm diagnosis.	No clear second objective test used in diagnosis Inappropriate population - diagnostic groups set a priori
2	Timonen 1997, (76)	Cross sectional study of school-aged children using questionnaire data and skin prick testing. No second objective test to confirm diagnosis.	No clear second objective test used in diagnosis Inappropriate population - diagnostic groups set a priori
3	Linna 1993, (154)	Cross-sectional observational study of school-aged children assessing reliability of home peak flow monitoring	Unclear how diagnosis of asthma made Unclear how many children had a positive peak expiratory flow variability test
4	Siersted 1994, (155)	Children from a national cohort study randomly selected for evaluation of PEFv and administered a symptom questionnaire.	Inappropriate population – unclear which children had current respiratory symptoms, others were assigned to doctor-diagnosed asthma a priori
5	Frischer 1995, (156)	Cohort study of primary school children assessing long term reproducibility of PEFv	Assessed repeatability of PEFR measurements No clear second objective test used in diagnosis Unclear on how doctor-diagnosis of asthma was reached
6	Ulrik CS 2005, (157)	Prospective population based study of asthma, allergy and hyperresponsiveness. Random sample of children selected; symptoms obtained from questionnaire and interview. PEFv, histamine challenge testing, spirometry and BDR performed.	Inappropriate population - diagnostic groups set a priori

Supplementary table 35: Excluded studies following full text screen for PICO 7 (allergy testing).

	Publication	Study design	Reason for exclusion / comments
1	Anderson et al, 2009 (158)	Cross-sectional study on the diagnostic accuracy of mannitol and methacholine to predict a clinical diagnosis of asthma	No results for allergy tests presented
2	Backer et al, 1989 (159)	Cross-sectional study on the prevalence and predictors of bronchial hyperresponsiveness	Not patients suspected for asthma Outcome is not asthma Non diagnostic study
3	Backer et al, 1992 (160)	Cross-sectional study on the distribution of serum IgE in a random sample of children	Not patients suspected for asthma Outcome is not asthma Non diagnostic study
4	Baumann et al, 2015 (161)	Cross-sectional study on the prevalence and risk factors for allergic rhinitis	Not patients suspected for asthma Outcome is not asthma Non diagnostic study
5	Boccaccino et al, 2007 (41)	Cross-sectional study on the ability of forced oscillometry to detect asthma in children	Asthma diagnosis not based on TF criteria
6	Braback et al, 2000 (162)	Cohort on the changes in prevalence and severity of asthma over time	Study design Non diagnostic study
7	Caillaud et al, 2014 (163)	Cross-sectional study on the relationship between exercise induced bronchospasm and rhinitis	Not patients suspected for asthma Outcome is not asthma Non diagnostic study
8	Carlsten et al, 2010 (164)	Birth cohort on the relationship between early exposures to allergens and later sensitization and asthma	Preschool children Non diagnostic study
9	Caudri et al, 2010 (165)	Birth cohort on the prediction of asthma	Study design Preschool children Asthma diagnosis not based on TF criteria
10	Chan et al, 2005 (166)	Case control study on the diagnostic aid of skin prick test for childhood asthma	Study design Preschool children

11	Chauveau et al, 2017 (167)	Cross-sectional study to evaluate the agreement between SPT and sIgE and to compare their association with allergic diseases.	Not patients suspected for asthma Asthma diagnosis not based on TF criteria
12	Christiansen et al, 2016 (168)	Birth cohort assessing the prevalence of atopic disease and the patterns of sensitization in adolescence	Preschool children Not patients suspected for asthma Asthma diagnosis not based on TF criteria Non diagnostic study
13	Cornish et al, 2014 (169)	Cohort study validating childhood asthma in an epidemiological study using linked electronic patient records	Study design Not patients suspected for asthma Asthma diagnosis not based on TF criteria
14	Croner et al, 1992 (170)	Birth cohort assessing the natural history of bronchial asthma in childhood	Study design Not patients suspected for asthma Non diagnostic study
15	Dalkan et al, 2014 (171)	Cross-sectional study assessing the prevalence of allergy.	Study design Not patients suspected for asthma Asthma diagnosis not based on TF criteria Non diagnostic study
16	Drkulec et al, 2013 (172)	Cross-sectional study assessing the ability of allergy test in differentiation of asthmatic children and children with chronic cough	Preschool children Asthma diagnosis not based on TF criteria
17	Eysink et al, 2005 (173)	Cohort study assessing the accuracy of specific IgE in the prediction of asthma	Study design Preschool children
18	Franklin et al, 2003 (174)	Cross-sectional study assessing the relationship between FeNO and asthma, atopy and increased airway responsiveness	Preschool children Not patients suspected for asthma Non diagnostic study
19	Frischer et al, 1993 (175)	Cross-sectional study screening for asthma with the ISAAC questionnaire and a standardized running test	Not patients suspected for asthma Asthma diagnosis not based on TF criteria
20	Gruchalla et al, 2003 (176)	Cross-sectional study screening for asthma and atopy with the ISAAC questionnaire and an exercise step test	Not patients suspected for asthma Asthma diagnosis not based on TF

			criteria
21	Grzelewska-Rzymowska et al, 2001 (177)	Cross-sectional study assessing the parameters leading to right diagnosis.	Preschool children Asthma diagnosis not based on TF criteria
22	Gudelj et al, 2012 (49)	Cross-sectional study assessing the prevalence of asthma, determine risk factors and validate the ISAAC questionnaire	Not patients suspected for asthma Asthma diagnosis not based on TF criteria
23	Hansen et al, 2015 (50)	Cross-sectional study validation of the ISAAC questionnaire	Not patients suspected for asthma Asthma diagnosis not based on TF criteria
24	Hirsch et al, 2000 (178)	Cross-sectional study assessing the prevalence of allergic sensitization	Not patients suspected for asthma Asthma diagnosis not based on TF criteria
25	Kim et al, 1997 (56)	Cross-sectional study assessing the prevalence of asthma and atopy	Not patients suspected for asthma Asthma diagnosis not based on TF criteria
26	Lazic et al, 2013 (179)	Birth cohort study assessing the association between atopy phenotypes and asthma	Study design Not patients suspected for asthma Asthma diagnosis not based on TF criteria Non diagnostic study
27	Lodrup et al, 2010 (180)	Cohort study assessing if IgE measurement or severity score at age 2 predicts asthma at age 10 better	Study design Preschool children Asthma diagnosis not based on TF criteria
28	Mai et al, 2002 (60)	Cross-sectional study evaluating the value of hypertonic saline challenge test in an epidemiological survey in children	Not patients suspected for asthma Asthma diagnosis not based on TF criteria
29	Maloca et al, 2017 (181)	Cross-sectional study assessing the diagnostic potential of a pattern of simple chemical biomarkers from exhaled breath condensates in diagnosing asthma	No results for allergy tests presented
30	Nissen et al, 2013 (182)	Birth cohort assessing the natural course of sensitization and allergic diseases	Study design Preschool children Not patients suspected for asthma

			Asthma diagnosis not based on TF criteria
31	Nolte et al, 1990 (183)	Cross-sectional study comparing the diagnostic value of common allergy tests with basophil histamine release	Outcome is not asthma
32	Ong et al, 2013 (184)	Birth cohort study assessing the value of methacholine challenge test as a diagnostic aid for asthma	Study design Not patients suspected for asthma Asthma diagnosis not based on TF criteria
33	Peat et al, 1993 (185)	Cohort study assessing the predictive nature of bronchial hyper responsiveness and recent wheeze to classify asthma	Study design Not patients suspected for asthma
34	Peat et al, 1991 (186)	Cross-sectional study assessing the relationship between atopy and respiratory illness	Not patients suspected for asthma Non diagnostic study
35	Prosperi et al, 2014 (187)	Birth cohort assessing association between patterns of allergen responses and asthma, rhino-conjunctivitis, wheeze, eczema and airway hyper-reactivity	Study design Not patients suspected for asthma Asthma diagnosis not based on TF criteria
36	Reinhardt et al, 2015 (188)	Cohort study assessing the reliability of the prick test	Study design Not patients suspected for asthma Asthma diagnosis not based on TF criteria
37	Rhodes et al, 2002 (189)	Birth cohort assessing the natural history of wheeze and atopic status	Study design Not patients suspected for asthma Outcome is not asthma
38	Ruggieri et al, 2017 (190)	Cross-sectional study assessing the relationship between respiratory symptoms and allergen sensitization	Not patients suspected for asthma Asthma diagnosis not based on TF criteria
39	Sachs-Olsen et al, 2010 (146)	Birth cohort assessing the diagnostic value of exhaled nitric oxide in childhood asthma and allergy	Study design Not patients suspected for asthma Asthma diagnosis not based on TF criteria
40	Sanchez-Garcia et al, 2012 (66)	Cross-sectional study assessing the accuracy of bronchial challenge tests to measure bronchial hyper responsiveness	Outcome is not asthma

41	Sarratud et al, 2010 (191)	Cross-sectional study assessing the value of a new point-of care-test in the diagnosis of atopy	Outcome is not asthma
42	Sporik et al, 1991 (192)	Birth cohort assessing the natural history of asthma and atopy	Study design Not patients suspected for asthma Asthma diagnosis not based on TF criteria
43	Turktas et al, 2006 (193)	Cross-sectional study assessing the diagnostic accuracy of skin-prick testing in young children with asthma	Preschool children Asthma diagnosis not based on TF criteria
44	Weinmayr et al, 2010 (194)	Cross-sectional study assessing the association between allergy tests and allergic symptoms	Not patients suspected for asthma Asthma diagnosis not based on TF criteria
45	Wolthers et al, 2013 (195)	Cross-sectional study assessing the diagnostic usefulness of the MAST CLA as compared to the Phadia Immunocap allergen-specific IgE test panel system	Outcome is not asthma

Supplementary table 36: Excluded studies following full text screen for PICO 8 (indirect bronchial challenge testing).

	Publication	Study design	Reason for exclusion / comments
1	Andregnette –Roscigno et al, 2010 (196)	Cross-sectional study in children with current asthma symptoms, different lung function test are compared.	Short report, calculation of sensitivity and specificity not possible
2	Andregnette –Roscigno et al, 2011 (123)	Cross-sectional study in children with current asthma symptoms, different lung function test are compared.	Conference abstract, calculation of sensitivity and specificity not possible
3	Backer et al, 1992 (197)	Cross-sectional study comparing different BHR tests	Mixed population (asthma, rhinitis and dermatitis), no separate analysis for asthma diagnosis.
4	Backer et al, 1991 (198)	Cross-sectional study investigating the role of BHR with histamine for later asthma	Asthma diagnosis made on the basis of questionnaire, reference standard not according to protocol.
5	Carey et al, 1996 (199)	Cohort study investigating the role of BHR to predict the incidence of wheeze	Diagnosis of asthma not according to TF definition.
6	Carlsten et al, 2011 (200)	Cohort study comparing different cut-off for BHR in children with confirmed asthma.	Diagnosis of asthma not according to TF definition. Clinical diagnosis made by the pediatric allergist based on symptoms of wheeze and cough, medication use and physical findings
7	Deliu et al,2014 (201)	Cross sectional study comparing factors association with different rhinitis phenotypes.	No calculation of sensitivity and specificity possible, since asthma is not the outcome.
8	Fitzgerald et al, 1996 (44)	Prospective study comparing peak flow variation to other bronchial provocation tests in asthma patients	Asthma diagnosis not according to protocol of the TF

9	James et al, 1997 (202)	Review article BHR using inhaled methacholine or histamine	No diagnostic study, review article.
10	Joseph-Bowen et al, 2004 (54)	Cohort study on risk factors for lung function deficits and asthma at school age	Asthma diagnosis not according to protocol of the TF, diagnosis not confirmed by objective test.
11	Koh et al, 2002 (203)	Cohort study assessing predictors for asthma in subjects with allergic rhinitis	Asthma diagnosis not according to protocol of the TF, diagnosis not confirmed by objective test.
12	Lang et al, 2008 (204)	Birth cohort assessing the prevalence of severe asthma in an urban population	No calculation of sensitivity and specificity possible, since the number are not reported in detail.
13	Lee et al, 2017 (205)	Cross-sectional study comparing different cut-offs for methacholine challenge tests	Asthma diagnosis not according to protocol of the TF, diagnosis not confirmed by objective test.
14	Levin et al, 2011 (206)	Cross-sectional study associating BHR with asthma and other atopic diseases.	Diagnosis of asthma not according to TF definition - self-reported symptoms of asthma in the last 12 months
15	Liem et al, 2008 (207)	Birth cohort study comparing different cut-offs for methacholine challenge in children with asthma	Asthma diagnosis not according to protocol of the TF, diagnosis made only be clinical decision based on symptoms.
16	Mallol et al, 2008 (208)	Cross-sectional study assessing the relationship between asthma symptoms and pulmonary function tests	Asthma outcome self-reported current wheezing, not asthma based on TF definition.
17	Nicolai et al, 1993 (209)	Cross-sectional study screening for asthma with cold air challenge	Asthma diagnosis not according to protocol of the TF, diagnosis only symptom based.
18	van den Nieuwenhof et al, 2008 (210)	Cohort study assessing the association between BHR in adolescence and asthma in adulthood.	Asthma diagnosis not according to protocol of the TF, diagnosis not confirmed by objective test.

19	Niggemann et al, 2001 (211)	Cross-sectional study assessing different cut-off values for BHR in children	Asthma diagnosis not according to protocol of the TF, diagnosis was parental reported asthma.
20	Pattemore et al, 1990 (136)	Cross-sectional study assessing the prevalence of BHR in asthma patients	Not patients suspected for asthma Asthma diagnosis not based on TF criteria
21	Porsbjerg et al, 2006 (212)	Prospective study describing the incidence and remission of asthma in children.	Asthma diagnosis not according to protocol of the TF.Asthma diagnosis not based on TF criteria
22	Remes et al, 2002 (213)	Cross-sectional study assessing the role of symptoms and BHR for the diagnosis of asthma	No diagnostic study, calculation of sensitivity and specify not possible.
23	Rhodes et al, 2002 (189)	Birth cohort study describing risk factors for atopy in adolescents	Asthma diagnosis confirmed by BHR, but diagnosis is not comparison to another objective test
24	Riiser et al, 2012 (214)	Birth cohort assessing the predictive value of BHR for asthma	Asthma diagnosis not according to protocol of the TF, diagnosis only symptom based.
25	Sears et al, 1991 (215)	Birth cohort assessing the relation between total IgE and BHR in children with and without asthma	Asthma diagnosis not according to protocol of the TF.
26	Siersted et al, 1994 (155)	Cross-sectional study assessing the role of peak expiratory flow to diagnose asthma	Asthma diagnosis not according to protocol of the TF, diagnosis only symptom based.
27	Siersted et al, 1996 (216)	Cross sectional study comparing different lung function tests in asthmatics	No diagnostic study, calculation of sensitivity and specificity not possible.
28	Sumino et al, 2012 (141)	Cohort study in asthmatics using methacholine challenge test to diagnose asthma	Mean age of study population 32 years, not data in children only reported.
29	Ulrik et al, 1998 (217)	Prospective study investigating the prevalence of BHR during	Asthma diagnosis not according to protocol of the TF, diagnosis only

		several time points	questionnaire based.
30	van der Mark et al, 2014 (218)	Cohort study assessing the predictive of environmental factors and symptoms for late later asthma	No diagnostic study on direct/indirect bronchial challenge.
31	Vasar M et al, 1996 (219)	Cross sectional survey on asthma symptoms, of which a subsample had lung function test done to describe prevalence of abnormal tests.	Publication not with the outcome asthma but respiratory symptoms and allergy.
32	Wong et al, 2002 (220)	Cross sectional study in Chinse children suspected for asthma. Prevalence of symptoms and abnormal lung function test was studied.	Asthma diagnosis not according to protocol of the TF, diagnosis not confirmed by objective test
33	Yang et al, 2017 (7)	Cross sectional study assessing the accuracy of diagnostic criteria for asthma in a community sample.	Asthma diagnosis not according to protocol of the TF, diagnosis only questionnaire based.

Supplementary table 37: Excluded studies following full text screen for PICO 9 (direct bronchial challenge testing).

	Publication	**Study design**	**Reason for exclusion / comments**
1	Avital et al, 1995 (221)	Clinical trial comparing methacholine and adenosine bronchial challenge in asthma patients (clinical rial registration)	Too few patients included, only 15 children which also have other diagnosis than asthma (pneumonia, CF, bronchiolitis obliterans).
2	Brannan et al, 2005 (222)	A phase III, multi-centre, open label, operator-blinded, crossover design, randomised trial to assess safety of mannitol and hypertonic saline to assess BHR.	Age distribution not according to TF protocol (mean age 35, range 6-83), no subgroup analysis in children completed..
3	Buechele et	Cross-sectional study comparing	Asthma diagnosis not according to

	al, 2007 (42)	different BHR test to diagnose asthma	protocol of the TF, diagnosis only questionnaire based.
4	Carlsen et al, 1998 (223)	Cross-sectional study comparing cold air inhalation and methacholine BHR to diagnose asthma	No diagnostic study, comparison of bronchial challenge testing between asthmatics and subjects with chronic lung disease.
5	Demissie et al, 1998 (43)	Cross sectional study comparing questionnaire data and BHR to diagnose asthma	Asthma diagnosis not according to protocol of the TF, diagnosis only questionnaire based.
6	Fuentes et al, 2011 (224)	Cross sectional study comparing lung function tests in asthmatic and non-asthmatic patients	No diagnostic study, case control design.
7	Galdes-Sebaldt et al, 1985 (225)	Cross sectional, case control study comparing cold air challenge and other bronchial provocation tests.	No diagnostic study, case control design.
8	Godfrey et al, 1999 (226)	Review, comparison of different cut-offs to induce BHR	Review article, no diagnostic study.
9	Jenkins et al, 1996 (227)	Cross sectional study comparing questionnaire assessed symptoms and objective lung function tests	Asthma diagnosis not according to protocol of the TF, diagnosis only questionnaire based.
10	Joseph et al, 1999 (228)	Comparative study on different asthma definitions, no original data in patients was obtained.	Reference standard does not match TF definition (self-reported physician diagnosis of asthma – no objective test).
11	Kussek et al, 2006 (229)	Cross sectional study assessing the effect of BHR in asthmatic and non-asthmatic children	No diagnostic study, case control design
12	Lazo-Velasquez et al, 2005 (230)	Cross-sectional study comparing prevalence of BHR in diferent severity type of asthma and non-asthmatic children.	No diagnostic study, case control design.
13	Lis et al, 1998 (231)	Cross-sectional study assessing BHR to different doses of hypertonic saline	Asthma diagnosis not according to protocol of the TF, diagnosis only questionnaire based; case control study.
14	Mai et al, 2002 (60)	Cross sectional study assessing the vlaue ISAAC questionnaire to BHR	Asthma diagnosis not according to protocol of the TF, diagnosis only questionnaire based; case control

			study.
15	Nicolai et al, 1993 (209)	Cross-sectional study screening for asthma with cold air challenge.	General population, asthma not confirmed by objective test but assessed by questionnaire.
16	Nja et al, 2000 (232)	Cross-sectional study assessing the prevalence of questionnaire based asthma diagnosis	Asthma diagnosis not according to protocol of the TF, diagnosis only questionnaire based.
17	Okupa et al. 2012 (233)	Cross-sectional study assessing the properties of a new mannitol powder to assess BHR	Conference abstract
18	Piotrowska et al, 2007 (234)	Cross-sectional study comparing methacholine and hypertonic saline provocation tests	General population, study gives only prevalence of symptoms in asthma vs. no asthma.
19	Ponsonby et al, 1996 (64)	Cross-sectional study comparing asthma symptoms reported in the ISAAC questionnaire to BHR results	Population does not match TF protocol. The population includes healthy
20	Riedler et al, 1994 (65)	Cross-sectional study assessing the hypertonic saline to diagnose asthma	Case control study.
21	Riiser et al, 2012 (214)	Birth cohort study assessing the association between methacholine and exercise challenge with later asthma diagnosis	Asthma diagnosis not according to protocol of the TF, no diagnostic test used for diagnosis.
22	Sanchez-Garcia et al, 2015 (235)	Cross sectional study comparing different challenge tests in subjects with asthma	Asthma diagnosis not according to protocol of the TF, no diagnostic test used for diagnosis.
23	Siersted et al, 1996 (216)	Cross-sectional study comparing the prevalence of asthma symptoms to different lung function tests	Reference standard does not match PICO question since methacholine test was used as part of reference standard to diagnose asthma
24	Smith et al, 1990 (236)	Cross-sectional study comparing different forms of bronchial provocation testing in asthma and non-asthma subjects	Age distribution not according to protocol (mean age 28 years), no results on the subgroup of 18 children reported.
25	Strauch et al, 2001 (237)	Prospective study assessing the prevalence of asthma like symptoms and BHR response	Asthma diagnosis not according to protocol of the TF, diagnosis only questionnaire based.

		over a two year peroid	
26	Subbarao et al, 2000 (238)	Cross-sectional study comparing mannitol and methacholine challenge to diagnose asthma	Case control study with only 25 asthmatics and 10 controls.
27	Sverrild et al, 2012 (239)	Review article on inhaled mannitol to diagnose asthma	No diagnostic study, review article.
28	Ublagger et al, 2005 (240)	Cross sectional study comparing prevalence of wheeze to BHR with hypertonic saline	No diagnostic study, comparison of BHR between asthmatics (diagnosis questionnaire based) and wheezing children.
29	West et al, 1996 (241)	Cross-sectional study testing an exercise challenge test with dry air inhalation.	No diagnostic study, comparison of exercise test between asthmatics (diagnosis questionnaire based) and healthy children.
30	Yanuar et al, 2009 (242)	Cross sectional study assessing asthma prevalence by ISAAC questionnaire and BHR, done with hypertonic saline.	Abstract only, no original paper.
31	Yunus et al, 2003 (83)	Cross sectional study assessing the asthma prevalence by ISAAC questions and bronchial provocation testing	Asthma diagnosis not according to protocol of the TF, diagnosis only questionnaire based.

Literature search strategies

PICO 1: Symptoms

Database: **Ovid Medline** <1980 to 31st August 2019>

1 exp ASTHMA/ (119870)
2 asthma*.ti. (88008)
3 1 or 2 (127588)
4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2323120)
5 sensitiv*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1523403)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (98905)
7 exp "SENSITIVITY AND SPECIFICITY"/ (528323)
8 specificity*.ti,ab. (413121)
9 ("pre test" adj probability).ti,ab. (647)
10 ("pretest" adj probability).ti,ab. (1283)
11 ("post test" adj probability).ti,ab. (498)
12 ("predictive value*" or PPV or NPV).ti,ab. (100458)
13 "likelihood ratio*".ti,ab. (13352)
14 "LIKELIHOOD FUNCTIONS"/ (20614)
15 ("roc curve*" or auc).ti,ab. (72522)
16 "gold standard*".ab. (54343)
17 *respiratory sounds/ (4455)
18 *cough/ (7949)
19 *dyspnea/ (8213)
20 exp *periodicity/ (70673)
21 (wheez* or rhonchi or cough* or breathless* or dyspn?ea).ti,ab. (89458)
22 ((difficult* or labo?r* or short*) adj2 breath*).ti,ab. (9430)
23 ((24h* or 24 hour* or 24 hr*) adj2 (rhythm* or varia* or change* or pattern* or symptom* or sign or signs)).ti,ab. (3135)
24 ((season* or diurnal or circadian or nyctohemeral or night* or nocturnal) adj3 (wheez* or rhonchi or cough* or breathless* or dyspn?ea or symptom or symptoms or sign or signs or asthma*)).ti,ab. (5615)
25 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (2050649)
26 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (176574)
27 3 and 4 and 25 and 26 (586)
28 limit 27 to yr="1980 -Current" (575)

Database: **Embase** <1980 to 31st August 2019>

1 exp ASTHMA/ (232071)

2 asthma*.ti. (112368)
3 1 or 2 (234143)
4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (2582949)
5 sensitiv*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1790744)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (442319)
7 exp "SENSITIVITY AND SPECIFICITY"/ (297163)
8 specificity*.ti,ab. (509365)
9 ("pre test" adj probability).ti,ab. (1404)
10 ("pretest" adj probability).ti,ab. (1960)
11 ("post test" adj probability).ti,ab. (694)
12 ("predictive value*" or PPV or NPV).ti,ab. (148470)
13 "likelihood ratio*".ti,ab. (17559)
14 ("roc curve*" or auc).ti,ab. (120539)
15 "gold standard*".ab. (87756)
16 diagnostic accuracy/ (226935)
17 diagnostic test accuracy study/ (85020)
18 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (2455699)
19 *wheezing/ (3807)
20 *irritative coughing/ (11)
21 *chronic cough/ (897)
22 *coughing/ (9511)
23 *dyspnea/ (10601)
24 *abnormal respiratory sound/ (1167)
25 *seasonal variation/ (9914)
26 exp *periodicity/ (50584)
27 ((difficult* or labo?r* or short*) adj2 breath*).ti,ab. (18627)
28 ((24h* or 24 hour* or 24 hr*) adj2 (rhythm* or varia* or change* or pattern* or symptom* or sign or signs)).ti,ab. (4899)
29 ((season* or diurnal or circadian or nyctohemeral or night* or nocturnal) adj3 (wheez* or rhonchi or cough* or breathless* or dyspn?ea or symptom or symptoms or sign or signs or asthma*)).ti,ab. (9017)
30 (wheez* or rhonchi or cough* or breathless* or dyspn?ea).ti,ab. (139681)
31 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (225105)
32 3 and 4 and 18 and 31 (998)

Database: **Cochrane Library** <1980 to 31st August 2019>

#1 MeSH descriptor: [Asthma] explode all trees 10827
#2 asthma*:ti 20597
#3 #1 or #2 22788
#4 diagnos*:ti,ab,kw 161910
#5 (sensitivity or specificity):ti,ab,kw 50739
#6 ((pre test or pretest or post test) near probability):ti,ab,kw 714

#7 (predictive value* or PPV or NPV):ti,ab,kw 16303
#8 likelihood ratio*:ti,ab,kw 3217
#9 (ROC or AUC):ti,ab,kw 17350
#10 gold standard:ti,ab,kw 5572
#11 #4 or #5 or #6 or #7 or #8 or #9 or #10 217466
#12 (child* or paediatr* or pediatr* or teen*or adolescen*):ti,ab 97730
#13 MeSH descriptor: [Respiratory Sounds] this term only 396
#14 MeSH descriptor: [Dyspnea] this term only 1081
#15 MeSH descriptor: [Cough] this term only 1199
#16 MeSH descriptor: [Periodicity] explode all trees 4203
#17 (wheez* or rhonchi or cough* or breathless* or dyspn?ea):ti,ab,kw 12781
#18 ((difficult* or labo?r* or short*) near/2 breath*):ti,ab,kw 1065
#19 24h* NEAR/2 (rhythm* OR varia* or change* or pattern* or symptom* or sign or signs):ti,ab,kw 58
#20 (24 hour*) NEAR/2 (rhythm* OR varia* or change* or pattern* or symptom* or sign or signs):ti,ab,kw 2802
#21 (24 hr*) NEAR/2 (rhythm* OR varia* or change* or pattern* or symptom* or sign or signs):ti,ab,kw 4504
#22 ((season* or diurnal or circadian or nyctohemeral or night* or nocturnal) near/3 (wheez* or rhonchi or cough* or breathless* or dyspn?ea or symptom or symptoms or sign or signs or asthma*)):ti,ab,kw 1951
#23 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 25093
#24 #3 and #11 and #12 and #23 with Cochrane Library publication date between Jan 1980 and Aug 2018 247

PICO 2: Trial of preventer treatment

Database: **Ovid Medline** <1980 to 31st August 2019>

1 exp ASTHMA/ (119696)
2 asthma*.ti,ab. (143295)
3 1 or 2 (163580)
4 (child* or paediatr* or pediatr* or teen*or adolescen*).ti,ab. (1378796)
5 sensitiv*.ti,ab. (1236893)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).ti,ab. (98388)
7 exp "SENSITIVITY AND SPECIFICITY"/ (527379)
8 specific*.ti,ab. (2767412)
9 ("pre test" adj probability).ti,ab. (646)
10 ("pretest" adj probability).ti,ab. (1279)
11 ("post test" adj probability).ti,ab. (495)
12 ("predictive value*" or PPV or NPV).ti,ab. (100249)
13 "likelihood ratio*".ti,ab. (13310)
14 "LIKELIHOOD FUNCTIONS"/ (20524)
15 ("roc curve*" or auc).ti,ab. (72365)
16 "gold standard*".ti,ab. (55437)
17 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (4054356)
18 (leukotriene* or leucotriene* or ltra or "anti leuk*" or "anti leuc*" or lukast* or montelukast* or singulair or zafirlukast* or accolate or pranlukast* or ultair).ti,ab. (23014)
19 *lukast/ (0)
20 exp *Leukotriene Antagonists/ (1798)
21 exp *Leukotrienes/ (7438)
22 (((steroid* or corticosteroid* or glucocorticoid*) and inhal*) or budesonide or Pulmicort or fluticasone or Flixotide or Flovent or ciclesonide or Alvesco or triamcinolone or Kenalog or beclomethasone or Becotide or Becloforte or Becodisk or QVAR or Flunisolide or AeroBid or mometasone or Asmanex or Symbicort or Advair or Inuvair).ti,ab. (28348)
23 exp *BUDESONIDE/ or exp *Glucocorticoids/ (85802)
24 exp *Mometasone Furoate/ (70)
25 exp *Steroids/ (446858)
26 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (501883)
27 3 and 4 and 17 and 26 (750)
28 limit 27 to yr="1980 -Current" (745)

Database: **Embase** <1980 to 31st August 2019>

1 exp ASTHMA/ (232453)
2 asthma*.ti,ab. (198585)
3 1 or 2 (260176)
4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (2588631)
5 sensitiv*.ti,ab. (1480557)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).ti,ab. (134307)
7 exp "SENSITIVITY AND SPECIFICITY"/ (298377)

8 specific*.ti,ab. (3348427)
9 ("pre test" adj probability).ti,ab. (1409)
10 ("pretest" adj probability).ti,ab. (1964)
11 ("post test" adj probability).ti,ab. (696)
12 ("predictive value*" or PPV or NPV).ti,ab. (148884)
13 "likelihood ratio*".ti,ab. (17617)
14 ("roc curve*" or auc).ti,ab. (121155)
15 "gold standard*".ti,ab. (89788)
16 diagnostic accuracy/ (227420)
17 diagnostic test accuracy study/ (85680)
18 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (4758272)
19 exp *leukotriene/ (11022)
20 exp *corticosteroid/ (263300)
21 exp *steroid/ (500887)
22 (((steroid* or corticosteroid* or glucocorticoid*) and inhal*) or budesonide or Pulmicort or fluticasone or Flixotide or Flovent or ciclesonide or Alvesco or triamcinolone or Kenalog or beclomethasone or Becotide or Becloforte or Becodisk or QVAR or Flunisolide or AeroBid or mometasone or Asmanex or Symbicort or Advair or Inuvair).ti,ab. (42156)
23 (leukotriene* or leucotriene* or ltra or "anti leuk*" or "anti leuc*" or lukast* or montelukast* or singulair or zafirlukast* or accolate or pranlukast* or ultair).ti,ab. (30015)
24 19 or 20 or 21 or 22 or 23 (548993)
25 3 and 4 and 18 and 24 (1467)

Database: **Cochrane Library** <1980 to 31st August 2019>

#1 MeSH descriptor: [Asthma] explode all trees 10843
#2 asthma*:ti 20696
#3 #1 or #2 22892
#4 diagnos*:ti,ab,kw 162985
#5 (sensitivity or specificity):ti,ab,kw 51028
#6 ((pre test or pretest or post test) NEAR probability):ti,ab,kw 719
#7 (predictive value* or PPV or NPV):ti,ab,kw 16401
#8 likelihood ratio*:ti,ab,kw 3250
#9 (ROC or AUC):ti,ab,kw 17488
#10 gold standard:ti,ab,kw 5631
#11 #4 or #5 or #6 or #7 or #8 or #9 or #10 218946
#12 (child* or paediatr* or pediatr* or teen*or adolescen*):ti,ab 98324
#13 (leukotriene* or leucotriene* or ltra or "anti leuk*" or "anti leuc*" or lukast* or montelukast* or singulair or zafirlukast* or accolate or pranlukast* or ultair):ti,ab 2726
#14 MeSH descriptor: [Leukotriene Antagonists] explode all trees 421
#15 MeSH descriptor: [Leukotrienes] explode all trees 435
#16 ((steroid* or corticosteroid* or glucocorticoid*) NEAR inhal*):ti,ab 5075
#17 (budesonide or Pulmicort or fluticasone or Flixotide or Flovent or ciclesonide or Alvesco or triamcinolone or Kenalog or beclomethasone or Becotide or Becloforte or Becodisk or QVAR or Flunisolide or AeroBid or mometasone or Asmanex or Symbicort or Advair or Inuvair):ti,ab 11514
#18 MeSH descriptor: [Budesonide] explode all trees1652
#19 MeSH descriptor: [Glucocorticoids] explode all trees 4177
#20 MeSH descriptor: [Mometasone Furoate] explode all trees 328
#21 MeSH descriptor: [Steroids] explode all trees 52609

#22 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 63979
#23 #3 and #11 and #12 and #22 with Cochrane Library publication date between Jan 1980 and Oct 2018 308

PICO 3: Spirometry

Database: **Ovid Medline** <1980 to 31st August 2019>

1 exp ASTHMA/ (119545)
2 asthma*.ti. (87740)
3 1 or 2 (127206)
4 spiromet*.ti. (3525)
5 vital capacity/ (14425)
6 forced expiratory volume/ (23590)
7 (fev1 or fvc or "fev 1").ti,ab. (30270)
8 ("flow volume" adj2 loop*).ti,ab. (669)
9 ("flow volume" adj2 curve*).ti,ab. (1477)
10 ("flow volume" adj2 graph*).ti,ab. (0)
11 ("forced expiratory volume*" adj6 "1").ti,ab. (10382)
12 ("forced expiratory volume*" adj6 one).ti,ab. (4832)
13 (force* adj2 "vital capacit*").ti,ab. (9831)
14 (time* adj2 "vital capacit*").ti,ab. (81)
15 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2315128)
16 sensitiv*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1517487)
17 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (98291)
18 exp "SENSITIVITY AND SPECIFICITY"/ (526009)
19 specificity*.ti,ab. (411353)
20 ("pre test" adj probability).ti,ab. (643)
21 ("pretest" adj probability).ti,ab. (1280)
22 ("post test" adj probability).ti,ab. (496)
23 ("predictive value*" or PPV or NPV).ti,ab. (99919)
24 "likelihood ratio*".ti,ab. (13259)
25 "LIKELIHOOD FUNCTIONS"/ (20514)
26 ("roc curve*" or auc).ti,ab. (71914)
27 "gold standard*".ab. (53921)
28 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (53202)
29 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (2042110)
30 3 and 15 and 28 and 29 (632)
31 limit 30 to yr="1980 -Current" (613)

Database: **Embase** <1980 to 31st August 2019>

1 exp ASTHMA/ (231366)
2 asthma*.ti. (112082)
3 1 or 2 (233429)
4 spiromet*.ti. (4554)
5 vital capacity/ (9011)

6 forced expiratory volume/ (55769)
7 (fev1 or fvc or "fev 1").ti,ab. (55447)
8 lung flow volume curve/ (1471)
9 ("flow volume" adj2 loop*).ti,ab. (901)
10 ("flow volume" adj2 curve*).ti,ab. (1609)
11 ("flow volume" adj2 graph*).ti,ab. (3)
12 ("forced expiratory volume*" adj6 "1").ti,ab. (12121)
13 ("forced expiratory volume*" adj6 one).ti,ab. (6045)
14 (force* adj2 "vital capacit*").ti,ab. (13266)
15 (time* adj2 "vital capacit*").ti,ab. (77)
16 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (2571478)
17 sensitiv*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1782336)
18 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (439750)
19 exp "SENSITIVITY AND SPECIFICITY"/ (294533)
20 specificity*.ti,ab. (506844)
21 ("pre test" adj probability).ti,ab. (1381)
22 ("pretest" adj probability).ti,ab. (1943)
23 ("post test" adj probability).ti,ab. (687)
24 ("predictive value*" or PPV or NPV).ti,ab. (147522)
25 "likelihood ratio*".ti,ab. (17425)
26 ("roc curve*" or auc).ti,ab. (119369)
27 "gold standard*".ab. (87004)
28 diagnostic accuracy/ (225901)
29 diagnostic test accuracy study/ (83468)
30 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (2444008)
31 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (93702)
32 3 and 16 and 30 and 31 (920)

Database: **Cochrane Library** <1980 to 31st August 2019>

Search Strategy: **For PICO 3, 4 and 6**

#1 MeSH descriptor: [Asthma] explode all trees 11462
#2 asthma*:ti 21161
#3 #1 or #2 23432
#4 diagnos*:ti,ab,kw 109829
#5 (sensitivity or specificity):ti,ab,kw 53580
#6 ((pre test or pretest or post test) near probability):ti,ab,kw 212
#7 (predictive value* or PPV or NPV):ti,ab,kw 17300
#8 likelihood ratio*:ti,ab,kw 3352
#9 (ROC or AUC):ti,ab,kw 17842
#10 gold standard:ti,ab,kw 5569
#11 #4 or #5 or #6 or #7 or #8 or #9 or #10 175528

#12 MeSH descriptor: [Vital Capacity] this term only 1871
#13 MeSH descriptor: [Forced Expiratory Volume] this term only 5085
#14 (FEV1 or "FEV 1" or FVC):ti,ab 9747
#15 (flow volume near/2 (loop* or curve* or graph*)):ti,ab 246
#16 (forced expiratory volume* near/6 ("1" or one)):ti,ab 4729
#17 ((force* or time*) near/2 vital capacit*):ti,ab 2309
#18 spirometry:ti 377
#19 #12 or #13 or #14 or #15 or #16 or #17 or #18 14034
#20 (child* or paediatr* or pediatr* or teen*or adolescen*):ti,ab 99696
#21 #3 and #11 and #19 and #20 Publication Year from 1980 to 2018 192
#22 MeSH descriptor: [Bronchodilator Agents] explode all trees 3971
#23 (test* or revers* or respons* or respond*):ti,ab 392261
#24 #22 and #23 1654
#25 ((bronchodilator* or bronchial dilat* or broncholytic*) near/3 (test* or revers* or respons* or respond*)):ti,ab,kw 870
#26 bronchoreversibility:ti,ab,kw 2
#27 (BDR or BDT):ti,ab,kw 56
#28 #24 or #25 or #26 or #27 2221
#29 #3 and #11 and #20 and #28 Publication Year from 1980 to 2018 41
#30 #29 or #21 Publication Year from 1980 to 2018 210
#31 pefv:ti,ab,kw 10
#32 ((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) near/3 (PEFR or PFR or peak expiratory flow* or peak flow*)):ti,ab,kw 507
#33 MeSH descriptor: [Peak Expiratory Flow Rate] this term only 1564
#34 MeSH descriptor: [Circadian Rhythm] explode all trees 2924
#35 #33 and #34 69
#36 #31 or #32 or #35 574
#37 #3 and #11 and #20 and #36 Publication Year from 1980 to 2018 17
#38 #37 or #30 Publication Year from 1980 to 2018 219

PICO 4: BDR

Database: **Ovid Medline** <1980 to 31st August 2019>

1 exp ASTHMA/ (119870)
2 asthma*.ti. (88008)
3 1 or 2 (127588)
4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2323120)
5 sensitiv*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1523403)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (98905)
7 exp "SENSITIVITY AND SPECIFICITY"/ (528323)
8 specificity*.ti,ab. (413121)
9 ("pre test" adj probability).ti,ab. (647)
10 ("pretest" adj probability).ti,ab. (1283)
11 ("post test" adj probability).ti,ab. (498)
12 ("predictive value*" or PPV or NPV).ti,ab. (100458)
13 "likelihood ratio*".ti,ab. (13352)
14 "LIKELIHOOD FUNCTIONS"/ (20614)
15 ("roc curve*" or auc).ti,ab. (72522)
16 "gold standard*".ab. (54343)
17 exp "BRONCHODILATOR AGENTS"/ (253059)
18 (bronchodilator* adj3 (test* or revers* or respons* or respond*)).ti,ab. (2048)
19 (test* or revers* or respons* or respond*).ti,ab. (5885077)
20 17 and 19 (94239)
21 ("bronchial dilat*" adj3 (test* or revers* or respons* or respond*)).ti,ab. (23)
22 (broncholytic* adj3 (test* or revers* or respons* or respond*)).ti,ab. (12)
23 (bdr or bdt or bronchoreversibility).ti,ab. (821)
24 18 or 20 or 21 or 22 or 23 (95725)
25 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (2050649)
26 3 and 4 and 24 and 25 (294)
27 limit 26 to yr="1980 -Current" (287)
28 17 or 18 or 21 or 22 or 23 (254541)
29 3 and 4 and 25 and 28 (487)
30 limit 29 to yr="1980 -Current" (472)

Database: **Embase** <1980 to 31st August 2019>

1 exp ASTHMA/ (232056)
2 asthma*.ti. (112380)
3 1 or 2 (234127)

4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (2581731)
5 sensitiv*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1789741)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (442095)
7 exp "SENSITIVITY AND SPECIFICITY"/ (296696)
8 specificity*.ti,ab. (509150)
9 ("pre test" adj probability).ti,ab. (1401)
10 ("pretest" adj probability).ti,ab. (1960)
11 ("post test" adj probability).ti,ab. (693)
12 ("predictive value*" or PPV or NPV).ti,ab. (148409)
13 "likelihood ratio*".ti,ab. (17554)
14 ("roc curve*" or auc).ti,ab. (120372)
15 "gold standard*".ab. (87638)
16 (bronchodilator* adj3 (test* or revers* or respons* or respond*)).ti,ab. (3229)
17 (test* or revers* or respons* or respond*).ti,ab. (7199174)
18 ("bronchial dilat*" adj3 (test* or revers* or respons* or respond*)).ti,ab. (31)
19 (broncholytic* adj3 (test* or revers* or respons* or respond*)).ti,ab. (16)
20 (bdr or bdt or bronchoreversibility).ti,ab. (1113)
21 diagnostic accuracy/ (226772)
22 diagnostic test accuracy study/ (84906)
23 exp *bronchodilating agent/ (72845)
24 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 21 or 22 (2454225)
25 17 and 23 (21987)
26 16 or 18 or 19 or 20 or 25 (24885)
27 3 and 4 and 24 and 26 (225)
28 16 or 18 or 19 or 20 or 23 (75742)
29 3 and 4 and 24 and 28 (299)

Database: **Cochrane Library** <1980 to 31st August 2019>

See PICO 3

PICO 5: FeNO

Database: **Ovid Medline** <1980 to 31st August 2019>

1 exp ASTHMA/ (119609)
2 asthma*.ti. (87813)
3 1 or 2 (127305)
4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2316992)
5 sensitiv*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1518622)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (98441)
7 exp "SENSITIVITY AND SPECIFICITY"/ (526338)
8 specificity*.ti,ab. (411691)
9 ("pre test" adj probability).ti,ab. (645)
10 ("pretest" adj probability).ti,ab. (1282)
11 ("post test" adj probability).ti,ab. (498)
12 ("predictive value*" or PPV or NPV).ti,ab. (100023)
13 "likelihood ratio*".ti,ab. (13279)
14 "LIKELIHOOD FUNCTIONS"/ (20524)
15 ("roc curve*" or auc).ti,ab. (72055)
16 "gold standard*".ab. (53989)
17 (Fraction* adj2 exhaled).ti,ab. (1320)
18 "BREATH TESTS"/ (13791)
19 BIOMARKERS/ (229322)
20 "NITRIC OXIDE"/ (83127)
21 EXHALATION/ (3427)
22 Feno.ti,ab. (1595)
23 18 or 19 or 21 (243495)
24 20 and 23 (4285)
25 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (2043713)
26 17 or 22 or 24 (5302)
27 23 or 24 (243495)
28 3 and 4 and 25 and 27 (321)
29 limit 28 to yr="1980 -Current" (321)

Database: **Embase** <1980 to 31st August 2019>

1 exp ASTHMA/ (231579)
2 asthma*.ti. (112170)
3 1 or 2 (233646)
4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (2575279)

5 sensitiv*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1785115)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (440572)
7 exp "SENSITIVITY AND SPECIFICITY"/ (295269)
8 specificity*.ti,ab. (507674)
9 ("pre test" adj probability).ti,ab. (1392)
10 ("pretest" adj probability).ti,ab. (1954)
11 ("post test" adj probability).ti,ab. (689)
12 ("predictive value*" or PPV or NPV).ti,ab. (147831)
13 "likelihood ratio*".ti,ab. (17466)
14 ("roc curve*" or auc).ti,ab. (119726)
15 "gold standard*".ab. (87285)
16 ((fe or exhal* or fraction*) adj2 (nitric or no or nitrogen)).ti,ab. (10402)
17 Feno.ti,ab. (3678)
18 diagnostic accuracy/ (226204)
19 diagnostic test accuracy study/ (83969)
20 *nitric oxide/ (56348)
21 *breath analysis/ (4590)
22 *expired air/ (1115)
23 *biological marker/ (61249)
24 *exhalation/ (741)
25 21 or 22 or 23 or 24 (67287)
26 20 and 25 (717)
27 16 or 17 or 26 (11234)
28 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 18 or 19 (2447935)
29 3 and 4 and 27 and 28 (369)

Database: **Cochrane Library** <1980 to 31st August 2019>

#1 MeSH descriptor: [Asthma] explode all trees 10827
#2 asthma*:ti 20597
#3 #1 or #2 22788
#4 diagnos*:ti,ab,kw 161907
#5 (sensitivity or specificity):ti,ab,kw 50736
#6 ((pre test or pretest or post test) near probability):ti,ab,kw 714
#7 (predictive value* or PPV or NPV):ti,ab,kw 16303
#8 likelihood ratio*:ti,ab,kw 3216
#9 (ROC or AUC):ti,ab,kw 17350
#10 gold standard:ti,ab,kw 5570
#11 #4 or #5 or #6 or #7 or #8 or #9 or #10 217460
#12 (child* or paediatr* or pediatr* or teen*or adolescen*):ti,ab 97724
#13 FeNO:ti,ab,kw 470
#14 ((Fe or exhal* or fraction*) near/2 (NO or nitric or nitrogen)):ti,ab,kw 1330
#15 ((NO or nitric or nitrogen) near/2 (marker* or biomarker* or breath* or test* or exhal* or expir*)):ti,ab,kw 5861
#16 {or #13-#15} 6160

#17 MeSH descriptor: [Nitric Oxide] explode all trees1919
#18 MeSH descriptor: [Breath Tests] explode all trees 1474
#19 MeSH descriptor: [Biomarkers] explode all trees 18189
#20 MeSH descriptor: [Exhalation] explode all trees 193
#21 #18 or #19 or #20 19675
#22 #21 and #17 402
#23 #22 or #16 6306
#24 #3 and #11 and #12 and #23 85

PICO 6: PEFR

Database: **Ovid Medline** <1980 to 31st August 2019>

1 exp ASTHMA/ (119652)
2 asthma*.ti. (87846)
3 1 or 2 (127353)
4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2318059)
5 sensitiv*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1519434)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (98520)
7 exp "SENSITIVITY AND SPECIFICITY"/ (526795)
8 specificity*.ti,ab. (411901)
9 ("pre test" adj probability).ti,ab. (646)
10 ("pretest" adj probability).ti,ab. (1280)
11 ("post test" adj probability).ti,ab. (498)
12 ("predictive value*" or PPV or NPV).ti,ab. (100073)
13 "likelihood ratio*".ti,ab. (13292)
14 "LIKELIHOOD FUNCTIONS"/ (20539)
15 ("roc curve*" or auc).ti,ab. (72103)
16 "gold standard*".ab. (54050)
17 pefv.ti,ab. (54)
18 ((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 (pef or pefr or pfr)).ti,ab. (1534)
19 ((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 "peak expiratory flow*").ab,ti. (867)
20 ((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 "peak flow*").ab,ti. (793)
21 Peak Expiratory Flow Rate/ (5512)
22 exp Circadian Rhythm/ (67390)
23 21 and 22 (263)
24 17 or 18 or 19 or 20 or 23 (3024)
25 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (2044910)
26 3 and 4 and 24 and 25 (70)
27 limit 26 to yr="1980 -Current" (69)

Database: **Embase** <1980 to 31st August 2019>

1 exp ASTHMA/ (231825)
2 asthma*.ti. (112268)
3 1 or 2 (233892)

4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (2578899)
5 sensitiv*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1787530)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (441335)
7 exp "SENSITIVITY AND SPECIFICITY"/ (295974)
8 specificity*.ti,ab. (508421)
9 ("pre test" adj probability).ti,ab. (1398)
10 ("pretest" adj probability).ti,ab. (1958)
11 ("post test" adj probability).ti,ab. (691)
12 ("predictive value*" or PPV or NPV).ti,ab. (148111)
13 "likelihood ratio*".ti,ab. (17514)
14 ("roc curve*" or auc).ti,ab. (120005)
15 "gold standard*".ab. (87485)
16 diagnostic accuracy/ (226492)
17 diagnostic test accuracy study/ (84410)
18 pefv.ti,ab. (49)
19 ((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 "peak expiratory flow*").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1051)
20 ((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 (pef or pefr or pfr)).ti,ab. (2034)
21 ((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 "peak flow*").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (964)
22 peak expiratory flow/ (11998)
23 circadian rhythm/ (78289)
24 22 and 23 (305)
25 18 or 19 or 20 or 21 or 24 (3796)
26 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (2451224)
27 3 and 4 and 25 and 26 (82)

Database: **Cochrane Library** <1980 to 31st August 2019>

See PICO 3

PICO 7: Allergy testing

Database: **Ovid Medline** <1980 to 31st August 2019>

1 exp ASTHMA/ (119768)
2 asthma*.ti,ab. (143401)
3 1 or 2 (163695)
4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2321466)
5 sensitiv*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1522640)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (98916)
7 exp "SENSITIVITY AND SPECIFICITY"/ (527857)
8 specific*.ti,ab. (2770591)
9 ("pre test" adj probability).ti,ab. (647)
10 ("pretest" adj probability).ti,ab. (1278)
11 ("post test" adj probability).ti,ab. (496)
12 ("predictive value*" or PPV or NPV).ti,ab. (100390)
13 "likelihood ratio*".ti,ab. (13334)
14 "LIKELIHOOD FUNCTIONS"/ (20529)
15 ("roc curve*" or auc).ti,ab. (72529)
16 "gold standard*".ti,ab. (55590)
17 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (4160510)
18 ((dust or housedust) adj mite*).ti,ab. (7031)
19 (dermatophagoides or euroglyphus).ti,ab. (3936)
20 pyroglyphidae/ (1778)
21 (cat or cats or feline*).ti,ab. (139557)
22 cats/ (132144)
23 (dog or dogs or canine*).ti,ab. (244270)
24 dogs/ (315744)
25 pollen*.ti,ab. (26106)
26 pollen/ (16711)
27 exp aspergillus/ (30192)
28 aspergillus.ti,ab. (38762)
29 alternaria/ (2158)
30 alternaria.ti,ab. (4230)
31 cladosporium/ (1227)
32 cladosporium.ti,ab. (2702)
33 ((air* or aero*) adj allergen*).ti,ab. (952)
34 aeroallergen*.ti,ab. (2806)
35 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (601051)
36 exp skin tests/ (61063)
37 "skin prick*".ti,ab. (8162)
38 "skin scratch*".ti,ab. (62)

39 "prick* test*".ti,ab. (9323)
40 "scratch* test*".ti,ab. (695)
41 "skin test*".ti,ab. (19732)
42 36 or 37 or 38 or 39 or 40 or 41 (72889)
43 35 and 42 (8439)
44 *radioallergosorbent test/ (372)
45 (RAST or radioallergosorbent).ti. (681)
46 *immunoglobulin E/ (14536)
47 IgE.ti. (13024)
48 "immunoglobulin E".ti. (1972)
49 44 or 45 or 46 or 47 or 48 (18191)
50 42 or 49 (87721)
51 3 and 4 and 17 and 50 (1994)
52 51 (1994)
53 limit 52 to yr="1980 -Current" (1881)
54 meta-analysis/ (90038)
55 meta-analysis as topic/ (16302)
56 ("meta analy*" or metanaly* or metaanaly*).ti,ab. (131074)
57 ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab. (156011)
58 ("reference list*" or bibliograph* or "hand search*" or "manual search*" or "relevant journals").ab. (37571)
59 ("search strategy" or "search criteria" or "systematic search" or "study selection" or "data extraction").ab. (43667)
60 (search* adj4 literature).ab. (51536)
61 (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. (173965)
62 cochrane.jw. (13772)
63 (("multiple treatment*" or indirect or mixed) adj2 comparison*).ti,ab. (2347)
64 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 (358945)
65 53 and 64 (28)
66 52 and 64 (28)

Database: **Embase** <1980 to 31st August 2019>

1 exp ASTHMA/ (232838)
2 asthma*.ti,ab. (198968)
3 1 or 2 (260616)
4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (2593640)
5 sensitiv*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1798084)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (444442)
7 exp "SENSITIVITY AND SPECIFICITY"/ (299051)
8 specific*.ti,ab. (3353879)
9 ("pre test" adj probability).ti,ab. (1410)

10 ("pretest" adj probability).ti,ab. (1965)
11 ("post test" adj probability).ti,ab. (696)
12 ("predictive value*" or PPV or NPV).ti,ab. (149170)
13 "likelihood ratio*".ti,ab. (17648)
14 ("roc curve*" or auc).ti,ab. (121454)
15 "gold standard*".ti,ab. (90023)
16 ((dust or housedust) adj mite*).ti,ab. (11137)
17 (dermatophagoides or euroglyphus).ti,ab. (5186)
18 pyroglyphidae/ (342)
19 (cat or cats or feline*).ti,ab. (139862)
20 (dog or dogs or canine*).ti,ab. (237528)
21 pollen*.ti,ab. (29930)
22 aspergillus.ti,ab. (48466)
23 alternaria.ti,ab. (5579)
24 cladosporium.ti,ab. (3343)
25 ((air* or aero*) adj allergen*).ti,ab. (1507)
26 aeroallergen*.ti,ab. (4948)
27 "skin prick*".ti,ab. (14875)
28 "skin scratch*".ti,ab. (73)
29 "prick* test*".ti,ab. (16818)
30 "scratch* test*".ti,ab. (909)
31 "skin test*".ti,ab. (24424)
32 *radioallergosorbent test/ (813)
33 (RAST or radioallergosorbent).ti. (650)
34 *immunoglobulin E/ (21201)
35 IgE.ti. (16353)
36 "immunoglobulin E".ti. (2111)
37 diagnostic test accuracy study/ (86183)
38 diagnostic accuracy/ (227719)
39 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 37 or 38 (5006405)
40 exp *dermatophagoides/ (2671)
41 *cat/ (8288)
42 *dog/ (20654)
43 *pollen/ (6681)
44 exp *aspergillus/ (20004)
45 exp *alternaria/ (1389)
46 exp *cladosporium/ (578)
47 exp *skin test/ (15419)
48 *grass pollen/ (1371)
49 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 48 (464066)
50 27 or 28 or 29 or 30 or 31 or 47 (49879)
51 49 and 50 (9439)
52 32 or 33 or 34 or 35 or 36 (26370)
53 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 37 or 38 (5006405)
54 51 or 52 (34500)
55 3 and 4 and 53 and 54 (2122)
56 systematic review/ (172810)
57 meta-analysis/ (146739)
58 ("meta analy*" or metanaly* or metaanaly*).ti,ab. (172307)
59 ((systematic or evidence) adj2 (review* or overview*)).ti,ab. (184344)

60 ("reference list*" or bibliograph* or "hand search*" or "manual search*" or "relevant journals").ab. (45709)
61 ("search strategy" or "search criteria" or "systematic search" or "study selection" or "data extraction").ab. (51956)
62 (search* adj4 literature).ab. (64813)
63 (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. (215101)
64 cochrane.jw. (22283)
65 (("multiple treatment*" or indirect or mixed) adj2 comparison*).ti,ab. (4106)
66 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 (477070)
67 55 and 66 (19)

Database: **Cochrane Library** <1980 to 31st August 2019>

#1 MeSH descriptor: [Asthma] explode all trees 10827
#2 asthma*:ti 20597
#3 #1 or #2 22788
#4 diagnos*:ti,ab,kw 161910
#5 (sensitivity or specificity):ti,ab,kw 50739
#6 ((pre test or pretest or post test) near probability):ti,ab,kw 714
#7 (predictive value* or PPV or NPV):ti,ab,kw 16303
#8 likelihood ratio*:ti,ab,kw 3217
#9 (ROC or AUC):ti,ab,kw 17350
#10 gold standard:ti,ab,kw 5572
#11 #4 or #5 or #6 or #7 or #8 or #9 or #10 217466
#12 (child* or paediatr* or pediatr* or teen*or adolescen*):ti,ab 97729
#13 (skin prick* or skin scratch* or prick* test* or scratch* test* or skin test*):ti,ab,kw 12873
#14 ((dust or housedust) near/1 mite*):ti,ab,kw 1191
#15 (dermatophagoides or euroglyphus or cat or cats or feline* or dog or dogs or canine* or pollen or aspergillus or alternaria or cladosporium or pyroglyphidae):ti,ab,kw 7553
#16 ((air* or aero*) near/1 allergen*):ti,ab 178
#17 aeroallergen*:ti,ab 211
#18 #14 or #15 or #16 or #17 8292
#19 #13 and #18 1126
#20 (immunoglobulin E or IgE or RAST or radioallergosorbent):ti,kw 2732
#21 #19 or #20 3414
#22 #3 and #11 and #12 and #20 with Cochrane Library publication date between Jan 1980 and Aug 2018 82

PICO 8: Direct bronchial challenge testing

Database: **Ovid Medline** <1980 to 31st August 2019>

1 exp ASTHMA/ (119545)
2 asthma*.ti. (87740)
3 1 or 2 (127206)
4 exp spirometry/ (20563)
5 spiromet*.ti. (3525)
6 exp vital capacity/ (24150)
7 exp forced expiratory volume/ (23590)
8 (fev1 or fvc or "fev 1").ti,ab. (30270)
9 ("flow volume" adj2 loop*).ti,ab. (669)
10 ("flow volume" adj2 curve*).ti,ab. (1477)
11 ("flow volume" adj2 graph*).ti,ab. (0)
12 ("forced expiratory volume*" adj6 "1").ti,ab. (10382)
13 ("forced expiratory volume*" adj6 one).ti,ab. (4832)
14 (force* adj2 "vital capacit*").ti,ab. (9831)
15 (time* adj2 "vital capacit*").ti,ab. (81)
16 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (73568)
17 3 and 16 (16755)
18 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2315128)
19 sensitiv*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1517487)
20 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (98291)
21 di.fs. (2354257)
22 exp "SENSITIVITY AND SPECIFICITY"/ (526009)
23 specificity*.ti,ab. (411353)
24 ("pre test" adj probability).ti,ab. (643)
25 ("pretest" adj probability).ti,ab. (1280)
26 ("post test" adj probability).ti,ab. (496)
27 ("predictive value*" or PPV or NPV).ti,ab. (99919)
28 "likelihood ratio*".ti,ab. (13259)
29 "LIKELIHOOD FUNCTIONS"/ (20514)
30 ("roc curve*" or auc).ti,ab. (71914)
31 "gold standard*".ab. (53921)
32 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 (4065844)
33 17 and 18 and 32 (1639)
34 (Fraction* adj2 exhaled).ti,ab. (1316)
35 ((fe or exhal* or fraction*) adj2 (nitric or no or nitrogen)).ti,ab. (7664)
36 exp "BREATH TESTS"/ (13784)
37 exp BIOMARKERS/ (651655)
38 exp "NITRIC OXIDE"/ (83071)
39 exp EXHALATION/ (3424)
40 Feno.ti,ab. (1591)

41 36 or 37 or 39 (665695)
42 38 and 41 (5196)
43 34 or 35 or 40 (7949)
44 42 or 43 (10938)
45 exp "BRONCHODILATOR AGENTS"/ (252662)
46 (bronchodilator* adj3 (test* or revers* or respons* or respond*)).ti,ab. (2040)
47 (test* or revers* or respons* or respond*).ti,ab. (5859679)
48 45 and 47 (94073)
49 ("bronchial dilat*" adj3 (test* or revers* or respons* or respond*)).ti,ab. (23)
50 (broncholytic* adj3 (test* or revers* or respons* or respond*)).ti,ab. (12)
51 (bdr or bdt or bronchoreversibility).ti,ab. (818)
52 46 or 48 or 49 or 50 or 51 (95557)
53 exp "METHACHOLINE CHLORIDE"/ (5217)
54 Methacholine*.ti,ab. (8839)
55 exp HISTAMINE/ (36663)
56 exp MANNITOL/ (12120)
57 histamine*.ti,ab. (56443)
58 mannitol*.ti,ab. (16966)
59 53 or 54 or 55 or 57 (74973)
60 (inhalation or provocation or provoke* or challenge*).ti,ab. (627853)
61 exp "BRONCHIAL PROVOCATION TESTS"/ (8487)
62 exp "BRONCHIAL HYPERREACTIVITY"/ (7192)
63 (hyperresponsiv* or hyperreactiv*).ti,ab. (16944)
64 60 or 61 or 62 or 63 (642142)
65 exp EXERCISE/ (166274)
66 exp SPORTS/ (163003)
67 (exercise* or sport*).ti,ab. (307057)
68 (physical* adj (train* or exert* or activit*)).ab,ti. (97390)
69 65 or 66 or 67 or 68 (490469)
70 Medical History Taking/ (18364)
71 (histories or history).ti,ab. (605547)
72 exp "Surveys and Questionnaires"/ (902347)
73 question*.ti,ab. (818264)
74 (symptom or symptoms).ti,ab. (860127)
75 70 or 71 or 72 or 73 or 74 (2625541)
76 69 and 75 (113322)
77 pefv.ti,ab. (54)
78 ((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 (pef or pefr or pfr)).ti,ab. (1531)
79 ((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 "peak expiratory flow*").ab,ti. (866)
80 ((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 "peak flow*").ab,ti. (793)
81 Peak Expiratory Flow Rate/ (5510)
82 exp Circadian Rhythm/ (67333)
83 81 and 82 (263)
84 77 or 78 or 79 or 80 or 83 (3020)
85 (Carbachol* or Carbamann or Carbamoylcholine or Carbamylcholine or Carbastat or Carboptic or Doryl or Jestryl or Miostat).ti,ab. (15804)
86 exp CARBACHOL/ (13601)
87 59 or 85 or 86 (92411)

88 64 and 87 (14633)
89 3 and 18 and 32 (9118)
90 88 and 89 (628)
91 16 or 44 or 52 or 76 or 84 (282353)
92 90 and 91 (389)
93 limit 92 to yr="1980 -Current" (380)
94 limit 90 to yr="1980 -Current" (611)

Database: **Embase** <1980 to 31st August 2019>

1 exp ASTHMA/ (231366)
2 asthma*.ti. (112082)
3 1 or 2 (233429)
4 spiromet*.ti. (4554)
5 vital capacity/ (9011)
6 forced expiratory volume/ (55769)
7 (fev1 or fvc or "fev 1").ti,ab. (55447)
8 lung flow volume curve/ (1471)
9 ("flow volume" adj2 loop*).ti,ab. (901)
10 ("flow volume" adj2 curve*).ti,ab. (1609)
11 ("flow volume" adj2 graph*).ti,ab. (3)
12 ("forced expiratory volume*" adj6 "1").ti,ab. (12121)
13 ("forced expiratory volume*" adj6 one).ti,ab. (6045)
14 (force* adj2 "vital capacit*").ti,ab. (13266)
15 (time* adj2 "vital capacit*").ti,ab. (77)
16 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (2571478)
17 sensitiv*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1782336)
18 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (439750)
19 exp "SENSITIVITY AND SPECIFICITY"/ (294533)
20 specificity*.ti,ab. (506844)
21 ("pre test" adj probability).ti,ab. (1381)
22 ("pretest" adj probability).ti,ab. (1943)
23 ("post test" adj probability).ti,ab. (687)
24 ("predictive value*" or PPV or NPV).ti,ab. (147522)
25 "likelihood ratio*".ti,ab. (17425)
26 ("roc curve*" or auc).ti,ab. (119369)
27 "gold standard*".ab. (87004)
28 ((fe or exhal* or fraction*) adj2 (nitric or no or nitrogen)).ti,ab. (10391)
29 Feno.ti,ab. (3673)
30 (bronchodilator* adj3 (test* or revers* or respons* or respond*)).ti,ab. (3221)
31 (test* or revers* or respons* or respond*).ti,ab. (7166585)
32 ("bronchial dilat*" adj3 (test* or revers* or respons* or respond*)).ti,ab. (31)
33 (broncholytic* adj3 (test* or revers* or respons* or respond*)).ti,ab. (16)

34 (bdr or bdt or bronchoreversibility).ti,ab. (1106)
35 Methacholine*.ti,ab. (11337)
36 histamine*.ti,ab. (60082)
37 mannitol*.ti,ab. (19239)
38 (inhalation or provocation or provoke* or challenge*).ti,ab. (763023)
39 (hyperresponsiv* or hyperreactiv*).ti,ab. (22029)
40 diagnostic accuracy/ (225901)
41 diagnostic test accuracy study/ (83468)
42 *nitric oxide/ (56316)
43 *breath analysis/ (4587)
44 *expired air/ (1113)
45 *biological marker/ (60994)
46 *exhalation/ (740)
47 43 or 44 or 45 or 46 (67026)
48 42 and 47 (716)
49 exp *bronchodilating agent/ (72778)
50 31 and 49 (21961)
51 30 or 32 or 33 or 34 or 50 (24847)
52 HISTAMINE/ (52510)
53 methacholine/ (12944)
54 MANNITOL/ (28612)
55 35 or 36 or 52 or 53 (89958)
56 inhalation test/ (3064)
57 provocation test/ (28476)
58 bronchus hyperreactivity/ (12026)
59 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (93702)
60 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 40 or 41 (2444008)
61 3 and 16 and 59 and 60 (920)
62 28 or 29 (11105)
63 48 or 62 (11222)
64 38 or 39 or 56 or 57 or 58 (790641)
65 (Carbachol* or Carbamann or Carbamoylcholine or Carbamylcholine or Carbastat or Carboptic or Doryl or Jestryl or Miostat).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (23495)
66 exp carbachol/ (20832)
67 55 or 65 or 66 (110696)
68 64 and 67 (19500)
69 1 and 16 and 60 and 68 (447)

Database: **Cochrane Library** <1980 to 31st August 2019>

#1 MeSH descriptor: [Asthma] explode all trees 11462
#2 asthma*:ti 21161
#3 #1 or #2 23432
#4 diagnos*:ti,ab,kw 109829
#5 (sensitivity or specificity):ti,ab,kw 53580
#6 ((pre test or pretest or post test) near probability):ti,ab,kw 212
#7 (predictive value* or PPV or NPV):ti,ab,kw 17300
#8 likelihood ratio*:ti,ab,kw 3352

#9 (ROC or AUC):ti,ab,kw 17842
#10 gold standard:ti,ab,kw 5569
#11 #4 or #5 or #6 or #7 or #8 or #9 or #10 175528
#12 (child* or paediatr* or pediatr* or teen*or adolescen*):ti,ab 99696
#13 (Carbachol* or Carbamann or Carbamoylcholine or Carbamylcholine or Carbastat or Carboptic or Doryl or Jestryl or Miostat):ti,ab 133
#14 MeSH descriptor: [Carbachol] explode all trees 68
#15 MeSH descriptor: [Histamine] explode all trees 1139
#16 MeSH descriptor: [Methacholine Chloride] explode all trees 731
#17 (histamine or methacholine):ti,ab 5024
#18 #13 or #14 or #15 or #16 or #17 5336
#19 MeSH descriptor: [Bronchial Provocation Tests] explode all trees 1343
#20 MeSH descriptor: [Bronchial Hyperreactivity] explode all trees 587
#21 (inhalation or provocation or provoke* or challenge*):ti,ab 30628
#22 (hyperresponsiv* or hyperreactiv*):ti,ab 1658
#23 #19 or #20 or #21 or #22 31813
#24 #18 and #23 Publication Year from 1980 to 20182476
#25 #3 and #11 and #12 and #24 Publication Year from 1980 to 2018 59

PICO 9: Indirect bronchial challenge testing

Database: **Ovid Medline** <1980 to 31st August 2019>

1 exp ASTHMA/ (119609)
2 asthma*.ti. (87813)
3 1 or 2 (127305)
4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2316992)
5 sensitiv*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1518622)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (98441)
7 exp "SENSITIVITY AND SPECIFICITY"/ (526338)
8 specificity*.ti,ab. (411691)
9 ("pre test" adj probability).ti,ab. (645)
10 ("pretest" adj probability).ti,ab. (1282)
11 ("post test" adj probability).ti,ab. (498)
12 ("predictive value*" or PPV or NPV).ti,ab. (100023)
13 "likelihood ratio*".ti,ab. (13279)
14 ("roc curve*" or auc).ti,ab. (72055)
15 "gold standard*".ab. (53989)
16 MANNITOL/ (12069)
17 mannitol*.ti,ab. (16972)
18 (inhalation or provocation or provoke* or challenge*).ti,ab. (628681)
19 (hyperresponsiv* or hyperreactiv*).ti,ab. (16952)
20 (exercise* or sport*).ti,ab. (307391)
21 (physical* adj (train* or exert* or activit*)).ab,ti. (97536)
22 (histories or history).ti,ab. (606120)
23 question*.ti,ab. (819240)
24 (symptom or symptoms).ti,ab. (860911)
25 "cold air".mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1215)
26 "Eucapnic Voluntary Hyperpnea".mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (61)
27 evh.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (209)
28 (voluntary adj2 hyperventilat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (415)

29 amp.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (133147)
30 "adenosine monophosphate".mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (24248)
31 "eucapnic hyperventilation".mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (51)
32 "hypertonic solution".mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (673)
33 "hypertonic saline".mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (5659)
34 "adenosine phosphate".mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (150)
35 hypervent*.ti. (2637)
36 "hypertonic sodium chloride".mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (299)
37 Likelihood Functions/ (20524)
38 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 37 (2043713)
39 16 or 17 (21963)
40 Bronchial Hyperreactivity/ (7193)
41 Bronchial Provocation Tests/ (8488)
42 18 or 19 or 40 or 41 (642973)
43 exp EXERCISE/ (166458)
44 exp Sports/ (163135)
45 20 or 21 or 43 or 44 (491005)
46 Medical History Taking/ (18369)
47 exp "Surveys and Questionnaires"/ (903193)
48 22 or 23 or 24 or 46 or 47 (2628167)
49 45 and 48 (113439)
50 25 or 26 or 27 (1449)
51 exp HYPERVENTILATION/ (6385)
52 28 or 31 or 35 or 51 (6880)
53 exp Adenosine Monophosphate/ (9620)
54 29 or 30 or 34 or 53 (143750)
55 exp Saline Solution, Hypertonic/ (5380)
56 32 or 33 or 36 or 55 (8981)
57 39 or 49 or 50 or 52 or 54 or 56 (294783)
58 2 and 4 and 38 and 42 and 57 (94)
59 limit 58 to yr="1980 -Current" (93)

Database: **Embase** <1980 to 31st August 2019>

1 exp ASTHMA/ (231579)
2 asthma*.ti. (112170)

3 1 or 2 (233646)
4 (child* or paediatr* or pediatr* or teen*or adolescen*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (2575279)
5 sensitiv*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1785115)
6 (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effective*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (440572)
7 exp "SENSITIVITY AND SPECIFICITY"/ (295269)
8 specificity*.ti,ab. (507674)
9 ("pre test" adj probability).ti,ab. (1392)
10 ("pretest" adj probability).ti,ab. (1954)
11 ("post test" adj probability).ti,ab. (689)
12 ("predictive value*" or PPV or NPV).ti,ab. (147831)
13 "likelihood ratio*".ti,ab. (17466)
14 ("roc curve*" or auc).ti,ab. (119726)
15 "gold standard*".ab. (87285)
16 MANNITOL/ (28646)
17 mannitol*.ti,ab. (19262)
18 (inhalation or provocation or provoke* or challenge*).ti,ab. (764925)
19 (hyperresponsiv* or hyperreactiv*).ti,ab. (22037)
20 (exercise* or sport*).ti,ab. (391510)
21 (physical* adj (train* or exert* or activit*)).ab,ti. (129525)
22 (histories or history).ti,ab. (866301)
23 question*.ti,ab. (1101741)
24 (symptom or symptoms).ti,ab. (1218852)
25 "cold air".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1746)
26 "Eucapnic Voluntary Hyperpnea".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (91)
27 evh.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (343)
28 (voluntary adj2 hyperventilat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (479)
29 amp.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (158695)
30 "adenosine monophosphate".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (13351)
31 "eucapnic hyperventilation".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (61)

32 "hypertonic solution".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (5450)
33 "hypertonic saline".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (7127)
34 diagnostic accuracy/ (226204)
35 diagnostic test accuracy study/ (83969)
36 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 34 or 35 (2447935)
37 exp *exercise/ (123948)
38 exp *sport/ (61889)
39 exp *anamnesis/ (7808)
40 exp *questionnaire/ (30460)
41 exp *breathing disorder/ (58590)
42 exp *coughing/ (16649)
43 20 or 21 or 37 or 38 (537254)
44 22 or 23 or 24 or 39 or 40 or 41 or 42 (2888636)
45 43 and 44 (124812)
46 exp cold air/ (889)
47 25 or 26 or 27 or 46 (2121)
48 exp adenosine phosphate/ (17761)
49 "adenosine phosphate".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (18244)
50 inhalation test/ (3064)
51 provocation test/ (28491)
52 bronchus hyperreactivity/ (12029)
53 18 or 19 or 50 or 51 or 52 (792554)
54 29 or 30 or 48 or 49 (169372)
55 exp hyperventilation/ (12888)
56 hypervent*.ti. (2609)
57 28 or 31 or 55 or 56 (13212)
58 16 or 17 (34471)
59 "hypertonic sodium chloride".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (292)
60 32 or 33 or 59 (11934)
61 45 or 47 or 57 or 58 or 60 (183152)
62 3 and 4 and 36 and 53 and 61 (193)

Database: **Cochrane Library** <1980 to 31st August 2019>

#1 MeSH descriptor: [Asthma] explode all trees
#2 asthma*:ti
#3 #1 or #2
#4 diagnos*:ti,ab,kw
#5 (sensitivity or specificity):ti,ab,kw
#6 ((pre test or pretest or post test) near probability):ti,ab,kw
#7 (predictive value* or PPV or NPV):ti,ab,kw
#8 likelihood ratio*:ti,ab,kw

#9 (ROC or AUC):ti,ab,kw
#10 gold standard:ti,ab,kw
#11 #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 (child* or paediatr* or pediatr* or teen*or adolescen*):ti,ab
#13 MeSH descriptor: [Mannitol] explode all trees
#14 mannitol:ti,ab
#15 (exercise* or sport*):ti,ab,kw
#16 (physical* near/1 (train* or exert* or activit*)):ti,ab,kw
#17 #15 or #16
#18 (histories or history or question*):ti,ab,kw
#19 (symptom or symptoms):ti,ab,kw
#20 #18 or #19
#21 #17 and #20
#22 #14 or #13
#23 MeSH descriptor: [Bronchial Provocation Tests] explode all trees
#24 MeSH descriptor: [Bronchial Hyperreactivity] explode all trees
#25 (inhalation or provocation or provoke* or challenge*):ti,ab
#26 (hyperresponsiv* or hyperreactiv*):ti,ab
#27 {or #23-#26}
#28 "cold air":ti,ab
#29 "Eucapnic Voluntary Hyperpnea" ;ti,ab
#30 evh:ti,ab
#31 voluntary near/2 hyperventilat*:ti,ab
#32 amp:ti,ab
#33 "adenosine monophosphate":ti,ab
#34 "eucapnic hyperventilation":ti,ab
#35 "hypertonic solution":ti,ab
#36 "hypertonic saline":ti,ab
#37 "adenosine phosphate":ti,ab
#38 hypervent*:ti
#39 "hypertonic sodium chloride":ti,ab
#40 MeSH descriptor: [Hyperventilation] explode all trees
#41 MeSH descriptor: [Adenosine Monophosphate] explode all trees
#42 MeSH descriptor: [Saline Solution, Hypertonic] explode all trees
#43 {or #28-#42}
#44 #22 or #21 or #43
#45 #3 and #11 and #12 and #27 and #44

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Supplementary figure 1A-I: PRISMA flowcharts of the outcomes of the literature searches for each PICO question.

1A) PICO 1: In children aged 5-16 years under investigation for asthma, should the presence of the symptoms wheeze, cough and breathing difficulty be used to diagnose asthma?

1B) PICO 2: In children aged 5-16 years under investigation for asthma, should an improvement in symptoms following a trial of preventer medication be used to diagnose asthma?

1C) PICO 3: In children aged 5-16 years under investigation for asthma, should spirometry testing be used to diagnose asthma?

1D) PICO 4: In children aged 5-16 years under investigation for asthma, should bronchodilator reversibility (BDR) testing be used to diagnose asthma?

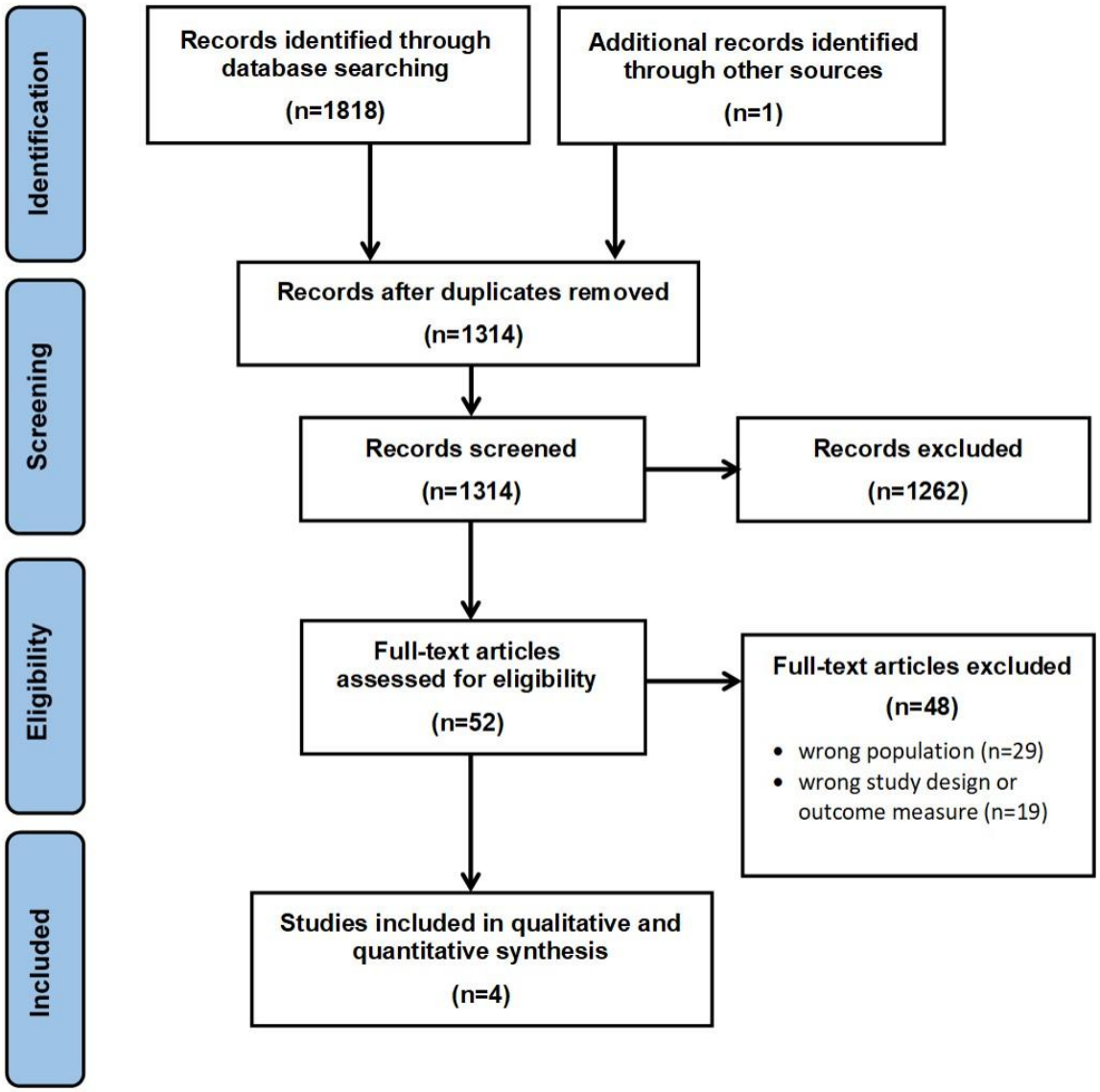
1E) PICO 5: In children aged 5-16 years under investigation for asthma, should FeNO testing be used to diagnose asthma?

1F) PICO 6: In children aged 5-16 years under investigation for asthma, should peak expiratory flow rate (PEFR) variability be used to diagnose asthma?

1G) PICO 7: In children aged 5-16 years under investigation for asthma, should allergy testing be used to diagnose asthma?

1H) PICO 8: In children aged 5-16 years under investigation for asthma, should direct bronchial challenge testing including methacholine and histamine be used to diagnose asthma?

1I) PICO 9: In children aged 5-16 years under investigation for asthma, should indirect bronchial challenge testing including exercise and mannitol be used to diagnose asthma?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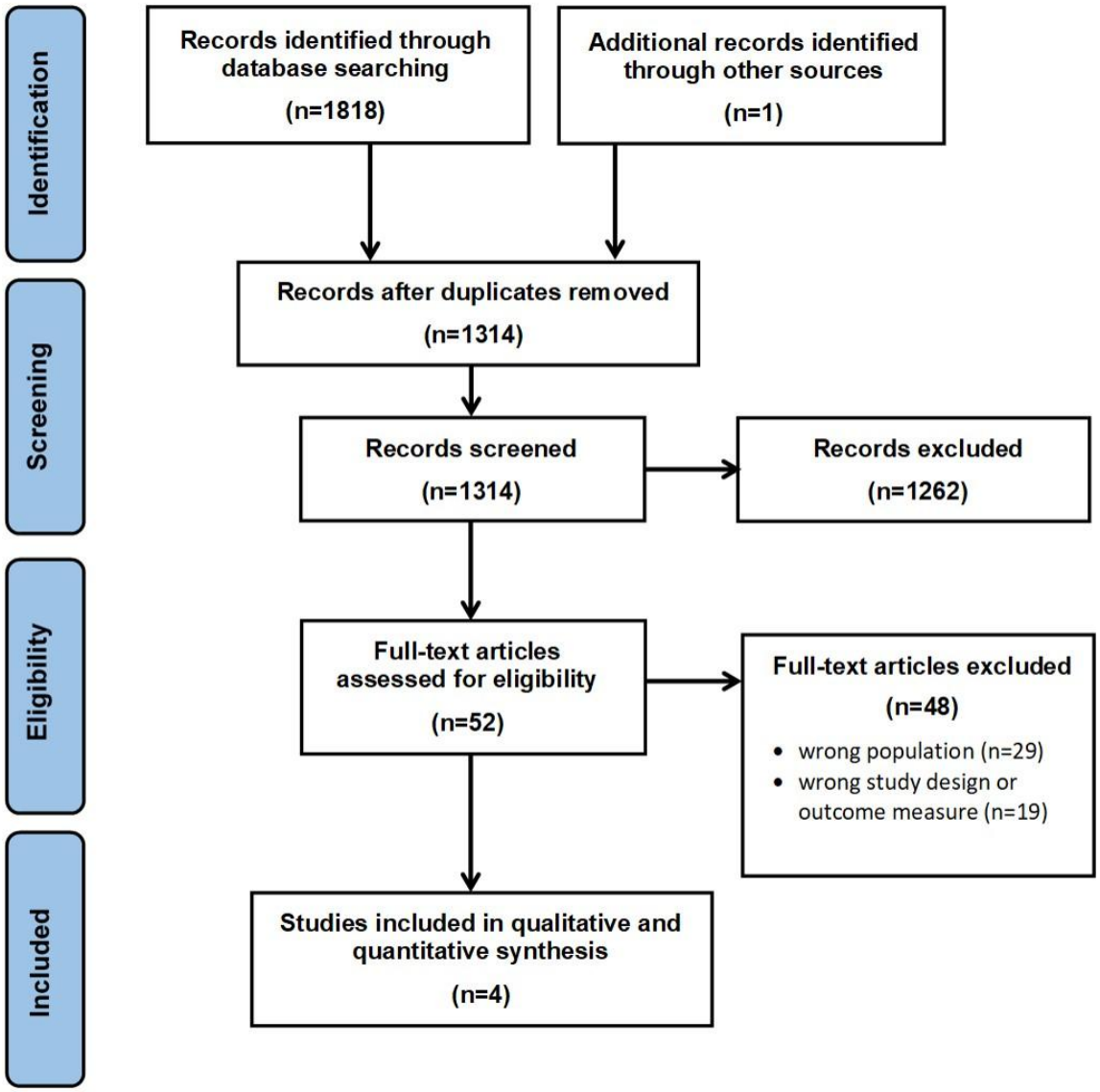
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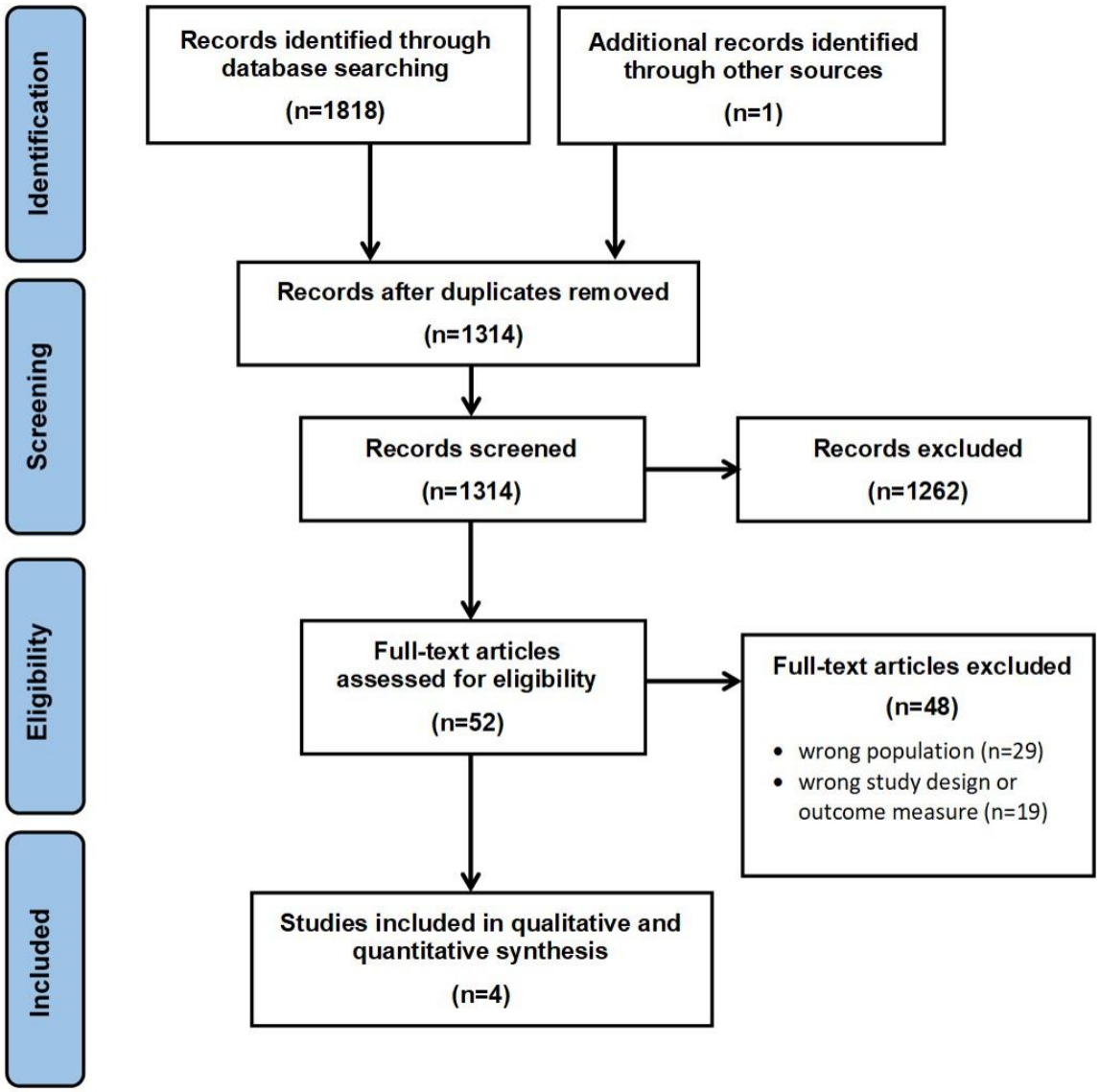
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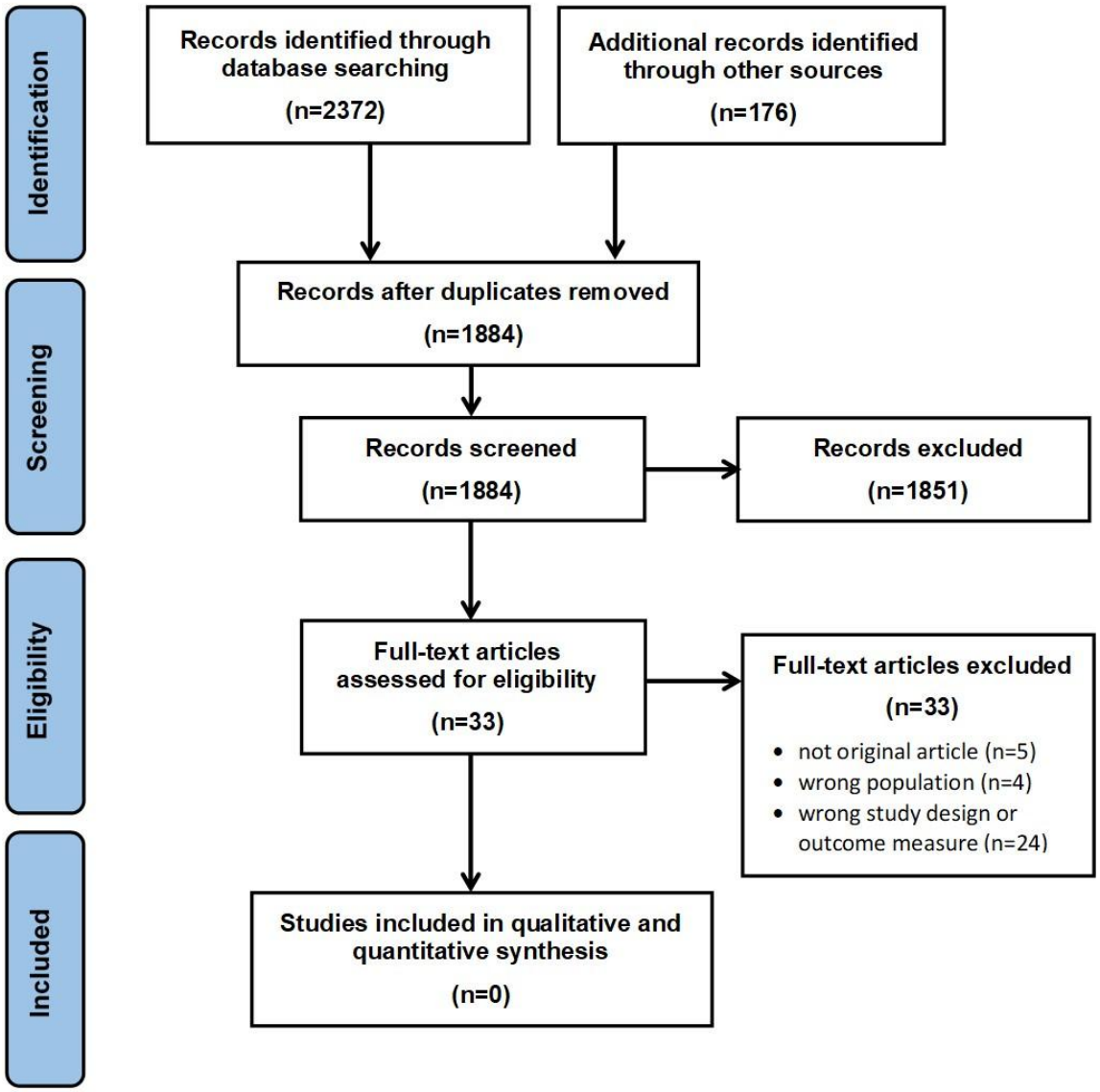
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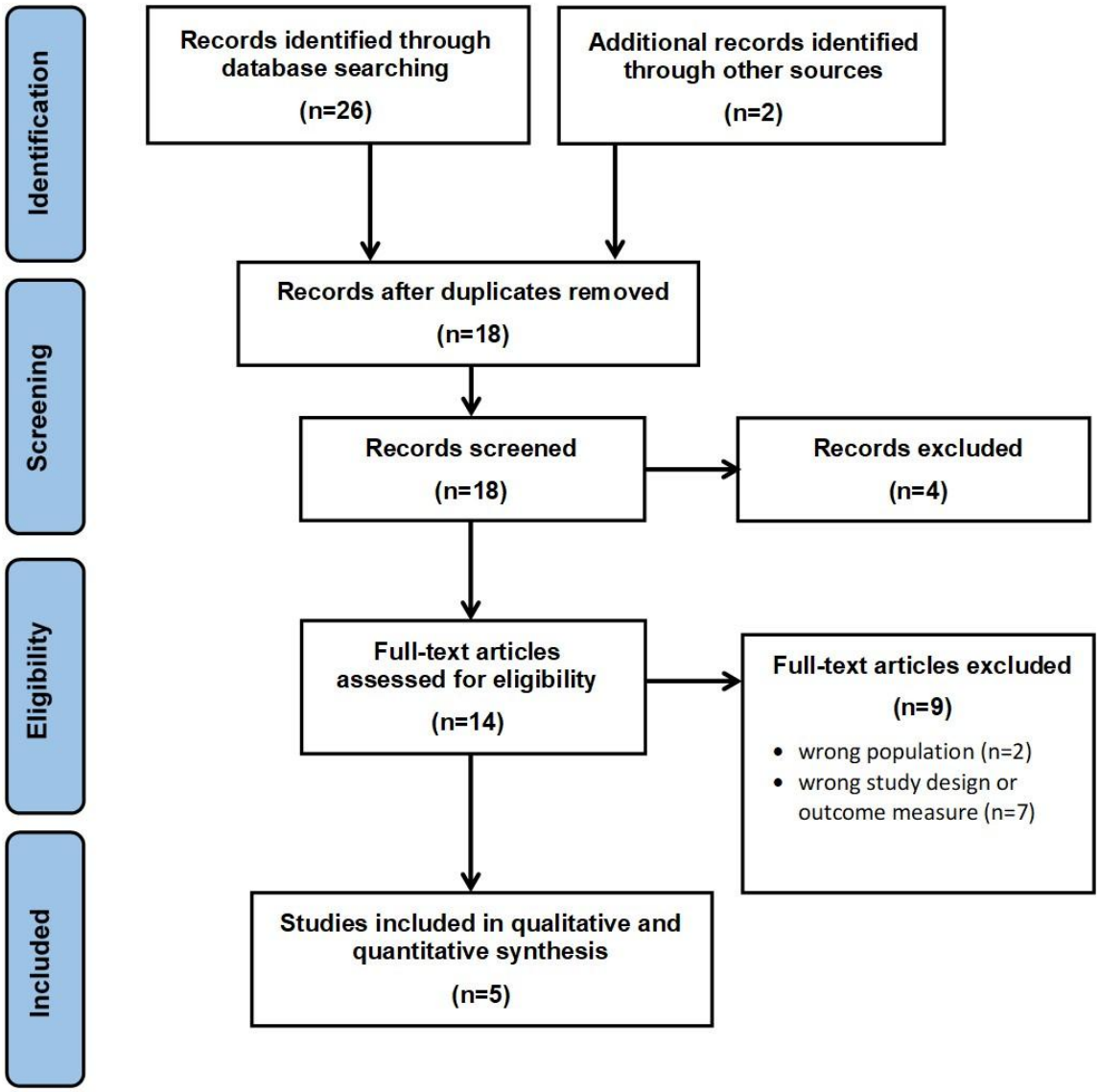
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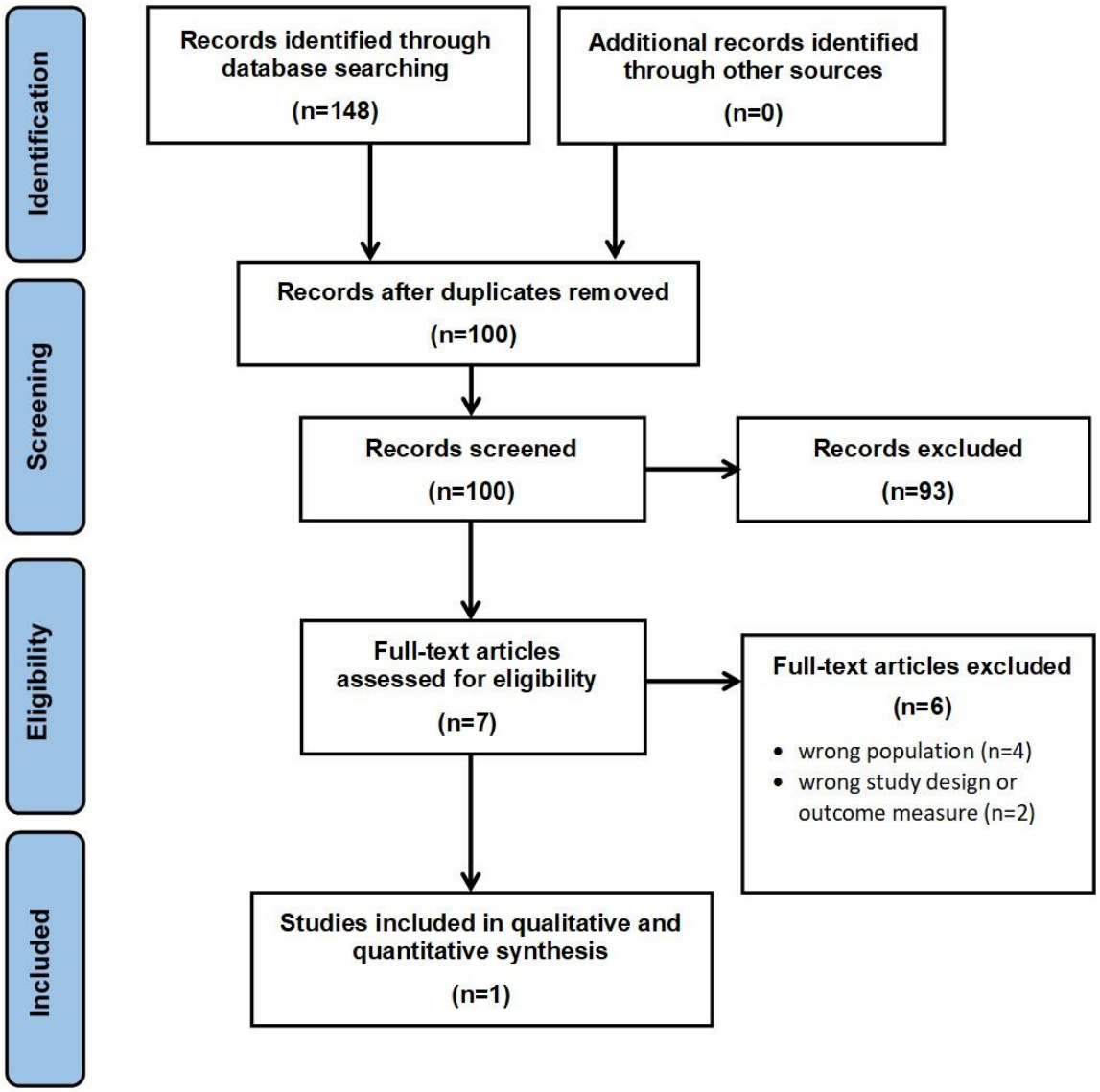
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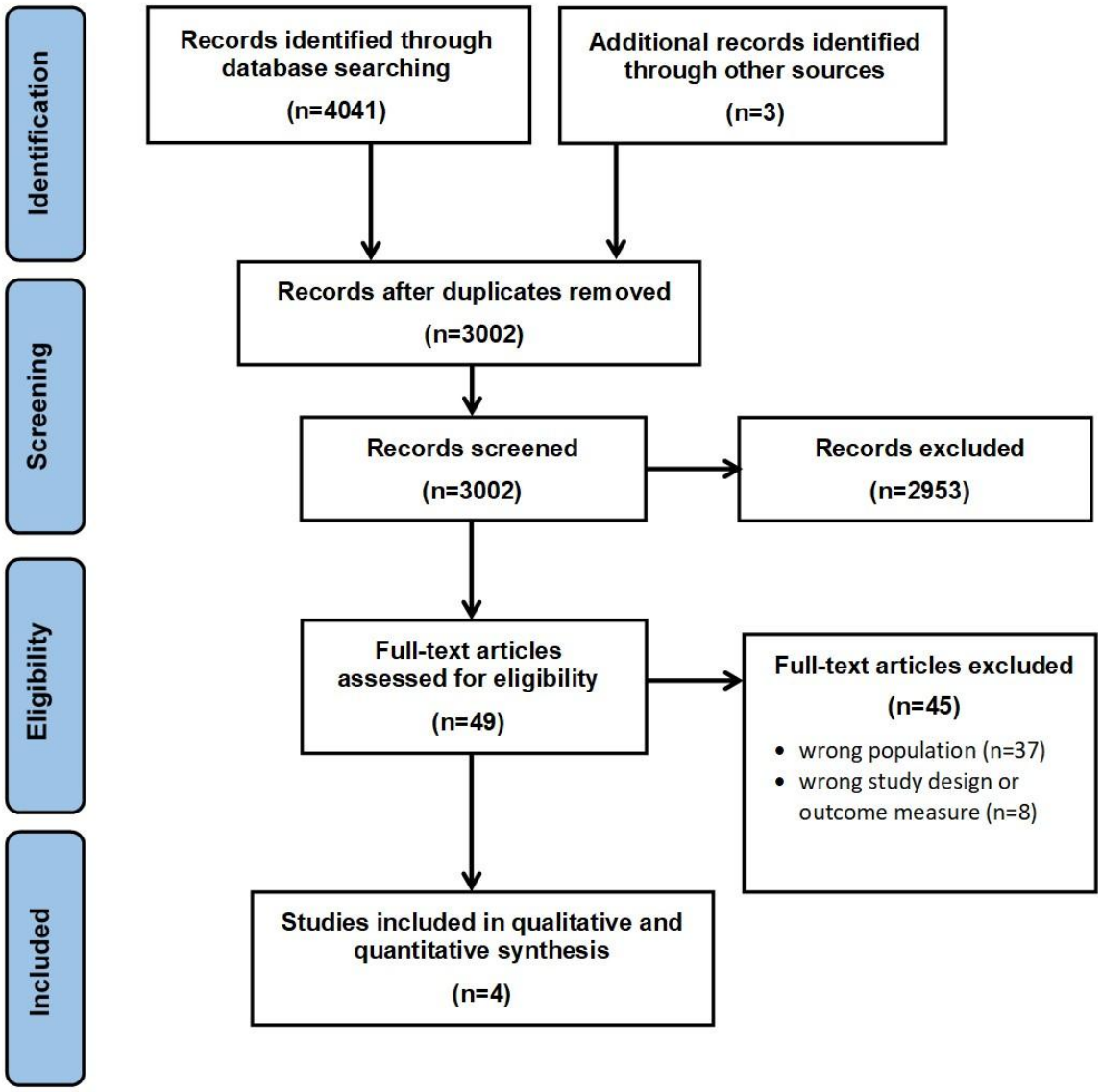
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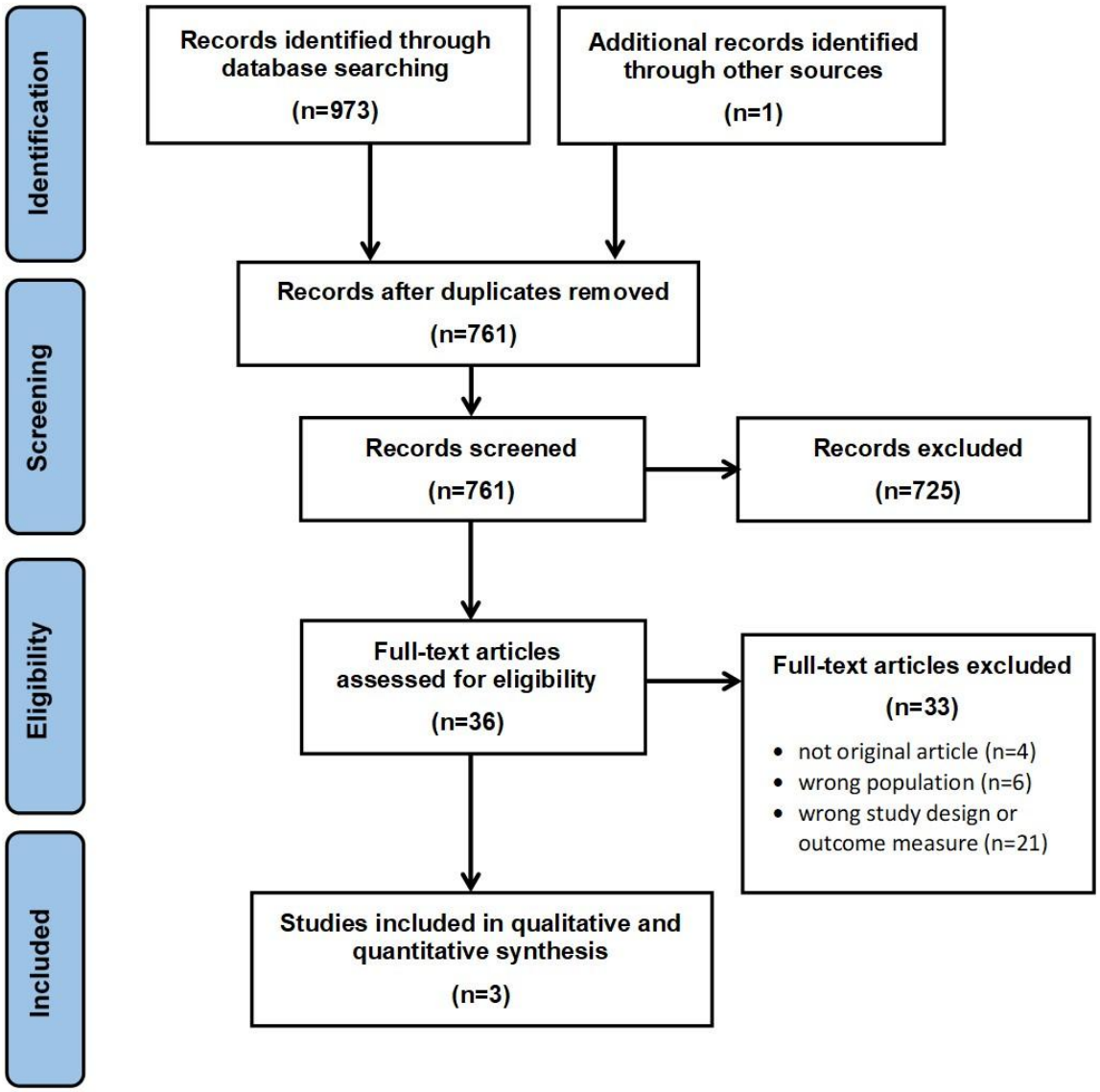
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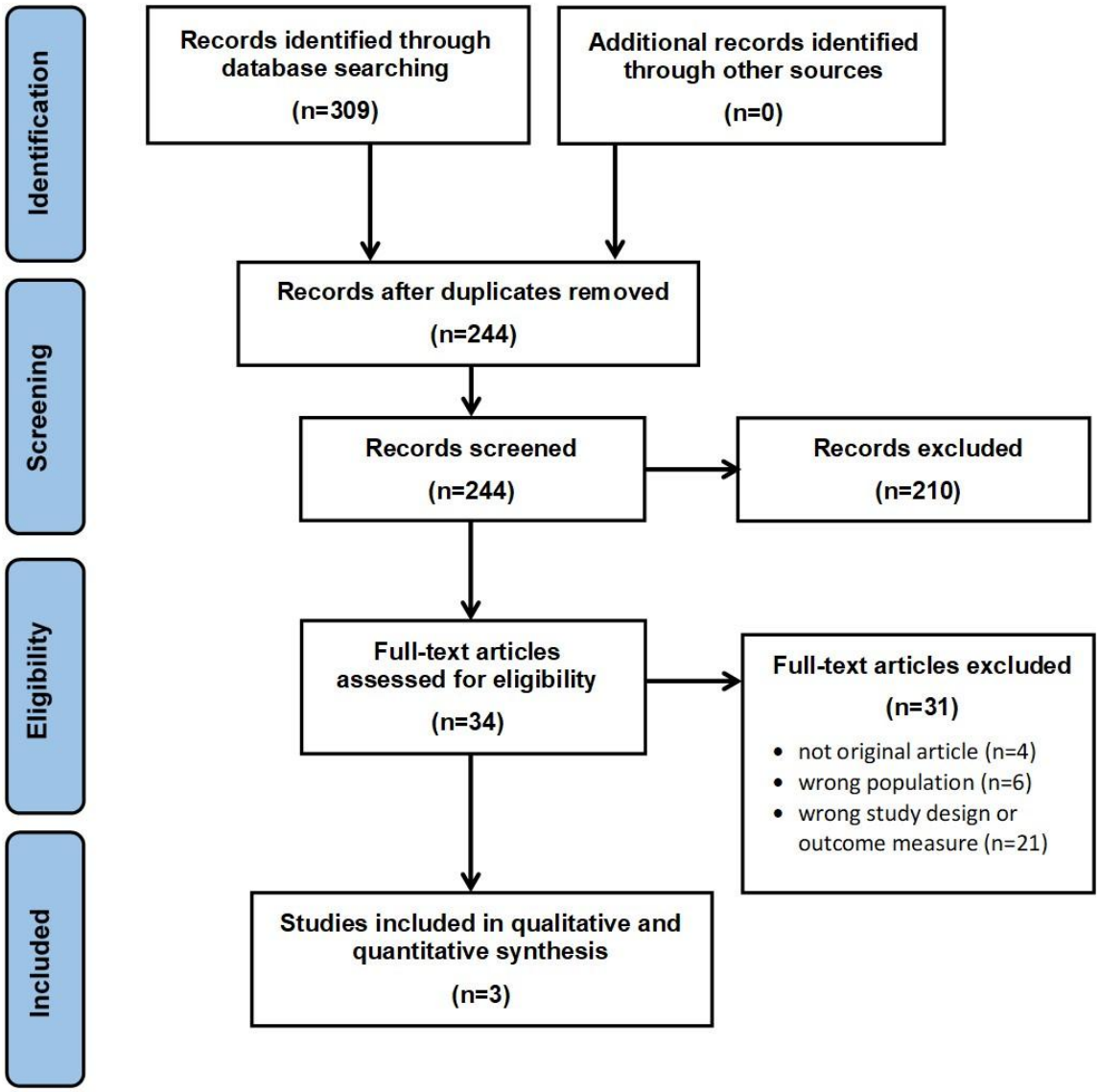
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