

Title:

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

Supplementary material

Authors:

Erol A Gaillard^{1,2}

Claudia E Kuehni^{3,4}

Steve Turner⁵,

Myrofora Goutaki^{3,4},

Karl A Holden¹,

Carmen C M de Jong³

Christiane Lex⁶,

David K H Lo^{1,2}

Jane S Lucas^{7,8}

Fabio Midulla⁹

Rebeca Mozun³

Giorgio Piacentini¹⁰

David Rigau¹¹

Bart Rottier^{12,,13}

Mike Thomas¹⁴

Thomy Tonia³

Jakob Usemann^{15,18}

Ozge Yilmaz¹⁶

Angela Zacharasiewicz¹⁷

Alexander Moeller¹⁸

Affiliations:

¹ University of Leicester, Department of Respiratory Sciences. Leicester NIHR Biomedical Research Centre (Respiratory theme)

² Department of Paediatric Respiratory Medicine. Leicester Children's Hospital, University Hospitals Leicester, Leicester, LE2 7LX, UK.

³ Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

- ⁴ Paediatric Respiratory Medicine, Children's University Children's Hospital, University of Bern, Switzerland
- ⁵ Child Health, University of Aberdeen, Aberdeen, UK
- ⁶ Department of Paediatric Cardiology, Intensive Care Medicine and Neonatology with Paediatric Pulmonology, University Medical Center Goettingen, Goettingen, Germany
- ⁷ Primary Ciliary Dyskinesia Centre, National Institute for Health Research, Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK
- ⁸ University of Southampton Faculty of Medicine, School of Clinical and Experimental Medicine, Southampton, UK
- ⁹ Maternal-Science Department, Sapienza University of Rome, Italy
- ¹⁰ University of Verona, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Italy
- ¹¹ Iberoamerican Cochrane Centre, Barcelona, Spain
- ¹² Department of Paediatric Pulmonology and Paediatric Allergology, University Medical Centre Groningen, Beatrix Children's Hospital, University of Groningen, Groningen, the Netherlands
- ¹³ University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands, Groningen Research Institute for Asthma and COPD, (GRIAC), Groningen, the Netherlands
- ¹⁴ Primary Care, Population Sciences and Medical Education (PPM), Faculty of Medicine, University of Southampton, UK
- ¹⁵ University Children's Hospital Basel (UKBB), Basel, Switzerland
- ¹⁶ Department of Pediatric Allergy and Pulmonology, Celal Bayar University, Manisa, Turkey
- ¹⁷ Department of Pediatrics and Adolescent Medicine, Wilhelminenspital, Teaching Hospital of the University of Vienna, Austria
- ¹⁸ Division of Respiratory Medicine, University Children's Hospital Zuerich and Childhood Research Center, Zuerich, Switzerland

Methods

Task Force and Work Group Composition

The membership and roles of the Task Force (TF) panel are summarised in Supplementary Table S1. 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 Kuehni 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 PICO questions 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 S1: 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 $\geq 75\%$ of participants agreed with a particular 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 S1). 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 considered 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 S1A 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 S1A) and four studies were included in the quantitative and qualitative analysis (supplementary table S2) (11-14). Excluded studies after full-text review are shown in supplementary table S29, the GRADE table for included studies in supplementary table S3 and S4 and the evidence to decision table for PICO 1 in supplementary table S5.

Supplementary table S2. 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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
De Jong 2019 Switzerland (11)	<ul style="list-style-type: none"> 111 children (aged 6-16y) referred to one of two hospitals due to suspected asthma 	One clinician made a diagnosis on the first assessment based on symptoms, skin prick tests, FeNO	Night time waking‡	0.33	0.84
			Wheeze†	0.80 (0.70, 0.88)	0.48 (0.30, 0.67)

	<ul style="list-style-type: none"> 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%) 	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 S3: GRADE table for PICO 1: Should the presence of wheeze be used to diagnose asthma in children?

Sensitivity		0.55 to 0.86		<div>Prevalence30%*</div>	
Specificity		0.48 to 0.90			

Outcome	No of studies (No 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 S4: GRADE table for PICO 1: Should the presence of cough be used to diagnose asthma in children?

Sensitivity		0.14 to 0.89		Prevalence		30%*			
Specificity		0.27 to 0.68							
Outcome	No of studies (No 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								224 to 511	

Outcome	No of studies (No 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%*	
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 S5: 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
<ul style="list-style-type: none"> ○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ Varies ○ Don't know 	<p>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.</p> <p>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.</p> <p>Results for breathing difficulty were variable and this symptom generally was non-specific (11-14).</p>	

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
<ul style="list-style-type: none"> ○ Trivial ○ Small ○ Moderate ○ Large 	<p>Wheeze heard by a health care professional has the best specificity (0.48-0.90) for the diagnosis of asthma of the classical symptoms</p>	<p>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</p>

<ul style="list-style-type: none"> ○ Varies ○ Don't know 	wheeze, cough and breathing 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
<ul style="list-style-type: none"> ○ 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
<ul style="list-style-type: none"> ○ Very low ○ Low ○ <u>Moderate</u> ○ 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
<ul style="list-style-type: none"> ○ Very low ○ Low ○ <u>Moderate</u> ○ 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.
<p>Certainty of the evidence of test result/management</p> <p>How certain is the link between the presence of the symptoms wheeze, cough and breathing difficulty and management decisions?</p>		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ 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.
<p>Balance of effects</p> <p>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?</p>		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ 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.	<p>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.</p> <p>This raises the risk of misdiagnosis leading to either over-treatment or under-treatment of asthma and the risk of missing the correct diagnosis.</p>

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large costs ○ Moderate costs ○ <u>Negligible costs and savings</u> ○ 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
<ul style="list-style-type: none"> ○ Reduced ○ <u>Probably reduced</u> ○ Probably no impact ○ <u>Probably increased</u> ○ Increased ○ Varies ○ Don't know 	Not reviewed as part of this TF.	<p>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.</p> <p>Unequal access to additional tests may result in less health equity in relevant populations. However using symptoms alone will result in a delay in appropriate asthma treatment or in over-treatment and potentially missing the correct diagnosis in a considerable number of children.</p>
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
<ul style="list-style-type: none"> ○ No ○ <u>Probably no</u> ○ 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 use of presence of the symptoms wheeze, cough and breathing difficulty for the diagnosis of asthma feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Not reviewed as part of this TF.	Evaluation of symptoms is part of every asthma consultation.

TYPE OF RECOMMENDATION

<u>Strong recommendation against the intervention</u> <input type="radio"/>	Conditional recommendation against the intervention <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input type="radio"/>	Strong recommendation for the intervention <input checked="" type="radio"/>
---	--	---	--	--

Conclusions

Recommendation

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

Remarks:

- 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
- 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 S1B). The exclusion reasons in the full-text screening (supplementary table S30) 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, Szeftler 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 S6.

Supplementary table S6: 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
<input type="radio"/> Very inaccurate <input checked="" type="radio"/> Inaccurate <input type="radio"/> Accurate <input type="radio"/> Very accurate <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate	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

<ul style="list-style-type: none"> ○ Large ○ Varies ○ <u>Don't know</u> 		an improvement in their symptoms after 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
<ul style="list-style-type: none"> ○ Large ○ <u>Moderate</u> ○ 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
<ul style="list-style-type: none"> ○ <u>Very low</u> ○ 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
<ul style="list-style-type: none"> ○ <u>Very low</u> ○ 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
<ul style="list-style-type: none"> ○ <u>Very low</u> ○ Low ○ Moderate 	Not reviewed as part of this TF.	In clinical practice, some physicians take into account symptom improvement after a trial of preventer medication to

<ul style="list-style-type: none"> ○ High ○ No included studies 		establish an asthma diagnosis, but never 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
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ <u>Does not favor either the intervention or the comparison</u> ○ 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
<ul style="list-style-type: none"> ○ Large costs ○ <u>Moderate costs</u> ○ 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
<ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ○ <u>Probably no impact</u> ○ 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
<input type="radio"/> No <input checked="" type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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	<u>Conditional recommendation against the intervention</u>	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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:

- 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 bronchodilator 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. FEV₁. Of the 2548 papers we identified 3 (supplementary table S7) 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 S1C). The reasons for exclusion of the papers following full text screening are shown in supplementary table S31. We show the GRADE table for PICO 3 in the supplementary table S8; 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 S9.

Supplementary table S7: 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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 $BDR \geq 12\%$	$FEV_1 / FVC < 80\%$	0.12 (0.10-0.13)	0.91 (0.89-0.93)
De Jong 2019 Switzerland (11)	<ul style="list-style-type: none"> 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 ≤ -0.8	0.44 (0.33-0.56)	0.77 (0.59-0.90)

Supplementary table S8: GRADE table for PICO 3: Should spirometry be used to diagnose asthma in children?

Sensitivity		0.12 to 0.52		<div>Prevalence</div> <div>30%*</div>					
Specificity		0.72 to 0.93							
Outcome	No of studies (No 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 <small>1,2,3,a</small>	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 <small>1,2,3^a</small>	not serious	not serious	not serious	none	504 to 651	⊕⊕⊕○ MODERATE
False positives (patients incorrectly								49 to 196	

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.

^aUnclear if reference standard results were interpreted without knowledge of the results of the index test

Supplementary table S9: 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

Assessment

Test accuracy How accurate is spirometry testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ <u>Varies</u> ○ 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
<ul style="list-style-type: none"> ○ Trivial ○ Small ○ <u>Moderate</u> ○ Large ○ Varies ○ 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
<ul style="list-style-type: none"> ○ Large ○ <u>Moderate</u> ○ Small ○ Trivial ○ Varies ○ Don't know 	<p>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.</p>	<p>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</p>

Certainty of the evidence of test accuracy

What is the overall certainty of the evidence of spirometry test accuracy?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ <u>Moderate</u> ○ High ○ No included studies 	<p>The certainty of the evidence of test accuracy is moderate.</p>	<p>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.</p>

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
<ul style="list-style-type: none"> ○ Very low ○ Low ○ <u>Moderate</u> 	<p>Not reviewed as part of this TF.</p>	<p>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</p>

<ul style="list-style-type: none"> ○ High ○ No included studies 		<p>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.</p>
<p>Certainty of the evidence of spirometry test result/management</p> <p>How certain is the link between spirometry test results and management decisions?</p>		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ○ <u>No included studies</u> 	<p>Not reviewed as part of this TF.</p>	<p>Spirometry by itself has low sensitivity and a normal spirometry does not rule out asthma.</p> <p>An abnormal spirometry test result is likely to guide management.</p>
<p>Balance of effects</p> <p>Does the balance between desirable and undesirable effects favor spirometry testing or the comparison?</p>		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ <u>Probably favors the intervention</u> ○ Favors the intervention ○ Varies ○ Don't know 	<p>Spirometry testing provides moderate to good specificity for diagnosing asthma. Normal spirometry does not rule out asthma.</p>	<p>The test is non-invasive and abnormal spirometry with positive BDR confirms the diagnosis.</p>

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large costs ○ <u>Moderate costs</u> ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know 	Not reviewed as part of this TF.	<p>Moderate cost for equipment and maintenance and training issues.</p> <p>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.</p>
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ <u>Don't know</u> 	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
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ○ <u>Varies</u> ○ Don't know 	Not reviewed as part of this TF.	<p>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.</p> <p>Acceptance may vary depending on resources, healthcare settings and travel times.</p>

Feasibility Is spirometry testing feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> 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	<u>Strong recommendation for the intervention</u>
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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:

- 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
- 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 S1D). 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 S10.

Supplementary table S10: 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
<ul style="list-style-type: none"> ○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ Varies ○ Don't know 	No studies identified that fulfilled the inclusion criteria.	<p>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 $\geq 12\%$ as confirmatory 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.</p>
Desirable Effects How substantial are the desirable anticipated effects of BDR testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know 	No studies identified that fulfilled the inclusion criteria.	<p>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 immediately 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.</p> <p>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.</p>

Undesirable Effects How substantial are the undesirable anticipated effects of BDR testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know 	No studies identified that fulfilled the inclusion criteria.	<p>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 standing. Due to moderate staff, equipment and training costs and low sensitivity the test is frequently not done in low resource and in primary care settings.</p>
Certainty of the evidence of test accuracy What is the overall certainty of the evidence of BDR test accuracy?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ○ Varies ○ No included studies 	No studies identified that fulfilled the inclusion criteria.	<p>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.</p> <p>Accuracy of the test itself depends on operator training and child cooperation and timing of the test is important.</p> <p>Uncertainty exists with the proposed cut-off of $\geq 12\%$ (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.</p>

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
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> <u>No included studies</u>	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
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> <u>No included studies</u>	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
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> <u>Probably favors the intervention</u> <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know	Not reviewed as part of this TF.	<p>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.</p> <p>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.</p>

Resources required		
How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large costs ○ <u>Moderate costs</u> ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know 	Not reviewed as part of this TF.	<p>Moderate cost for equipment, consumables, maintenance and training.</p> <p>Spirometry alone takes approximately 5 minutes, spirometry with BDR testing approximately 30 minutes of operator time (30).</p> <p>Cost-effectiveness has not been evaluated as part of this evidence synthesis.</p>
Equity		
What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ <u>Don't know</u> 	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
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ○ Yes ○ <u>Varies</u> ○ Don't know 	Not reviewed as part of this TF.	<p>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.</p> <p>Acceptance by stakeholders will vary depending on resources and healthcare setting.</p>

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

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	<u>Strong recommendation for the intervention</u>
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

CONCLUSIONS

Recommendation

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

Remarks:

- Consider an increase in $FEV_1 \geq 12\%$ and/or 200 ml following inhalation of 400 micrograms of a short acting beta2-agonist as diagnostic of asthma
- A BDR $< 12\%$ does not exclude asthma
- 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 FEV₁.

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.

Subgroup considerations

The TF recommends BDR testing in children with abnormal spirometry. The TF is aware that in some settings BDR testing is also performed in children with normal spirometry as a small number of these children will have BDR \geq 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 S1D). Five studies were included in the quantitative and qualitative analysis (supplementary table S11). Excluded studies after full-text review are shown in supplementary table S33 and the GRADE table for included studies in supplementary table S12. Sensitivity and specificity analysis for different FeNO cut-offs obtained from the included studies are shown in table S13. The evidence to decision table for PICO 5 is shown in supplementary table S14.

Supplementary table S11: 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)	<ul style="list-style-type: none"> 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 FEV₁ 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> Retrospective analysis case notes of 3612 children (age 6-18y) years attending an allergy clinic with symptoms 	According to GINA 2012 symptoms plus FEV ₁ ≥ 12%	>16 ppb	0.59 (0.56- 0.62)	0.47 (0.44, 0.51)

	<p>suggestive of asthma and who had at least two year's follow up</p> <ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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 S12: GRADE table for PICO 5: Should FeNO be used to diagnose asthma in children?

Sensitivity		0.57 to 0.86		<div>Prevalence</div> <div>30%*</div>					
Specificity		0.36 to 0.89							
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	

Outcome	No of studies (No 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 negatives (patients without [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	252 to 623	⊕⊕⊕○ 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.

^aUnclear if reference standard results were interpreted without knowledge of the results of the index test

Supplementary table S13: 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 S14: 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
<ul style="list-style-type: none"> ○ Very inaccurate ○ Inaccurate ○ <u>Accurate</u> ○ Very accurate ○ Varies ○ Don't know 	<p>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.</p>	<p>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.</p> <p>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.</p>
Desirable Effects How substantial are the desirable anticipated effects of FeNO testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Trivial ○ Small ○ <u>Moderate</u> ○ Large ○ Varies ○ Don't know 	<p>A FeNO \geq 25ppb has moderate specificity (moderate mean specificity 0.81) as a diagnostic test for asthma in children.</p>	<p>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.</p>
Undesirable Effects How substantial are the undesirable anticipated effects of FeNO testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ <u>Moderate</u> ○ Small ○ Trivial ○ Varies ○ Don't know 	<p>There is evidence that FeNO \geq 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,</p>	<p>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.</p>

	moderate specificity can result 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
<input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> <u>Moderate</u> <input type="radio"/> High <input type="radio"/> 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
<input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> <u>Moderate</u> <input type="radio"/> High <input type="radio"/> 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
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> <u>No included studies</u>	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
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ <u>Probably favors the intervention</u> ○ Favors the intervention ○ Varies ○ Don't know 	FeNO testing provides low sensitivity and moderate 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
<ul style="list-style-type: none"> ○ Large costs ○ <u>Moderate costs</u> ○ 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
<ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ○ Probably no impact ○ <u>Probably increased</u> ○ 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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	<u>Strong recommendation for the intervention</u>
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>

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 ≥ 25 ppb in a child with asthma symptoms should be considered as supportive of a diagnosis of asthma
1. A FeNO value < 25 ppb 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 S13) 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 S1E). No additional papers were identified through other sources including reference screening. One research paper was included in the qualitative and quantitative analysis (supplementary table S15) (12). Excluded studies after full-text review are shown in supplementary table S34, the GRADE table for the included study in supplementary table S16 and the evidence to decision table for PICO 6 in supplementary table S17.

Supplementary table S15: 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)	<ul style="list-style-type: none"> 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 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).	12.3%	0.50 (0.30-0.70)	0.72 (0.56-0.86)

Supplementary table S16: GRADE table for PICO 6: Should peak expiratory flow variability be used to diagnose asthma in children?

Sensitivity	0.50 (95% CI: 0.30 to 0.70)		Prevalence		30%*				
Specificity	0.72 (95% CI: 0.56 to 0.84)								
Outcome	No of studies (No 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	No of studies (No 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.

^aUnclear if reference standard results were interpreted without knowledge of the results of the index test

Supplementary table S17: 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
<input type="radio"/> Very inaccurate <input type="radio"/> Inaccurate <input type="radio"/> Accurate <input type="radio"/> Very accurate <input type="radio"/> Varies <input type="radio"/> 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.	<p>The evidence is based on a single study that met inclusion criteria.</p> <p>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.</p>

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Trivial <input type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	The test only detected asthma in half of the cases in the one study included.	<p>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.</p>

Undesirable Effects How substantial are the undesirable anticipated effects of PEFR variability testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ <u>Moderate</u> ○ 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
<ul style="list-style-type: none"> ○ Very low ○ Low ○ <u>Moderate</u> ○ 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
<ul style="list-style-type: none"> ○ Very low ○ <u>Low</u> ○ 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
<ul style="list-style-type: none"> ○ Very low ○ Low 	Not reviewed as part of this TF.	There is uncertainty of the link between PERF variability and management decisions in children

<ul style="list-style-type: none"> ○ Moderate ○ High ○ <u>No included studies</u> 		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
<ul style="list-style-type: none"> ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ <u>Probably favors the intervention</u> ○ 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	<p>. A negative test does not rule out asthma. The test is widely available, cheap and non-invasive.</p> <p>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.</p> <p>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.</p>
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large costs ○ Moderate costs ○ <u>Negligible costs and savings</u> ○ 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
<ul style="list-style-type: none"> ○ 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

<input type="radio"/> Increased <input checked="" type="radio"/> Varies <input type="radio"/> Don't know		improve diagnostic accuracy compared to no 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> 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 <input type="radio"/>	<u>Conditional recommendation against the intervention</u> <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
---	--	---	--	---

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 $\geq 12\%$ 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 PEF 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 PEF 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 S1F). Of these, four were included in the qualitative and quantitative evaluation (supplementary table S18) (11,12,24,33). We show excluded studies after full-text review in supplementary table S35, the GRADE tables for included studies in supplementary table S19 and S20 and the evidence to decision table for PICO 7 in supplementary table S21.

Supplementary table S18: 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)	<ul style="list-style-type: none"> 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, <i>Alternaria</i> , 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)	<ul style="list-style-type: none"> 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 $\geq 12\%$ BDR and/or methacholine PC ₂₀ $\leq 8\text{mg/mL}$	Any positive skin prick tests for dust mites, <i>Alternaria</i> , <i>Cladosporium</i> , <i>Aspergillus</i> , <i>Mucor</i> , <i>Penicillium</i> , 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)	<ul style="list-style-type: none"> 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 FEV₁ 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)

	<ul style="list-style-type: none"> Asthma diagnosed in 21 (34%) 56% (34) had IgE specific for inhaled allergens 				
Grzelewski 2014 Poland (24)	<ul style="list-style-type: none"> 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 ≥ 0.35 kU/L for dust mites, moulds, cat and/or dog	0.58 (0.54-0.62)	0.65 (0.61-0.69)
			Specific IgE ≥ 0.35 kU/L for tree pollen and/or grass pollen	0.63 (0.59-0.67)	0.56 (0.52-0.61)

Supplementary table S19: GRADE table for PICO 7: Should skin prick tests be used to diagnose asthma in children?

Sensitivity		0.77 to 0.90		Prevalence		30%*			
Specificity		0.23 to 0.40							
Outcome	No of studies (No 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	cross-sectional (cohort type accuracy study)	serious ^a	not serious	not serious	not serious	none	161 to 280	⊕⊕⊕○ MODERATE

Outcome	No of studies (No 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])	(11,33)							420 to 539	

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 S20: GRADE table for PICO 7: Should specific IgE testing be used to diagnose asthma in children?

Sensitivity		0.58 to 0.90		<div>Prevalence30%*</div>					
Specificity		0.56 to 0.58							
Outcome	No of studies (No 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								294 to 308	

Outcome	No of studies (No 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%*	
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 S21: 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
<input type="radio"/> Very inaccurate <input checked="" type="radio"/> Inaccurate <input type="radio"/> Accurate <input type="radio"/> Very accurate <input type="radio"/> Varies <input type="radio"/> Don't know	<p>4 studies were included to answer PICO question 7. Two studies assessed skin prick tests, 2 studies assessed specific IgE.</p> <p>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.</p> <p>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.</p> <p>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)</p>	<p>Both for SPT and IgE, sensitivity and specificity were dependent on the cut-off chosen (number of positive tests).</p> <p>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.</p> <p>In contrast to other measurements, allergy tests have less temporal variation. There is a slight seasonal variation, but that is not strong, and there is no diurnal variation. This is an advantage and explains partly the high sensitivity.</p> <p>All these aspects were not covered in the few publications identified by the search and need to be considered in future research.</p>

Desirable Effects

How substantial are the desirable anticipated effects of allergy testing?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Trivial ○ Small ○ <u>Moderate</u> ○ Large ○ Varies ○ Don't know 	<p>There is evidence that positive allergy tests have moderate to good sensitivity but low specificity for the diagnosis of asthma.</p> <p>The taskforce decided that the low specificity outweighs the desirable effect (high sensitivity) because this results in overdiagnosis of asthma.</p>	<p>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.</p>

Undesirable Effects

How substantial are the undesirable anticipated effects of allergy testing?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ <u>Moderate</u> ○ Small ○ Trivial ○ Varies ○ Don't know 	<p>There is evidence that positive allergy tests have low specificity for the diagnosis of asthma.</p> <p>Reliance on allergy tests to diagnose asthma leads to a risk of asthma overdiagnosis, particularly in children with allergic rhinitis.</p> <p>There is also a risk of underdiagnosis of non-allergic asthma.</p>	<p>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.</p> <p>Both skin prick tests and taking blood are slightly disagreeable to children, but not associated with relevant side effects.</p>

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
<ul style="list-style-type: none"> ○ Very low ○ Low ○ <u>Moderate</u> ○ 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
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ○ <u>No included studies</u> 	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
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ○ <u>No included studies</u> 	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
<ul style="list-style-type: none"> ○ Favors the comparison ○ <u>Probably favors the comparison</u> ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know 		<p>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.</p> <p>Allergy tests have, however, a role in asthma management after the diagnosis is made, for instance for choosing tertiary prevention.</p>
Resources required		
How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large costs ○ <u>Moderate costs</u> ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know 	Not reviewed as part of this TF.	<p>SPT are time-consuming and there is a cost for consumables and the individual allergens.</p> <p>IgE tests are relatively costly, depending on the number of tests done.</p>
Equity		
What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Reduced ○ Probably reduced ○ <u>Probably no impact</u> ○ 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Not reviewed as part of this TF.	<p>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.</p> <p>Patients and parents usually accept allergy tests if recommended. Discomfort when taking blood can be reduced by application of anaesthetic creams.</p> <p>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.</p>
Feasibility Is allergy testing feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Not reviewed as part of this TF.	<p>Both types of tests can be implemented in all care settings.</p> <p>Skin prick tests need experienced examiners (training) and adequate storage of ingredients (in fridge, timely replacements)</p>

Type of recommendation

<u>Strong recommendation against the intervention</u> ○	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 S1H). 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 S22). (11,37,38) Excluded studies after full-text review are shown in supplementary table S36, the GRADE table for included studies in supplementary table S23 and the evidence to decision table for PICO 8 in supplementary table S24. We found no studies to assess the diagnostic accuracy of histamine challenge testing in children under investigation for asthma.

Supplementary table S22: 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)	<ol style="list-style-type: none"> 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. Five visits <ol style="list-style-type: none"> Questionnaire, spirometry, BDR, skin prick reactivity +1-4 days, exercise test +1-4 days, exercise test Mannitol or methacholine challenge Challenge not done at visit 4 <ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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 S23: GRADE table for PICO 8: Should a direct bronchial challenge test with methacholine be performed to diagnose asthma in children?

Sensitivity		0.66 to 0.85				<div>Prevalence30%*</div>			
Specificity		0.63 to 0.82							
Outcome	No of studies (No 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	No of studies (No 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.

^aNo statistical approach used, point estimates and 95%CI overlap

^bIt has not been possible to pool accuracy data, 95%CIs are not known and absolute results represent central point estimates.

Supplementary table S24: 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

Assessment

Test accuracy		
How accurate is the test?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Very inaccurate <input type="radio"/> Inaccurate <input checked="" type="radio"/> Accurate <input type="radio"/> Very accurate <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large	There is evidence that a positive direct bronchial challenge test has moderate sensitivity and specificity to	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

<ul style="list-style-type: none"> ○ Varies ○ Don't know 	confirm the diagnosis of asthma in children.	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
<ul style="list-style-type: none"> ○ Large ○ <u>Moderate</u> ○ Small ○ Trivial ○ Varies ○ Don't know 	Despite moderate sensitivity and specificity of direct bronchial challenge tests, there are significant numbers of children 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
<ul style="list-style-type: none"> ○ Very low ○ Low ○ <u>Moderate</u> ○ High ○ No included studies 	The certainty of the evidence of test accuracy is moderate based on the 3 studies included.	<p>Good quality studies have shown that direct bronchial challenge tests have a moderate sensitivity and specificity to support an asthma diagnosis in children.</p> <p>Accuracy of the test itself depends on operator training and child cooperation</p> <p>The certainty of an asthma diagnosis is high with a positive direct bronchial challenge test.</p>

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
<input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> 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
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> 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
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> 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,

<input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know		the child remains symptomatic and other diagnoses have been considered.
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Large costs <input checked="" type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> Reduced <input type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input checked="" type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> <u>Varies</u> <input type="radio"/> Don't know	Not reviewed as part of this TF.	<p>The intervention is non-invasive and lay members of the TF found it acceptable.</p> <p>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.</p>
Feasibility		
Is direct bronchial challenge testing with methacholine feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> <u>Varies</u> <input type="radio"/> Don't know	Not reviewed as part of this TF.	<p>Lay members of TF found this acceptable in carefully selected children.</p> <p>There are equipment and consumables costs.</p> <p>There are training costs to perform the test and interpret the test results.</p> <p>Lay members of TF found this acceptable in carefully selected children</p> <p>A barrier for implementation may be the need for referral to a specialist laboratory especially if this laboratory is a long distance away.</p>

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	<u>Conditional recommendation for the intervention</u>	Strong recommendation for the intervention
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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 reserved 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 S1I). 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 S37. Data from three papers were included in the final report (supplementary table S25) (11,37,38). We show the GRADE tables for included studies in supplementary table S26 and S27 and the evidence to decision table for PICO 9 in supplementary table S28.

Supplementary table S25: 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)	<ul style="list-style-type: none"> 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 <ol style="list-style-type: none"> Questionnaire, spirometry, BDR, skin prick reactivity +1-4 days, exercise test +1-4 days, exercise test Mannitol or methacholine challenge 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> • 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	$\geq 10\%$ FEV ₁ fall	0.77 (0.62-0.89)	0.68 (0.55-0.80)
------------------------------------	--	------------------------	-----------------------------------	---------------------	---------------------

Supplementary table S26: GRADE table for PICO 9: Should an indirect bronchial challenge test with exercise be used to diagnose asthma in children?

Sensitivity		0.37 to 0.77			Prevalence 30%*				
Specificity		0.68 to 0.77							
Outcome	No of studies (No 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								161 to 224	

Outcome	No of studies (No 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.

^aAccuracy values represent range of point estimates and 95%CI are not available, however range of results varies broadly.

^bIt has not been possible to pool accuracy data, 95%CI are not known and absolute results represent central point estimates.

Supplementary table S27: GRADE table for PICO 9: Should indirect bronchial challenge test with mannitol be used to diagnose asthma in children?

Sensitivity		0.39 to 0.63			Prevalence30%*				
Specificity		0.81 to 0.97							
Outcome	No of studies (No 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								133 to 171	

Outcome	No of studies (No 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.

^aAccuracy values represent range of point estimates and 95%CI are not available, however range of results varies broadly.

^bIt has not been possible to pool accuracy data, 95%CI are not known and absolute results represent central point estimates.

Supplementary table S28: 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

Assessment

Test accuracy		
How accurate is indirect bronchial challenge testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ Varies ○ Don't know 	<p>3 studies are included to answer PICO question 9.</p> <p>2 data sets reported treadmill exercise testing and 2 data sets reported mannitol challenge testing.</p> <p>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)</p> <p>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)</p>	<p>Sensitivity was very low (0.44) at the 12% cut-off (11) but specificity was good (0.92).</p>

Desirable Effects		
How substantial are the desirable anticipated effects of indirect bronchial challenge testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Trivial ○ Small ○ <u>Moderate</u> ○ Large ○ Varies ○ Don't know 	<p>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.</p>	<p>Indirect bronchial challenge testing, particularly 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.</p>
Undesirable Effects		
How substantial are the undesirable anticipated effects of indirect bronchial challenge testing?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ <u>Moderate</u> ○ Small ○ Trivial ○ Varies ○ Don't know 	<p>Indirect bronchial challenge tests have only low to moderate sensitivity in diagnosing asthma in children.</p>	<p>Indirect bronchial challenge tests are time consuming and require a specialist setting. Therefore, children may need to be referred to a specialist laboratory.</p> <p>Exercise tests are tiring and can be considered bothersome by some children. As a result some children do not complete the test.</p> <p>Children often find the mannitol challenge test unpleasant.</p> <p>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</p>

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
<input type="radio"/> Very low <input checked="" type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> 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
<input type="radio"/> Very low <input type="radio"/> Low <input checked="" type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> 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
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High	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.

<p>○ <u>No included studies</u></p>		
<p>Balance of effects</p> <p>Does the balance between desirable and undesirable effects favor indirect bronchial challenge testing or the comparison?</p>		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<p>○ Favors the comparison</p> <p>○ Probably favors the comparison</p> <p>○ Does not favor either the intervention or the comparison</p> <p>○ <u>Probably favors the intervention</u></p> <p>○ Favors the intervention</p> <p>○ Varies</p> <p>○ Don't know</p>	<p>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.</p>	<p>The test is non-invasive and a positive test confirms the diagnosis of asthma.</p> <p>However, the test is time consuming and requires a specialist setting and hence, children may not be referred to such a centre.</p> <p>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.</p> <p>The TF considered that indirect bronchial challenge test using a treadmill or a bicycle should be offered to children with exercise related symptoms</p>
<p>Resources required</p> <p>How large are the resource requirements (costs)?</p>		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<p>○ Large costs</p> <p>○ <u>Moderate costs</u></p> <p>○ Negligible costs and savings</p> <p>○ Moderate savings</p> <p>○ Large savings</p> <p>○ Varies</p> <p>○ Don't know</p>	<p>Not reviewed as part of this TF.</p>	<p>Moderate cost for equipment, consumables, and maintenance and training issues.</p> <p>An indirect bronchial challenge test requires approximately 30-45 minutes of time for patients and operators.</p> <p>There is limited availability for mannitol in most countries.</p>

Equity		
What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Reduced <input type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input checked="" type="radio"/> Varies <input type="radio"/> 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
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input type="radio"/> Yes <input checked="" type="radio"/> Varies <input type="radio"/> Don't know	Not reviewed as part of this TF.	<p>The intervention is non-invasive and lay members of TF found it acceptable.</p> <p>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</p> <p>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.</p>

Feasibility		
Is indirect bronchial challenge testing feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes	Not reviewed as part of this TF.	There are equipment and consumables costs.

<input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		<p>There are training costs to perform the test and interpret the test results.</p> <p>A barrier for implementation may be the need for referral to a specialist centre or laboratory.</p> <p>Lay members of TF found the tests acceptable in selected children</p>
---	--	---

TYPE OF RECOMMENDATION

Strong recommendation against the intervention <input type="radio"/>	Conditional recommendation against the intervention <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	<u>Conditional recommendation for the intervention</u> <input type="radio"/>	Strong recommendation for the intervention <input type="radio"/>
---	--	---	--	---

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:

- A fall in FEV₁ of > 10% from baseline should be taken as a positive test
- 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 reserved 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 S29. 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 hyperresponsiveness and not asthma.	Inappropriate outcome
2	Bailly 2011 (40)	Cohort study of children with suspected asthma. Outcome bronchial hyperresponsiveness and not asthma.	Inappropriate outcome
3	Boccaccino 2007 (41)	Cohort study of children with suspected asthma. Outcome bronchial hyperresponsiveness 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 hyperresponsiveness 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 hyperresponsiveness 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 hyperresponsiveness 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-hyperresponsiveness 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 hyperresponsiveness and not asthma.	Inappropriate 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 asthma with a questionnaire.	Inappropriate 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 S30: 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 (108)	Systematic review and meta-analysis of randomized controlled trials evaluating the efficacy ICS in children with episodic viral wheeze	Non-diagnostic study
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	Szeffler 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 (116)	Cross-sectional study assessing asthma diagnosis in children referred for clinical suspicion of asthma	Not original article
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 S31: 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 S32: 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 S33: 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 S34: 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 S35: 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 S36: 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 specificity 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 several time points	Asthma diagnosis not according to protocol of the TF, diagnosis only 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 Chinese 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 S37: 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 trial 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	Age distribution not according to TF protocol (mean age 35, range 6-83), no subgroup analysis in children completed..

		safety of mannitol and hypertonic saline to assess BHR.	
3	Buechele et al, 2007 (42)	Cross-sectional study comparing different BHR test to diagnose asthma	Asthma diagnosis not according to 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 different 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 over a two year period	Asthma diagnosis not according to protocol of the TF, diagnosis only questionnaire based.
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 pediater* 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 pediater* 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 accolat 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 Itra 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 pediater* or teen* or adolescen*):ti,ab | 98324 |
| #13 | (leukotriene* or leucotriene* or Itra 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 trees | 1652 |
| #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 pediater* 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 pediater* 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 pediater* 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 pediater* 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 pediater* 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 pediater* 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 trees	1919
#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 pediater* 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 pediater* 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 pediater* 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 pediater* 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 pediater* 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 Jestril 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 pediater* 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 Jestril 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 Jestril 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 2018 2476
 #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 pediater* 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

References

- (1) Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006 Aug;101(8):1900-20; quiz 1943.
- (2) https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf
- (3) <https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/>
- (4) <https://www.nice.org.uk/guidance/ng80>
- (5) Looijmans-van den Akker I, van Luijn K, Verheij T. Overdiagnosis of asthma in children in primary care: a retrospective analysis. *Br J Gen Pract* 2016 Mar;66(644):e152-7.
- (6) Brožek GM, Farnik M, Lawson J, Zejda JE. Underdiagnosis of childhood asthma: A comparison of survey estimates to clinical evaluation. *Int J Occup Med Environ Health* 2013 Dec;26(6):900-909.
- (7) Yang CL, Simons E, Foty RG, Subbarao P, To T, Dell SD. Misdiagnosis of asthma in schoolchildren. *Pediatr Pulmonol* 2017 Mar;52(3):293-302.
- (8) Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011 Oct 18;155(8):529-536.
- (9) Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ* 2016 Jun 28;353:i2016.
- (10) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009 Jul 21;6(7):e1000097.
- (11) de Jong CCM, Pedersen ESL, Mozun R, Goutaki M, Trachsel D, Barben J, et al. Diagnosis of asthma in children: the contribution of a detailed history and test results. *Eur Respir J* 2019 Dec 4;54(6):10.1183/13993003.01326-2019. Print 2019 Dec.
- (12) Brouwer A.F.J., Visser C.A.N., Duiverman E.J., Roorda R.J., Brand PLP. Is home spirometry useful in diagnosing asthma in children with nonspecific respiratory symptoms? *Pediatr Pulmonol* 2010 April 2010;45(4):326-332.
- (13) Santos M.C., Cunha AA. A brief questionnaire for screening asthma among children and adolescents in Rio de Janeiro, Brazil. *Allergol Immunopathol* 2005 January;33(1):20-26.

- (14) Ma TT, Zhuang Y, Gong HY, Yii AC, Wang XY, Shi HZ. Predictive value of respiratory symptoms for the diagnosis of pollen-induced seasonal asthma among children and adults in Inner Mongolia. *Ther Clin Risk Manag* 2017 Aug 4;13:967-974.
- (15) Morice AH, Millqvist E, Bieksiene K, Birring SS, Diczpinigaitis P, Domingo Ribas C, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J* 2020 Jan 2;55(1):10.1183/13993003.01136-2019. Print 2020 Jan.
- (16) Baxter-Jones AD, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, et al. Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial. *Health Technol Assess* 2000;4(28):1-89.
- (17) Szeffler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005 Feb;115(2):233-242.
- (18) Murray CS, Foden P, Lowe LA, Durrington H, Custovic A, Simpson A. Diagnosing asthma in children using spirometry: Evidence from a birth cohort study. *Thorax* 2016;71:A179.
- (19) Murray C, Foden P, Lowe L, Durrington H, Custovic A, Simpson A. Diagnosis of asthma in symptomatic children based on measures of lung function: an analysis of data from a population-based birth cohort study. *The Lancet Child and Adolescent Health* 2017;1:114-123.
- (20) Lo DK, Beardsmore CS, Roland D, Richardson M, Yang Y, Danvers L, et al. Lung function and asthma control in school-age children managed in UK primary care: a cohort study. *Thorax* 2020 Feb;75(2):101-107.
- (21) Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Götz M, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008 Jan;63(1):5-34.
- (22) Bush A, Fleming L. Diagnosis and management of asthma in children. *BMJ* 2015 Mar 5;350:h996.
- (23) Sivan Y., Gadish T., Fireman E., Soferman R. The Use of Exhaled Nitric Oxide in the Diagnosis of Asthma in School Children. *J Pediatr* 2009 August 2009;155(2):211-216.
- (24) Grzelewski T, Witkowski K, Makandjou-Ola E, Grzelewska A, Majak P, Jerzynska J, et al. Diagnostic value of lung function parameters and FeNO for asthma in schoolchildren in large, real-life population. *Pediatr Pulmonol* 2014;49:632-640.
- (25) Lo D, Beardsmore C, Roland D, Richardson M, Yang Y, Danvers L, et al. Spirometry and FeNO testing for asthma in children in UK primary care: a prospective observational cohort study of feasibility and acceptability. *Br J Gen Pract* 2020 Oct 19.

- (26) Nuttall AGL, Velasquez W, Beardsmore CS, Gaillard EA. Lung clearance index: assessment and utility in children with asthma. *Eur Respir Rev* 2019 Nov 20;28(154):10.1183/16000617.0046-2019. Print 2019 Dec 31.
- (27) <https://www.who.int/respiratory/asthma/definition/en/>
- (28) <http://www.globalasthmareport.org/> <https://ginasthma.org/gina-reports/>
- (29) Tse SM, Gold DR, Sordillo JE, Hoffman EB, Gillman MW, Rifas-Shiman S, et al. Diagnostic accuracy of the bronchodilator response in children. *J Allergy Clin Immunol* 2013;132:554.
- (30) Lo D, Maniyar A, Gupta S, Gaillard E. High prevalence of bronchiectasis on chest CT in a selected cohort of children with severe Asthma. *BMC Pulm Med* 2019 Jul 26;19(1):136-019-0900-0.
- (31) Dundas I, Chan EY, Bridge PD, McKenzie SA. Diagnostic accuracy of bronchodilator responsiveness in wheezy children. *Thorax* 2005;60:13-16.
- (32) Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005 Nov;26(5):948-968.
- (33) Woo S, Lee J, Kim H, Kang J, Sun Y, Hahn Y. Utility of fractional exhaled nitric oxide (F(E)NO) measurements in diagnosing asthma. *Respir Med* 2012;106:1103-1109.
- (34) D'Alonzo GE, Steinijs VW, Keller A. Measurements of morning and evening airflow grossly underestimate the circadian variability of FEV1 and peak expiratory flow rate in asthma. *Am J Respir Crit Care Med* 1995 Sep;152(3):1097-1099.
- (35) Chowieńczyk PJ, Parkin DH, Lawson CP, Cochrane GM. Do asthmatic patients correctly record home spirometry measurements? *BMJ* 1994 Dec 17;309(6969):1618.
- (36) Kamps AW, Roorda RJ, Brand PL. Peak flow diaries in childhood asthma are unreliable. *Thorax* 2001 Mar;56(3):180-182.
- (37) Anderson S.D., Charlton B., Weiler J.M., Nichols S., Spector S.L., Pearlman DS. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. *Respiratory Research* 2009;10:Arte Number: 4. ate of Pubaton: 23 Jan 2009.
- (38) Zaczeniuk M., WoickaKolejwa K., Stelmach W., Podlecka D., Jerzynska J., Stelmach I. Methacholine challenge testing is superior to the exercise challenge for detecting asthma in children. *Annals of Allergy, Asthma and Immunology* 2015 01 Dec 2015;115(6):481-484.
- (39) Ater D., Amirav I., Attias M., Nakash E., Newhouse M.T., Mandelberg A. Evaluation of clinically and physiologically atypical asthma: If it doesn't wheeze it may still be asthma. *Journal of Asthma* 2018 01 Feb 2018:1-6.

- (40) Bailly C., Crenesse D., Albertini M. Evaluation of impulse oscillometry during bronchial challenge testing in children. *Pediatr Pulmonol* 2011 December 2011;46(12):1209-1214.
- (41) Boccaccino A, Peroni DG, Pietrobelli A, Piacentini GL, Aversano MP, Spinosa E, et al. Forced oscillometry is applicable to epidemiological settings to detect asthmatic children. *Allergy & Asthma Proceedings* 2007 Mar-Apr;28(2):170-173.
- (42) Büchele G, Rzehak P, Weinmayr G, Keil U, Leupold W, von Mutius E, et al. Assessing bronchial responsiveness to hypertonic saline using the stepwise protocol of Phase Two of the International Study of Asthma and Allergies in Childhood (ISAAC II). *Pediatr Pulmonol* 2007 Feb;42(2):131-140.
- (43) Demissie K., White N., Joseph L., Ernst P. Bayesian estimation of asthma prevalence, and comparison of exercise and questionnaire diagnostics in the absence of a gold standard. *Ann Epidemiol* 1998 April 1998;8(3):201-208.
- (44) Fitzgerald JM. Relation of airway responsiveness to methacholine to parent and child reporting of symptoms suggesting asthma. *Canadian Respiratory Journal* 1996 1996;3(2):115-123.
- (45) Fouzas S., Skylogianni E., Bolis K., Priftis K.N., Anthracopoulos M.B., Brand PLP. Clinical predictive rules to identify preschool wheezers at risk for subsequent asthma: Can we rely on them? Could we improve their performance? *European Respiratory Journal* 2012 Respiratory Society Annual Congress;Conference:European.
- (46) Godfrey S, Uwytyed K, Springer C, Avital A. Is clinical wheezing reliable as the endpoint for bronchial challenges in preschool children? *Pediatr Pulmonol* 2004 Mar;37(3):193-200.
- (47) Goldberg S., Schwartz S., Izbicki G., Hamami R.B., Picard E. Sensitivity of exercise testing for asthma in adolescents is halved in the summer. *Chest* 2005 October 2005;128(4):2408-2411.
- (48) Goldstein M.F., Veza B.A., Dunskey E.H., Dvorin D.J., Belecanech G.A., Haralabatos IC. Comparisons of peak diurnal expiratory flow variation, postbronchodilator FEV1 responses, and methacholine inhalation challenges in the evaluation of suspected asthma. *Chest* 2001 2001;119(4):1001-1010.
- (49) Gudelj I, Mrkić Kobal I, Munivrana Škvorc H, Miše K, Vrbica Z, Plavec D, et al. Intraregional differences in asthma prevalence and risk factors for asthma among adolescents in Split-Dalmatia County, Croatia. *Med Sci Monit* 2012 Apr;18(4):PH43-50.
- (50) Hansen T.E., Evjenth B., Holt J. Validation of a questionnaire against clinical assessment in the diagnosis of asthma in school children. *Journal of Asthma* 2015 01 Apr 2015;52(3):262-267.

- (51) Hensley MJ, Chalmers A, Clover K, Gibson PG, Toneguzzi R, Lewis PR. Symptoms of asthma: comparison of a parent-completed retrospective questionnaire with a prospective daily symptom diary. *Pediatr Pulmonol* 2003 Dec;36(6):509-513.
- (52) IvkovicJurekovic I., Matijasic N., Navratil M., Topalusic I., GolmajerVlahovic I. Bronchial methacholine challenge in children. *Allergy: European Journal of Allergy and Clinical Immunology* 2017 Annual Congress of the European Academy of Allergy and Clinical Immunology, EAACI;Conference:36th.
- (53) Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *BMJ* 1995 May 13;310(6989):1225-1229.
- (54) Joseph-Bowen J, De Klerk NH, Firth MJ, Kendall GE, Holt PG, Sly PD. Lung function, bronchial responsiveness, and asthma in a community cohort of 6-year-old children. *American Journal of Respiratory and Critical Care Medicine* 2004;169:850-854.
- (55) Kannisto S, Vanninen E, Remes K, Korppi M. Use of a pocket-sized turbine spirometer in monitoring exercise-induced bronchospasm and bronchodilator responses in children. *Pediatric Allergy and Immunology* 1999;10:266-271.
- (56) Kim YY, Cho SH, Kim WK, Park JK, Song SH, Kim YK, et al. Prevalence of childhood asthma based on questionnaires and methacholine bronchial provocation test in Korea. *Clin Exp Allergy* 1997 Jul;27(7):761-768.
- (57) Lang J.E., Feng H., Lima JJ. Body mass index-percentile and diagnostic accuracy of childhood asthma. *Journal of Asthma* 2009 April 2009;46(3):291-299.
- (58) Lee J, Shim JY, Kwon J, Kim HY, Seo J, Kim B, et al. Exhaled nitric oxide as a better diagnostic indicator for evaluating wheeze and airway hyperresponsiveness in preschool children. *The Journal of asthma : official journal of the Association for the Care of Asthma* 2015;52:1054-1059.
- (59) Lee DH, Kwon J, Kim HY, Seo J, Kim H, Lee S, et al. Asthma predictive index as a useful diagnostic tool in preschool children: a cross-sectional study in Korea. *Clin Exp Pediatr* 2020;63:104-109.
- (60) Mai XM, Nilsson L, Kjellman NI, Björkstén B. Hypertonic saline challenge tests in the diagnosis of bronchial hyperresponsiveness and asthma in children. *Pediatr Allergy Immunol* 2002 Oct;13(5):361-367.
- (61) Malmberg LP, Pelkonen AS, Mattila PS, Hammaren-Malmi S, Makela MJ. Exhaled nitric oxide and exercise-induced bronchoconstriction in young wheezy children - interactions with atopy. *Pediatric Allergy & Immunology* 2009 Nov;20(7):673-678.

- (62) Mata Fernández C, Fernández-Benítez M, Pérez Miranda M, Guillén Grima F. Validation of the Spanish version of the Phase III ISAAC questionnaire on asthma. *J Investig Allergol Clin Immunol* 2005;15(3):201-210.
- (63) Mitra AD, Ogston S, Crichton A, Mukhopadhyay S. Lung function and asthma symptoms in children: relationships and response to treatment. *Acta Paediatrica* 2002;91(7):789-792.
- (64) Ponsonby AL, Couper D, Dwyer T, Carmichael A, Wood-Baker R. Exercise-induced bronchial hyperresponsiveness and parental ISAAC questionnaire responses. *European Respiratory Journal* 1996 Jul;9(7):1356-1362.
- (65) Riedler J., Reade T., Dalton M., Holst D.I., Robertson C. Hypertonic saline challenge in an epidemiologic survey of asthma in children. *American Journal of Respiratory and Critical Care Medicine* 1994;150:ate of Pubaton: eember 1994.
- (66) SanchezGarcia S., Fermin I., Andregnette V., Del RP, Escudero C., Ibanez MD. Bronchial hyperresponsiveness in children with suggestive asthma symptoms. *World Allergy Organization Journal.Conference: 22nd World Allergy Congress.Cancun Mexico.Conference Publication: (var.pagings) 2012 February 2012;5:S183-S184.*
- (67) Saraçlar Y, Kuyucu S, Tuncer A, Sekerel B, Saçkesen C, Kocabaş C. Prevalence of asthmatic phenotypes and bronchial hyperresponsiveness in Turkish schoolchildren: an International Study of Asthma and Allergies in Childhood (ISAAC) phase 2 study. *Ann Allergy Asthma Immunol* 2003 Nov;91(5):477-484.
- (68) Seear M., Wensley D., West N. How accurate is the diagnosis of exercise induced asthma among Vancouver schoolchildren? *Arch Dis Child* 2005 September 2005;90(9):898-902.
- (69) Shapiro GG, Furukawa CT, Pierson WE, Bierman CW. Methacholine bronchial challenge in children. *Journal of Allergy & Clinical Immunology* 1982 Apr;69(4):365-369.
- (70) Sheikh S, Ryan-Wenger N, Pitts J, McCoy K. Screening for asthma-like symptoms and acute care utilization can be used to identify children in the community who may be at risk for undiagnosed asthma. *Eur Respir J* 2013;42(Suppl 57):P1163, Abstract.
- (71) Skylogianni E, Bolis K, Anthracopoulos M, Fouzas S. Prolonged bronchodilator responsiveness after preschool virus-induced wheezing episodes may predict asthma persistence. *European Respiratory Journal* 2015;46.
- (72) Sockrider MM, Tortolero SR, Bartholomew LK, Markham CM, Abramson SL, Fernandez M, et al. Pilot study of a screening questionnaire for asthma. *Pediatric Asthma, Allergy and Immunology* 2001;15(1).

- (73) Stensballe LG, Klansø L, Jensen A, Haerskjold A, Thomsen SF, Simonsen J. The validity of register data to identify children with atopic dermatitis, asthma or allergic rhinoconjunctivitis. *Pediatr Allergy Immunol* 2017 Sep;28(6):535-542.
- (74) Timonen KL, Schwartz J, Nielsen J, Brunekreef B. Associations between markers of respiratory morbidity in European children. *Eur Respir J* 2002 Mar;19(3):479-486.
- (75) Timonen KL, Pekkanen J, Korppi M, Vahteristo M, Salonen RO. Prevalence and characteristics of children with chronic respiratory symptoms in eastern Finland. *Eur Respir J* 1995 Jul;8(7):1155-1160.
- (76) Timonen KL, Nielsen J, Schwartz J, Gotti A, Vondra V, Gratziau C, et al. Chronic respiratory symptoms, skin test results, and lung function as predictors of peak flow variability. *American Journal of Respiratory & Critical Care Medicine* 1997 Sep;156(3):776-782.
- (77) Vieira T., Brito H., Almeida S., Gomes E., Falcao H. Bronchial hyperreactivity, methacholine test and small airways. *Allergy: European Journal of Allergy and Clinical Immunology*.Conference: 31st Congress of the European Academy of Allergy and Clinical Immunology.Geneva Switzerland.Conference Publication: (var.pagings) 2012 November 2012;67:624.
- (78) Wang Q, Xu C, Xu D, Liu C, Chen Y. Risks on asthma among city children in China:a nationwide case-control study. *Zhonghua Liu Xing Bing Xue Za Zhi* 2014 Mar;35(3):237-241.
- (79) Wegienka G, Havstad S, Zoratti EM, Ownby DR, Johnson CC. Association of early life wheeze and lung function. *Ann Allergy Asthma Immunol* 2009 Jan;102(1):29-34.
- (80) Yang CL, To T, Foty RG, Stieb DM, Dell SD. Verifying a questionnaire diagnosis of asthma in children using health claims data. *BMC Pulm Med* 2011 Nov 22;11:52-2466-11-52.
- (81) Yeh F, Rhoades ER, Tarpay M, Eichner JE. Advantages of video questionnaire in estimating asthma prevalence and risk factors for school children: findings from an asthma survey in American Indian youth. *J Asthma* 2010 Sep;47(7):711-717.
- (82) Yu ITS, Wong TW, Li W. Using child reported respiratory symptoms to diagnose asthma in the community. *Arch Dis Child* 2004 Jun;89(6):544-548.
- (83) Yunus F, Antaria R, Rasmin M, Mangunegoro H, Jusuf A, Bachtiar A. Asthma prevalence among high school students in east Jakarta, 2001, based on ISAAC questionnaire. *Medical Journal of Indonesia* 2003;12(3):178-186.
- (84) Zejda JE, Brozek GM, Cholewa Z, Kowalska M. Prevention of childhood bronchial asthma--needs, abilities, limitations. *Wiad Lek* 2002;55 Suppl 1:599-602.

- (85) Abrams EM, Szeffler SJ, Becker AB. Effect of asthma therapies on the natural course of asthma. *Ann Allergy Asthma Immunol* 2016 Dec;117(6):627-633.
- (86) Bacharier LB, Guilbert TW. Diagnosis and management of early asthma in preschool-aged children. *J Allergy Clin Immunol* 2012 Aug;130(2):287-96; quiz 297-8.
- (87) Beigelman A, Chipps BE, Bacharier LB. Update on the utility of corticosteroids in acute pediatric respiratory disorders. *Allergy Asthma Proc* 2015 Sep-Oct;36(5):332-338.
- (88) Beigelman A, Bacharier LB. Management of preschool recurrent wheezing and asthma: a phenotype-based approach. *Curr Opin Allergy Clin Immunol* 2017 Apr;17(2):131-138.
- (89) Bossley CJ, Saglani S, Kavanagh C, Payne DN, Wilson N, Tsartsali L, et al. Corticosteroid responsiveness and clinical characteristics in childhood difficult asthma. *Eur Respir J* 2009 Nov;34(5):1052-1059.
- (90) Brand PL, Luz Garcia-Garcia M, Morison A, Vermeulen JH, Weber HC. Ciclesonide in wheezy preschool children with a positive asthma predictive index or atopy. *Respir Med* 2011 Nov;105(11):1588-1595.
- (91) Brodlić M, Gupta A, Rodriguez-Martinez CE, Castro-Rodriguez JA, Ducharme FM, McKean MC. Leukotriene receptor antagonists as maintenance and intermittent therapy for episodic viral wheeze in children. *Cochrane Database Syst Rev* 2015 Oct 19;2015(10):CD008202.
- (92) Chang AB, Phelan PD, Carlin JB, Sawyer SM, Robertson CF. A randomised, placebo controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. *Arch Dis Child* 1998 Jul;79(1):6-11.
- (93) Chang AB, Winter D, Acworth JP. Leukotriene receptor antagonist for prolonged non-specific cough in children. *Cochrane Database Syst Rev* 2006 Apr 19;(2):CD005602. doi(2):CD005602.
- (94) Chong J, Haran C, Chauhan BF, Asher I. Intermittent inhaled corticosteroid therapy versus placebo for persistent asthma in children and adults. *Cochrane Database Syst Rev* 2015 Jul 22;(7):CD011032. doi(7):CD011032.
- (95) Clemmer G.L., Wu A.C., Rosner B., McGeachie M.J., Litonjua A.A., Tantisira K.G., et al. Measuring the corticosteroid responsiveness endophenotype in asthmatic patients. *J Allergy Clin Immunol* 2015 01 Aug 2015;136(2):274-281.e8.
- (96) Dahl R, Engelstätter R, Trebas-Pietras E, Kuna P. A 24-week comparison of low-dose ciclesonide and fluticasone propionate in mild to moderate asthma. *Respir Med* 2010 Aug;104(8):1121-1130.

- (97) Ducharme FM, Lasserson TJ, Cates CJ. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. *Cochrane Database Syst Rev* 2011 May 11;(5):CD003137. doi(5):CD003137.
- (98) Ebisawa M, Terada A, Sato K, Kurosaka F, Kondo N, Sugizaki C, et al. Intermittent and episode-driven use of pranlukast to reduce the frequency of wheezing in atopic children: a randomized, double-blind, placebo-controlled trial. *World Allergy Organ J* 2015 Apr 2;8(1):11-015-0062-3. eCollection 2015.
- (99) Edmonds M.L., Milan S.J., Camargo Jr. C.A., Pollack C.V., Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane database of systematic reviews (Online)* 2012 2012;12:002308.
- (100) Galant SP, Morpew T, Guijon O, Pham L. The bronchodilator response as a predictor of inhaled corticosteroid responsiveness in asthmatic children with normal baseline spirometry. *Pediatr Pulmonol* 2014;49:1162-1169.
- (101) Hirst C, Castellsague J, Calingaert B, Stanford RH. Asthma exacerbations associated with inhaled corticosteroid/long-acting beta-agonists or other inhaled corticosteroid regimens in pediatrics: Meta-analysis of observational studies. *J Allergy Clin Immunol* 2010;125(2):Suppl 1, AB71; Abstract.
- (102) Hussein HR, Gupta A, Broughton S, Ruiz G, Brathwaite N, Bossley CJ. A meta-analysis of montelukast for recurrent wheeze in preschool children. *Eur J Pediatr* 2017 Jul;176(7):963-969.
- (103) Ismaila A.S., Risebrough N., Li C., Corriveau D., Hawkins N., Mark FJ, et al. COST-effectiveness of salmeterol/fluticasone propionate combination (Advair) in uncontrolled asthma in Canada. *Respir Med* 2014 01 Sep 2014;108(9):1292-1302.
- (104) Jehan N, Rehman MU, Zarkoon MH. To determine the efficacy of inhaled corticosteroids compared to montelukast in reducing exacerbation in uncontrolled asthma in children 6 months to 5 years. *Pakistan Journal of Medical and Health Sciences* 2014;8:662-666.
- (105) Kaiser SV, Huynh T, Bacharier LB, Rosenthal JL, Bakel LA, Parkin PC, et al. Preventing Exacerbations in Preschoolers With Recurrent Wheeze: A Meta-analysis. *Pediatrics* 2016 Jun;137(6):e20154496. doi: 10.1542/peds.2015-4496.
- (106) Klug B, Bisgaard H. Lung function and short-term outcome in young asthmatic children. *Eur Respir J* 1999 Nov;14(5):1185-1189.

- (107) Koster ES, Raaijmakers JA, Vijverberg SJ, Maitland-van der Zee AH. Inhaled corticosteroid adherence in paediatric patients: the PACMAN cohort study. *Pharmacoepidemiol Drug Saf* 2011 Oct;20(10):1064-1072.
- (108) McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database Syst Rev* 2000;(2):CD001107. doi(2):CD001107.
- (109) Miller E, FitzGerald JM. Budesonide/formoterol as maintenance and reliever treatment compared to fixed dose combination strategies - a Canadian economic evaluation. *Canadian Journal of Clinical Pharmacology* 2008;15(2):e165-76.
- (110) Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A, IFWIN study team. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy INfants (IFWIN): double-blind, randomised, controlled study. *Lancet* 2006 Aug 26;368(9537):754-762.
- (111) Nwokoro C, Pandya H, Turner S, Eldridge S, Griffiths CJ, Vulliamy T, et al. 2015 Nov.
- (112) Reijonen TM, Kotaniemi-Syrjänen A, Korhonen K, Korppi M. Predictors of asthma three years after hospital admission for wheezing in infancy. *Pediatrics* 2000 Dec;106(6):1406-1412.
- (113) Sekerel BE, Sackesen C, Tuncer A, Adalioglu G. The effect of nebulized budesonide treatment in children with mild to moderate exacerbations of asthma. *Acta Paediatr* 2005 Oct;94(10):1372-1377.
- (114) Spahn JD, Szefer SJ. Steroid therapy for asthma in children. *Curr Opin Pediatr* 2007 Jun;19(3):300-305.
- (115) Tomerak AA, McGlashan JJ, Vyas HH, McKean MC. Inhaled corticosteroids for non-specific chronic cough in children. *Cochrane Database Syst Rev* 2005 Oct 19;(4):CD004231. doi(4):CD004231.
- (116) Vasilopoulou I, Salavoura K, Laliotou N, Kaditis A, Gemou-Engesaeth V. Definitions of asthma: Do we achieve control of asthma in children in clinical praxis according to how we define asthma? *Allergy: European Journal of Allergy and Clinical Immunology* 2014;69:587-588.
- (117) Wasfi Y., Kemp J.P., Villaran C., Massaad R., Xin W., Smugar S.S., et al. Protection against exercise-induced bronchoconstriction two hours after a single dose of montelukast in children. *Journal of Allergy and Clinical Immunology*.Conference: 2011 American Academy of Allergy, Asthma and Immunology, AAAAI Annual Meeting.San Francisco, CA United States.Conference Publication: (var.pagings) 2011 February 2011;127(2):AB85.
- (118) Watts K, Chavasse RJ. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. *Cochrane Database Syst Rev* 2012 May 16;(5):CD006100. doi(5):CD006100.

- (119) Wolthers OD. Assessment of primary care doctor's diagnosed bronchial asthma in schoolchildren. *Eur Respir J* 2011 European Respiratory Society;38(Suppl 55):p1174.
- (120) Koh YY, Park Y, Kim CK. Maximal airway response in adolescents with long-term asthma remission and persisting airway hypersensitivity: its profile and the effect of inhaled corticosteroids. *Chest* 2002;122:1214-1221.
- (121) Zielen S, Christmann M, Kloska M, Dogan-Yildiz G, Lieb A, Rosewich M, et al. Predicting short term response to antiinflammatory therapy in young children with asthma. *Current medical research and opinion* 2010;26:483-492.
- (122) Anderson S.D., Pearlman D.S., Weiler J.M., Perry C.P., Charlton B. Mannitol and methacholine tests to identify EIB and asthma in children with symptoms but no definite diagnosis: A phase 3 study. *Journal of Allergy and Clinical Immunology*.Conference: 2010 Annual Meeting of the American Academy of Allergy, Asthma and Immunology, AAAAI.New Orleans, LA United States.Conference Publication: (var.pagings) 2010 February 2010;125(2):AB3.
- (123) Andregnette M., FernandezNieto M., Sanchez S., Garcia M., Aguado E., Ibanez M., et al. Comparison of bronchial hyperresponsiveness to methacholine and mannitol in asthmatic children. *Journal of Allergy and Clinical Immunology*.Conference: 2011 American Academy of Allergy, Asthma and Immunology, AAAAI Annual Meeting.San Francisco, CA United States.Conference Publication: (var.pagings) 2011 February 2011;127(2):AB134.
- (124) Bibi H, Montgomery M, Pasterkamp H, Chernick V. Relationship between response to inhaled salbutamol and methacholine bronchial provocation in children with suspected asthma. *Pediatr Pulmonol* 1991;10:244-248.
- (125) Brozek G., Zejda J., Farnik M., WypychSlusarska A., Skoczynski S. Validation of simple and composed screening test of childhood asthma. *European Respiratory Journal* 2016 Respiratory Society Annual Congress;Conference:European.
- (126) Ciprandi G., Capasso M., Tosca M., Salpietro C., Salpietro A., Marseglia G., et al. A forced expiratory flow at 25-75% value >65% of predicted should be considered abnormal: A real-world, cross-sectional study. *Allergy and Asthma Proceedings* 2012 January-February 2012;33(1):e5-e8.
- (127) Del Rio-Navarro BE, Hernandez-Roman M, Espinola Reyna G, Berber A, Escalante-Dominguez A, Gonzalez-Reyes M, et al. A comparative study of bronchodilator reversibility with albuterol, between asthma symptomatic and asymptomatic children according to ISAAC questionnaire in Mexico City. *Allergol Immunopathol* 2004;32:334-339.

- (128) Denboba W., Venn A., Britton J., Davey G. Repeatability and validity of IUATLD Respiratory Questionnaire responses as a measure of asthma in an Ethiopian population. *East Afr Med J* 2008 Dec 2008;85(12):582-588.
- (129) Fang LC, Shyur SD, Wang JY, Kao YH, Yang CH, Yu YT. Exhaled nitric oxide helps discriminating asthmatic children with and without positive specific IgE to aeroallergens. *Asian Pac J Allergy Immunol* 2018 Sep;36(3):145-151.
- (130) Francisco B., Ner Z., Ge B., Hewett J., Konig P. Sensitivity of different spirometric tests for detecting airway obstruction in childhood asthma. *Journal of Asthma* 2015 01 Jun 2015;52(5):505-511.
- (131) Galant SP, Morphew T, Amaro S, Liao O. Value of the bronchodilator response in assessing controller naive asthmatic children. *J Pediatr* 2007;151:457.
- (132) Gerald LB, Grad R, Turner-Henson A, Hains C, Tang S, Feinstein R, et al. Validation of a multistage asthma case-detection procedure for elementary school children. *Pediatrics* 2004 Oct;114(4):e459-68.
- (133) Grzelewski T, Stelmach W, Stelmach R, Janas A, Grzelewska A, Witkowski K, et al. Spirometry-adjusted fraction of exhaled nitric oxide allows asthma diagnosis in children, adolescents, and young adults. *Respir Care* 2016;61:162-172.
- (134) Jerzynska J, Janas A, Galica K, Stelmach W, Woicka-Kolejwa K, Stelmach I. Total specific airway resistance vs spirometry in asthma evaluation in children in a large real-life population. *Annals of Allergy, Asthma and Immunology* 2015;115:272-276.
- (135) Kannisto S, Vanninen E, Remes K, Korppi M. Interrupter technique for evaluation of exercise-induced bronchospasm in children. *Pediatr Pulmonol* 1999;27:203-207.
- (136) Pattemore P.K., Asher M.I., Harrison A.C., Mitchell E.A., Rea H.H., Stewart AW. The interrelationship among bronchial hyperresponsiveness, the diagnosis of asthma, and asthma symptoms. *Am Rev Respir Dis* 1990 1990;142(3):549-554.
- (137) Ratageri VH, Kabra SK, Lodha R, Dwivedi SN, Seth V. Lung function tests in asthma: which indices are better for assessment of severity? *J Trop Pediatr* 2001;47(1):57-59.
- (138) Cavaleiro Rufo J, Paciência I, Mendes FC, Farraia M, Rodolfo A, Silva D, et al. Exhaled breath condensate volatilome allows sensitive diagnosis of persistent asthma. *Allergy* 2019 Mar;74(3):527-534.

- (139) Saada I., Cherif J., Toujani S., Zakhama H., Ouahchi Y., Salah NB, et al. Contribution of lung function tests in asthma screening: About a representative population. European Respiratory Journal 2012 Respiratory Society Annual Congress;Conference:European.
- (140) Smith A.D., Cowan J.O., Filsell S., McLachlan C., MontiSheehan G., Jackson P., et al. Diagnosing Asthma: Comparisons between Exhaled Nitric Oxide Measurements and Conventional Tests. American Journal of Respiratory and Critical Care Medicine 2004 15 Feb 2004;169(4):473-478.
- (141) Sumino K, Sugar EA, Irvin CG, Kaminsky DA, Shade D, Wei CY, et al. Methacholine challenge test: diagnostic characteristics in asthmatic patients receiving controller medications. Journal of Allergy & Clinical Immunology 2012 Jul;130(1):69-75.e6.
- (142) Tavakol M, Gharagozlou M, Afaride M, Movahedi M, Tavakol Z. Asthma diagnosis and treatment-1002. FEF25-75%: a more sensitive indicator in the early detection of asthma. World Allergy Organization Journal 2013;6.
- (143) Viložni D, Hakim F, Livnat G, Ofek M, Bar-Yoseph R, Bentur L. Assessment of Airway Bronchodilation by Spirometry Compared to Airway Obstruction in Young Children with Asthma. Canadian Respiratory Journal 2016;2016:5394876.
- (144) Jerzyńska J, Majak P, Janas A, Stelmach R, Stelmach W, Smejda K, et al. Predictive value of fractional nitric oxide in asthma diagnosis-subgroup analyses. Nitric Oxide 2014 Aug 31;40:87-91.
- (145) Linkosalo L, Lehtimäki L, Holm K, Kaila M, Moilanen E. Relation of bronchial and alveolar nitric oxide to exercise-induced bronchoconstriction in atopic children and adolescents. Pediatr Allergy Immunol 2012 Jun;23(4):360-366.
- (146) Sachs-Olsen C, Lodrup Carlsen KC, Mowinckel P, Haland G, Devulapalli CS, Munthe-Kaas M, et al. Diagnostic value of exhaled nitric oxide in childhood asthma and allergy. Pediatric Allergy & Immunology 2010 Feb;21(1):e213-21.
- (147) Yao T.C., Ou L.S., Lee W.I., Yeh K.W., Chen L.C., Huang J.L. Exhaled nitric oxide discriminates children with and without allergic sensitization in a population-based study. Clinical and Experimental Allergy 2011 April 2011;41(4):556-564.
- (148) Perez Tarazona S, Martinez Camacho RM, Alfonso Diego J, Escolano Serrano S, Talens Gandia J. Diagnostic value of exhaled nitric oxide measurement in mild asthma]. Anales de Pediatría 2011 Nov;75(5):320-328.
- (149) Zhu H, Zhang R, Hao C, Yu X, Tian Z, Yuan Y. Fractional Exhaled Nitric Oxide (FeNO) Combined with Pulmonary Function Parameters Shows Increased Sensitivity and Specificity for the Diagnosis of Cough Variant Asthma in Children. Med Sci Monit 2019 May 23;25:3832-3838.

- (150) An SH, Tian WQ, Li JY. Utility of fractional exhaled nitric oxide in children with asthma. *Zhongguo Dang Dai Er Ke Za Zhi* 2015 Feb;17(2):134-137.
- (151) Ramser M., Hammer J., Amacher A., Trachsel D. The value of exhaled nitric oxide in predicting bronchial hyperresponsiveness in children. *Journal of Asthma* 2008 April 2008;45(3):191-195.
- (152) Avital A., Uwytyed K., Berkman N., Godfrey S., BarYishay E., Springer C. Exhaled nitric oxide and asthma in young children. *Pediatr Pulmonol* 2001 2001;32(4):308-313.
- (153) Pattemore PK, Lampe FC, Smith S, Clough JB, Holgate ST, Johnston SL. Asthma survey items as predictors of respiratory problems in children 2 yrs later: a longitudinal study. *Eur Respir J* 1999 Sep;14(3):650-658.
- (154) Linna OV. Twice-daily peak expiratory flow rate monitoring for the assessment of childhood asthma. *Allergy Proceedings* 1993 Jan-Feb;14(1):33-36.
- (155) Siersted H.C., Hansen H.S., Hansen N.C.G., Hyldebrandt N., Mostgaard G., Oxhøj H. Evaluation of peak expiratory flow variability in an adolescent population sample: The Odense Schoolchild Study. *American Journal of Respiratory and Critical Care Medicine* 1994;149(598-603):ate of Pubaton: Marh 1994.
- (156) Frischer T, Meinert R, Urbanek R, Kuehr J. Variability of peak expiratory flow rate in children: short and long term reproducibility. *Thorax* 1995 Jan;50(1):35-39.
- (157) Ulrik CS, Postma DS, Backer V. Recognition of asthma in adolescents and young adults: which objective measure is best? *J Asthma* 2005 Sep;42(7):549-554.
- (158) Anderson SD, Charlton B, Weiler JM, Nichols S, Spector SL, Pearlman DS, et al. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. *Respir Res* 2009 Jan 23;10:4-9921-10-4.
- (159) Backer V, Bach-Mortensen N, Dirksen A. Prevalence and predictors of bronchial hyperresponsiveness in children aged 7-16 years. *Allergy* 1989 Apr;44(3):214-219.
- (160) Backer V, Ulrik CS, Wendelboe D, Bach-Mortensen N, Hansen KK, Laursen EM, et al. Distribution of serum IgE in children and adolescents aged 7 to 16 years in Copenhagen, in relation to factors of importance. *Allergy* 1992 Oct;47(5):484-489.
- (161) Baumann LM, Romero KM, Robinson CL, Hansel NN, Gilman RH, Hamilton RG, et al. Prevalence and risk factors for allergic rhinitis in two resource-limited settings in Peru with disparate degrees of urbanization. *Clin Exp Allergy* 2015 Jan;45(1):192-199.

- (162) Bråbäck L, Appelberg J, Jansson U, Kälvesten L. Changes in prevalence and severity of asthma among schoolchildren in a Swedish district between 1985 and 1995. *Acta Paediatr* 2000 Apr;89(4):465-470.
- (163) Caillaud D, Horo K, Baiz N, Banerjee S, Charpin D, Lavaud F, et al. Exercise-induced bronchospasm related to different phenotypes of rhinitis without asthma in primary schoolchildren: the French Six Cities Study. *Clin Exp Allergy* 2014 Jun;44(6):858-866.
- (164) Carlsten C, Dimich-Ward H, Becker AB, Ferguson A, Chan HW, DyBuncio A, et al. Indoor allergen exposure, sensitization, and development of asthma in a high-risk birth cohort. *Pediatr Allergy Immunol* 2010 Jun;21(4 Pt 2):e740-6.
- (165) Caudri D, Wijga AH, Hoekstra MO, Kerkhof M, Koppelman GH, Brunekreef B, et al. Prediction of asthma in symptomatic preschool children using exhaled nitric oxide, Rint and specific IgE. *Thorax* 2010 Sep;65(9):801-807.
- (166) Chan EY, Dundas I, Bridge PD, Healy MJ, McKenzie SA. Skin-prick testing as a diagnostic aid for childhood asthma. *Pediatr Pulmonol* 2005 Jun;39(6):558-562.
- (167) Chauveau A, Dalphin ML, Mauny F, Kaulek V, Schmausser-Hechfellner E, Renz H, et al. Skin prick tests and specific IgE in 10-year-old children: Agreement and association with allergic diseases. *Allergy* 2017 Sep;72(9):1365-1373.
- (168) Christiansen ES, Kjaer HF, Eller E, Bindslev-Jensen C, Høst A, Mortz CG, et al. The prevalence of atopic diseases and the patterns of sensitization in adolescence. *Pediatr Allergy Immunol* 2016 Dec;27(8):847-853.
- (169) Cornish R.P., Henderson J., Boyd A.W., Granell R., Van ST, Macleod J. Validating childhood asthma in an epidemiological study using linked electronic patient records. *BMJ Open* 2014;4(4):Arte Number: e005345. ate of Pubaton: 2014.
- (170) Croner S, Kjellman NI. Natural history of bronchial asthma in childhood. A prospective study from birth up to 12-14 years of age. *Allergy* 1992 Apr;47(2 Pt 2):150-157.
- (171) Dalkan C, Galip N, Tekguc H, Cobanoglu N, Bahceciler N. High prevalence of allergy in North Cypriot children. *Paediatr Int Child Health* 2014 Feb;34(1):37-42.
- (172) Drkulec V, Nogalo B, Perica M, Plavec D, Pezer M, Turkalj M. Sensitization profile in differential diagnosis: allergic asthma vs. chronic (nonspecific) cough syndrome. *Med Sci Monit* 2013 May 29;19:409-415.

- (173) Eysink P.E.D., ter RG, Aalberse R.C., van AW, Roos C.M., van der ZJ, et al. Accuracy of specific IgE in the prediction of asthma: Development of a scoring formula for general practice. *British Journal of General Practice* 2005 February 2005;55(511):125-131.
- (174) Franklin PJ, Turner SW, Le Souef PN, Stick SM. Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. *Thorax* 2003;58:1048-1052.
- (175) Frischer T, Kühr J, Meinert R. Asthma screening with a standardized running test. *Pneumologie* 1993 Feb;47(2):84-85.
- (176) Gruchalla RS, Gan V, Roy L, Bokovoy J, McDermott S, Lawrence G, et al. Results of an inner-city school-based asthma and allergy screening pilot study: a combined approach using written questionnaires and step testing. *Ann Allergy Asthma Immunol* 2003 May;90(5):491-499.
- (177) Grzelewska-Rzymowska I, Kowejsza A, Kwiatkowska S. Atopy with recurrent wheezy bronchitis in children. *Pneumonol Alergol Pol* 2001;69(1-2):73-83.
- (178) Hirsch T, Stappenbeck C, Neumeister V, Weiland SK, Von Mutius E, Keil U, et al. Exposure and allergic sensitization to cockroach allergen in East Germany. *Clin Exp Allergy* 2000 Apr;30(4):529-537.
- (179) Lazic N., Roberts G., Custovic A., Belgrave D., Bishop C.M., Winn J., et al. Multiple atopy phenotypes and their associations with asthma: Similar findings from two birth cohorts. *Allergy: European Journal of Allergy and Clinical Immunology* 2013 June 2013;68(6):764-770.
- (180) Lødrup Carlsen KC, Söderström L, Mowinckel P, Håland G, Pettersen M, Munthe Kaas MC, et al. Asthma prediction in school children; the value of combined IgE-antibodies and obstructive airways disease severity score. *Allergy* 2010 Sep;65(9):1134-1140.
- (181) Maloca Vuljanko I, Turkalj M, Nogalo B, Bulat Lokas S, Plavec D. Diagnostic value of a pattern of exhaled breath condensate biomarkers in asthmatic children. *Allergol Immunopathol* 2017 Jan;45(1):2-10.
- (182) Nissen SP, Kjaer HF, Høst A, Nielsen J, Halken S. The natural course of sensitization and allergic diseases from childhood to adulthood. *Pediatr Allergy Immunol* 2013 Sep;24(6):549-555.
- (183) Nolte H, Storm K, Schiøtz PO. Diagnostic value of a glass fibre-based histamine analysis for allergy testing in children. *Allergy* 1990 Apr;45(3):213-223.
- (184) Ong M., Becker A., ChanYeung M., Chan E., Ramsey C. A longitudinal study on the value of the methacholine challenge test as a diagnostic aid for asthma in high-risk adolescents. *American Journal*

of Respiratory and Critical Care Medicine 2013 Thoracic Society International Conference, ATS;Conference:Ameran.

(185) Peat JK, Toelle BG, Salome CM, Woolcock AJ. Predictive nature of bronchial responsiveness and respiratory symptoms in a one year cohort study of Sydney schoolchildren. *European Respiratory Journal* 1993 May;6(5):662-669.

(186) Peat JK, Woolcock AJ. Sensitivity to common allergens: relation to respiratory symptoms and bronchial hyper-responsiveness in children from three different climatic areas of Australia. *Clin Exp Allergy* 1991 Sep;21(5):573-581.

(187) Prosperi MC, Belgrave D, Buchan I, Simpson A, Custovic A. Challenges in interpreting allergen microarrays in relation to clinical symptoms: a machine learning approach. *Pediatr Allergy Immunol* 2014 Feb;25(1):71-79.

(188) Reinhardt D. Reliability of the prick test improves with age. *MMW Fortschr Med* 2015 May 28;157(10):34-015-3127-x.

(189) Rhodes HL, Thomas P, Sporik R, Holgate ST, Cogswell JJ. A birth cohort study of subjects at risk of atopy: twenty-two-year follow-up of wheeze and atopic status. *Am J Respir Crit Care Med* 2002 Jan 15;165(2):176-180.

(190) Ruggieri S, Drago G, Longo V, Colombo P, Balzan M, Bilocca D, et al. Sensitization to dust mite defines different phenotypes of asthma: A multicenter study. *Pediatr Allergy Immunol* 2017 Nov;28(7):675-682.

(191) Sarratud T, Donnanno S, Terracciano L, Trimarco G, Martelli A, Petersson CJ, et al. Accuracy of a point-of-care testing device in children with suspected respiratory allergy. *Allergy Asthma Proc* 2010 Mar-Apr;31(2):e11-7.

(192) Sporik R, Holgate ST, Cogswell JJ. Natural history of asthma in childhood--a birth cohort study. *Arch Dis Child* 1991 Sep;66(9):1050-1053.

(193) Turktas I, Harmanci K, Bakirtas A. Diagnostic accuracy of skin-prick testing in young children with asthma. *Pediatr Pulmonol* 2006 Apr;41(4):386-387.

(194) Weinmayr G, Genuneit J, Nagel G, Björkstén B, van Hage M, Priftanji A, et al. International variations in associations of allergic markers and diseases in children: ISAAC Phase Two. *Allergy* 2010 Jun 1;65(6):766-775.

- (195) Wolthers OD, Staberg M. The usefulness of the multiple allergen simultaneous test-chemiluminescent as compared to the Phadia Immunocap IgE test panel system in children and adolescents. *Recent Pat Inflamm Allergy Drug Discov* 2013 Jan 1;7(1):96-99.
- (196) Andregnette V., Aguado E., Garcia Del PM, FernandezNieto M., Sastre J. Comparison of bronchial hyperresponsiveness to methacholine and mannitol in asthmatic children. *Allergy: European Journal of Allergy and Clinical Immunology*.Conference: 29th Congress of the European Academy of Allergy and Clinical Immunology, EAACI.London United Kingdom.Conference Publication: (var.pagings) 2010 June 2010;65:677.
- (197) Backer V, Ulrik CS. Bronchial responsiveness to exercise in a random sample of 494 children and adolescents from Copenhagen. *Clinical and Experimental Allergy* 1992;22:741-747.
- (198) Backer V, Groth S, Dirksen A, Bach-Mortensen N, Hansen KK, Laursen EM, et al. Sensitivity and specificity of the histamine challenge test for the diagnosis of asthma in an unselected sample of children and adolescents. *European Respiratory Journal* 1991;4:1093-1100.
- (199) Carey VJ, Weiss ST, Tager IB, Leeder SR, Speizer FE. Airways responsiveness, wheeze onset, and recurrent asthma episodes in young adolescents. The East Boston Childhood Respiratory Disease Cohort. *Am J Respir Crit Care Med* 1996 Jan;153(1):356-361.
- (200) Carlsten C, Dimich-Ward H, Ferguson A, Becker A, Dybuncio A, Chan-Yeung M. Airway hyperresponsiveness to methacholine in 7-year-old children: sensitivity and specificity for pediatric allergist-diagnosed asthma. *Pediatr Pulmonol* 2011 Feb;46(2):175-178.
- (201) Deliu M, Belgrave D, Simpson A, Murray CS, Kerry G, Custovic A. Impact of rhinitis on asthma severity in school-age children. *Allergy* 2014 Nov;69(11):1515-1521.
- (202) James A, Ryan G. Testing airway responsiveness using inhaled methacholine or histamine. *Respirology* 1997 Jun;2(2):97-105.
- (203) Koh YY, Kang EK, Min Y, Kim CK. The importance of maximal airway response to methacholine in the prediction of asthma development in patients with allergic rhinitis. *Clinical & Experimental Allergy* 2002 Jun;32(6):921-927.
- (204) Lang A, Carlsen KH, Haaland G, Devulapalli CS, Munthe-Kaas M, Mowinckel P, et al. Severe asthma in childhood: assessed in 10 year olds in a birth cohort study. *Allergy* 2008 Aug;63(8):1054-1060.
- (205) Lee E., Kim Y.H., Han S., Yang S.I., Jung Y.H., Seo J.H., et al. Different cutoff values of methacholine bronchial provocation test depending on age in children with asthma. *World Journal of Pediatrics* 2017 01 Oct 2017;13(5):439-445.

- (206) Levin ME, Muloiwa R, Motala C. Associations between asthma and bronchial hyper-responsiveness with allergy and atopy phenotypes in urban black South African teenagers. *S Afr Med J* 2011 Jun 27;101(7):472-476.
- (207) Liem JJ, Kozyrskyj AL, Cockcroft DW, Becker AB. Diagnosing asthma in children: what is the role for methacholine bronchoprovocation testing? *Pediatr Pulmonol* 2008 May;43(5):481-489.
- (208) Mallol J, Castro-Rodriguez JA, Cortez E, Aguirre V, Aguilar P, Barrueto L. Heightened bronchial hyperresponsiveness in the absence of heightened atopy in children with current wheezing and low income status. *Thorax* 2008 Feb;63(2):167-171.
- (209) Nicolai T., Mutius E.V., Reitmeir P., Wjst M. Reactivity to cold-air hyperventilation in normal and in asthmatic children in a survey of 5,697 schoolchildren in southern Bavaria. *Am Rev Respir Dis* 1993 1993;147(3):565-572.
- (210) van den Nieuwenhof L, Schermer T, Heijdra Y, Bottema B, Akkermans R, Folgering H, et al. Are asymptomatic airway hyperresponsiveness and allergy risk factors for asthma? A longitudinal study. *Eur Respir J* 2008 Jul;32(1):70-76.
- (211) Niggemann B, Illi S, Madloch C, Volkel K, Lau S, Bergmann R, et al. Histamine challenges discriminate between symptomatic and asymptomatic children. MAS-Study Group. Multicentre Allergy Study. *European Respiratory Journal* 2001 Feb;17(2):246-253.
- (212) Porsbjerg C, von Linstow ML, Ulrik CS, Nepper-Christensen S, Backer V. Risk factors for onset of asthma: a 12-year prospective follow-up study. *Chest* 2006 Feb;129(2):309-316.
- (213) Remes S.T., Pekkanen J., Remes K., Salonen R.O., Korppi M. In search of childhood asthma: Questionnaire, tests of bronchial hyperresponsiveness, and clinical evaluation. *Thorax* 2002 2002;57(2):120-126.
- (214) Riiser A., Hovland V., Carlsen K.H., Mowinckel P., Lidorup Carlsen KC. Does bronchial hyperresponsiveness in childhood predict active asthma in adolescence? *American Journal of Respiratory and Critical Care Medicine* 2012 15 Sep 2012;186(6):493-500.
- (215) Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med* 1991 Oct 10;325(15):1067-1071.
- (216) Siersted HC, Mostgaard G, Hyldebrandt N, Hansen HS, Boldsen J, Oxhøj H. Interrelationships between diagnosed asthma, asthma-like symptoms, and abnormal airway behaviour in adolescence: the Odense Schoolchild Study. *Thorax* 1996 May;51(5):503-509.

- (217) Ulrik CS, Backer V. Longitudinal determinants of bronchial responsiveness to inhaled histamine. *Chest* 1998 Apr;113(4):973-979.
- (218) van der Mark LB, van Wonderen KE, Mohrs J, van Aalderen WM, ter Riet G, Bindels PJ. Predicting asthma in preschool children at high risk presenting in primary care: development of a clinical asthma prediction score. *Prim Care Respir J* 2014 Mar;23(1):52-59.
- (219) Vasar M, Bråbäck L, Julge K, Knutsson A, Riikjärv MA, Björkstén B. Prevalence of bronchial hyperreactivity as determined by several methods among Estonian schoolchildren. *Pediatr Allergy Immunol* 1996 Aug;7(3):141-146.
- (220) Wong GW, Li ST, Hui DS, Fok TF, Zhong NS, Chen YZ, et al. Individual allergens as risk factors for asthma and bronchial hyperresponsiveness in Chinese children. *Eur Respir J* 2002 Feb;19(2):288-293.
- (221) Avital A., Springer C., BarYishay E., Godfrey S. Adenosine, methacholine, and exercise challenges in children with asthma or paediatric chronic obstructive pulmonary disease. *Thorax* 1995;50(5):511-516.
- (222) Brannan J.D., Anderson S.D., Perry C.P., FreedMartens R., Lassig A.R., Charlton B., et al. The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: A phase 3 comparison study with hypertonic (4.5%) saline. *Respiratory Research* 2005;6:Arte Number: 144. ate of Pubaton: 09 e 2005.
- (223) Carlsen K.H., Engh G., Mork M., Schroder E. Cold air inhalation and exercise-induced bronchoconstriction in relationship to metacholine bronchial responsiveness: Different patterns in asthmatic children and children with other chronic lung diseases. *Respir Med* 1998 February 1998;92(2):308-315.
- (224) Fuentes C., Contreras S., Padilla O., CastroRodriguez J.A., Moya A., Caussade S. Exercise challenge test: Is a 15% fall in FEV1 sufficient for diagnosis? *Journal of Asthma* 2011 September 2011;48(7):729-735.
- (225) Galdes-Sebaldo M, McLaughlin FJ, Levison H. Comparison of cold air, ultrasonic mist, and methacholine inhalations as tests of bronchial reactivity in normal and asthmatic children. *J Pediatr* 1985 Oct;107(4):526-530.
- (226) Godfrey S., Springer C., BarYishay E., Avital A. Cut-off points defining normal and asthmatic bronchial reactivity to exercise and inhalation challenges in children and young adults. *European Respiratory Journal* 1999 1999;14(3):659-668.

- (227) Jenkins MA, Clarke JR, Carlin JB, Robertson CF, Hopper JL, Dalton MF, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996 Jun;25(3):609-616.
- (228) Joseph CL, Foxman B, Leickly FE, Peterson E, Ownby D. Sensitivity and specificity of asthma definitions and symptoms used in a survey of childhood asthma. *J Asthma* 1999 Oct;36(7):565-573.
- (229) Kussek P., Rosario FN, Cat M. Bronchial hyperresponsiveness to hypertonic saline challenge in children and adolescents. *Jornal Brasileiro de Pneumologia* 2006 2006;32(3):195-201.
- (230) LazoVelasquez J.C., Lozada A.R., Cruz HM. Evaluation of severity of bronchial asthma through an bronchial challenge. *Pediatr Pulmonol* 2005 November 2005;40(5):457-463.
- (231) Lis G, Pietrzyk JJ. Response-dose ratio as an index of bronchial responsiveness to hypertonic saline challenge in an epidemiological survey of asthma in Polish children. *Pediatr Pulmonol* 1998 Jun;25(6):375-382.
- (232) Nja F, Roksund OD, Svidal B, Nystad W, Carlsen KH. Asthma and allergy among schoolchildren in a mountainous, dry, non-polluted area in Norway. *Pediatric Allergy & Immunology* 2000 Feb;11(1):40-48.
- (233) Okupa A.Y., Jackson D.J., Sorkness C.A., Rajamanickam V.P., Kang T.J., Awoyinka I.A., et al. Mannitol bronchoprovocation in the evaluation of airway reactivity in a high-risk pediatric cohort. *Journal of Allergy and Clinical Immunology*.Conference: 2012 Annual Meeting of the American Academy of Allergy, Asthma and Immunology, AAAAI 2012.Orlando, FL United States.Conference Publication: (var.pagings) 2012 February 2012;129(2):AB2.
- (234) Piotrowska T., Siergiejko G., Siergiejko Z. Comparison of sensitivity and specificity of two bronchial provocation tests with methacholine and hypertonic saline in bronchial hyperreactivity evaluation in asthmatics. *Polski Merkuriusz Lekarski* 2007 2007;22(128):126-129.
- (235) SanchezGarcia S., Rodriguez del RP, Escudero C., GarciaFernandez C., Ibanez MD. Exercise-induced bronchospasm diagnosis in children. Utility of combined lung function tests. *Pediatric Allergy and Immunology* 2015 01 Feb 2015;26(1):73-79.
- (236) Smith C.M., Anderson SD. Inhalational challenge using hypertonic saline in asthmatic subjects: A comparison with responses to hyperpnoea, methacholine and water. *European Respiratory Journal* 1990 1990;3(2):144-151.
- (237) Strauch E, Neupert T, Ihorst G, Storm van's Gravesande K, Bohnet W, Hoeldke B, et al. Bronchial hyperresponsiveness to 4.5% hypertonic saline indicates a past history of asthma-like symptoms in children. *Pediatr Pulmonol* 2001 Jan;31(1):44-50.

- (238) Subbarao P., Brannan J.D., Ho B., Anderson S.D., Chan H.K., Coates AL. Inhaled mannitol identifies methacholine-responsive children with active asthma. *Pediatr Pulmonol* 2000 April 2000;29(4):291-298.
- (239) Sverrild A., Porsbjerg C., Backer V. The use of inhaled mannitol in the diagnosis and management of asthma. *Expert Opin Pharmacother* 2012 January 2012;13(1):115-123.
- (240) Ublagger E, Schreuer M, Eder W, von Mutius E, Benz MR, Braun-Fahrlander C, et al. Validation of questions on asthma and wheeze in farming and anthroposophic children. *Clinical & Experimental Allergy* 2005 Aug;35(8):1033-1039.
- (241) West J.V., Robertson C.F., Roberts R., Olinsky A. Evaluation of bronchial responsiveness to exercise in children as an objective measure of asthma in epidemiological surveys. *Thorax* 1996 1996;51(6):590-595.
- (242) Yanuar M., Mustofa J., Fitriani F., Yunus F., Wiyono WH. Prevalence of asthma in a group of 13- to 14-year-old students using the ISAAC written questionnaire, bronchial provocation test and peak flow rate in central Jakarta. *Respirology.Conference: 14th Congress of the APSR and 3rd Joint Congress of the APSR/ACCP.Seoul South Korea.Conference Publication: (var.pagings)* 2009 November 2009;14:A241.