

Asthma

Asthma: diagnosis and monitoring of asthma in adults, children and young people

Clinical Guideline

Appendices A - P

January 2015

Draft for Consultation

*Commissioned by the National Institute for
Health and Care Excellence*

Disclaimer

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1 **Appendices**

2 **Appendix A: Scope**

FINAL SCOPE

**NATIONAL INSTITUTE FOR HEALTH AND
CARE EXCELLENCE**

SCOPE

1 Guideline title

Asthma: diagnosis and monitoring of asthma in adults, children and young people

1.1 Short title

Asthma: diagnosis and monitoring

2 The remit

The Department of Health has asked NICE: 'to prepare a guideline on the diagnosis and management of asthma'.

3 Clinical need for the guideline

3.1 Epidemiology

- a) Asthma is a chronic inflammatory respiratory disease that can affect people of any age but often starts in childhood. It is characterised by attacks of breathlessness and wheezing, with the severity and frequency of attacks varying from person to person. The attacks are associated with variable airflow obstruction within the lung, which is often reversible with or without treatment.
- b) The World Health Organization estimates that worldwide 235 million people suffer from asthma and that it is the most common chronic condition affecting children. In the UK 5.4 million people are receiving treatment for asthma, including 1.1 million children.
- c) Studies of adults diagnosed with asthma suggest that up to 30% do not have clear evidence of asthma. Some may have had asthma in

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the past, but it is likely that many have been given an incorrect diagnosis.

- d) The causes of asthma are not well understood. A combination of risk factors is associated with the condition. Risk factors include both genetic (the condition clusters in families) and environmental (such as inhalation of allergens or chemical irritants) influences. Occupational causes of asthma in adults are often unrecognised.

3.2 Current practice

- a) Asthma is diagnosed principally on the basis of a careful history taken by an experienced clinician. Initial clinical assessment includes questions about symptoms (wheezing, cough, breathing and chest problems) and any personal or family history of allergies, atopic disorders or asthma. Various tests can be used to support a diagnosis, but there is no single test that serves as a gold standard.
- b) A number of methods and assessments are available to determine the likelihood of asthma. These include measures of airflow obstruction (spirometry and peak flow) and measures of reversibility with bronchodilators, both of which are widely used in current practice. However, normal results do not exclude asthma and abnormal results could be indicators of other respiratory diseases.
- c) Testing for airway inflammation is increasingly used as a diagnostic strategy in clinical practice. This includes measuring sputum eosinophil counts and fractional exhaled nitric oxide (FeNO). However, there is some uncertainty about both the sensitivity and specificity of FeNO, particularly whether it can distinguish general atopy from asthma.
- d) Other diagnostic strategies include blood or skin prick tests to detect allergic reactions to environmental influences, exercise tests to detect evidence of bronchoconstriction, and measures of airway

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hyper-reactivity, such as histamine/methacholine PC20 and mannitol challenge. However, it is debatable which test or measure, or combination- of them, is the most effective to accurately diagnose asthma.

- e) It is recognised that asthma control is suboptimal in many people with asthma. This has an impact on their quality of life, their use of healthcare services and the associated costs. Asthma control can be monitored by measuring airway inflammation and by using validated questionnaires, but the most effective monitoring strategy is uncertain.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider.

It is based on the referral from the Department of Health, but now covers the diagnosis and monitoring of asthma and excludes other aspects of management. This is because there is evidence that incorrect diagnosis is a significant problem whereas management of correctly diagnosed asthma is straightforward in most cases. Also, NICE technology appraisal guidance covers some of the available asthma therapies. In the future NICE will consider whether further guidance on asthma covering the aspects omitted from the current scope is needed.

The areas that will be addressed by the current guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

- a) Adults, children and young people who are being investigated for suspected asthma, or who have been diagnosed with asthma and are having their condition monitored.
- b) Specific consideration will be given to subgroups based on age, broadly divided into younger children, older children, and older people (aged over 75 years).

4.2 Healthcare setting

- a) Primary, secondary and community care settings in which NHS-funded care is provided.

4.3 Diagnosis and monitoring

4.3.1 Key clinical issues that will be covered

Diagnosis

Initial clinical assessment

- a) The value of specific signs and symptoms in making a diagnosis of asthma. For example, wheezing, cough, breathlessness and other respiratory symptoms including diurnal and seasonal variations; symptoms in response to exercise; and symptoms after taking drugs such as aspirin, other non-steroidal anti-inflammatory drugs and beta-blockers.
- b) The value of a family or personal history of atopic disorders in making a diagnosis of asthma.
- c) Case identification of occupational asthma.

Objective tests

The value of the following tests in making a diagnosis of asthma:

- d) Measures of lung function and airway obstruction including spirometry/flow volume loop, peak expiratory flow (PEF) variability,

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bronchodilator response (using PEF or forced expiratory volume in 1 second), and measures of airway hyper-reactivity, such as histamine/methacholine PC20 and mannitol challenge.

- e) Biomarkers of airway inflammation and allergy: skin tests for the common aero-allergens, serum total IgE, peripheral blood eosinophil count and FeNO.
- f) Measures of exercise-induced bronchoconstriction.

Monitoring

- g) Assessment of asthma control using self- or parental reports such as symptom scores or diaries, and validated asthma control questionnaires such as the asthma control test (ACT), the children's asthma control test (CACT), the asthma control questionnaire-7 (ACQ-7), and the Royal College of Physicians 3 (RCP3) questions.
- h) Use of tele-healthcare as a route for assessment.
- i) Monitoring adherence.
- j) Inhaler technique.
- k) Assessment of asthma control using tests such as measures of pulmonary function (for example, spirometry and peak expiratory flow meters) and measures of airway hyper-reactivity.
- l) Assessments of asthma control using tests or measures such as FeNO.

4.3.2 Clinical issues that will not be covered

- a) Tertiary care setting.
- b) Severe, difficult to control asthma.
- c) Sputum cell counts.

- d) Treating asthma.

4.4 Main outcomes

- a) Objective response to treatment.
- b) Accuracy of diagnostic tests.
- c) Frequency of asthma attacks.
- d) Need for oral corticosteroids and short-acting beta-agonists.
- e) Unscheduled use of healthcare services.
- f) Health-related quality of life.
- g) Time off school or work.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.6 Status

4.6.1 Scope

This is the final version of the scope.

4.6.2 Timing

The development of the guideline recommendations will begin in August 2013.

5 Related NICE guidance

5.1 *Published guidance and quality standards*

- [Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 and over and adults](#) (review of TA133 and TA201) NICE technology appraisal guidance TA278 (2013).
- [Quality standard for asthma](#). NICE quality standard 25 (2013).
- [Bronchial thermoplasty for severe asthma](#). NICE interventional procedure guidance 419 (2012).
- [Roflumilast for the management of severe chronic obstructive pulmonary disease](#). NICE technology appraisal guidance 244 (2012).
- [Chronic obstructive pulmonary disease \(updated\)](#). NICE clinical guideline 101 (2009).
- [Respiratory tract infections](#). NICE clinical guideline 69 (2008).
- [Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over](#). NICE technology appraisal guidance 138 (2008).
- [Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years](#). NICE technology appraisal guidance 131 (2007).
- [Inhaler devices for routine treatment of chronic asthma in older children \(aged 5–15 years\)](#). NICE technology appraisal guidance 38 (2002).
- [Guidance on the use of inhaler systems \(devices\) in children under the age of 5 years with chronic asthma](#). NICE technology appraisal guidance 10 (2000).

5.2 *Guidance under development*

NICE is currently developing the following related guidance (details available from the NICE website).

- Measuring fractional exhaled nitric oxide concentration in asthma – NIOX MINO, NIOX VERO and NObreath. NICE diagnostic assessment programme. Publication expected April 2014.

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- Bronchiolitis: diagnosis and management of bronchiolitis in children. NICE clinical guideline. Publication expected April 2015.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS
- [The guidelines manual](#).

Information on the progress of the guideline will also be available from the [NICE website](#).

Appendix B: Declarations of interest

The 2007 version of the NICE code of practice for declaring and dealing with conflicts of interest policy was applied to this guideline.

Andrew Menzies-Gow (GDG Chair)

Date	Item declared	Classification	Action taken
GDG1 (29.7.13)	Received payment for attending advisory boards for Roche, NAPP, Boehringer Ingelheim and Novartis. Received lecture fees for presenting and chairing education meetings from Novartis, Glaxo SmithKline and NAPP. Royal Brompton and Harefield NHS Foundation Trust has received payment for participation in phase II and III studies on severe asthma where I am the principal investigator from Glaxo SmithKline, Novartis and Roche. I hold one current grant from Asthma UK. Member of the BTS severe asthma network and BTS asthma SAG. I have resigned my position on the BTS/SIGN asthma guidelines.	Non-specific personal pecuniary Non-specific non-personal pecuniary – (monitoring questionnaires review) ACT and CACT developed by GSK but both are freely available (non-profit making). Personal non-pecuniary	Declare and participate Declare and participate Declare and participate
GDG2 (3.9.13)	Payment for advisory board attendance for Amgen who are trialling a novel monoclonal antibody for use in severe asthma, October 2013.	Non-specific personal pecuniary	Declare and participate
GDG3 (8.10.13)	No change to existing declarations.	n/a	n/a
GDG4 (19.11.13)	No change to existing declarations.	n/a	n/a
GDG5&6 (27.1.14 & 28.1.14)	Attending advisory boards for Roche on Lebrikizumab in severe asthma, January and February 2014.	Non-specific personal pecuniary	Declare and participate
GDG7 (3.3.14)	Presenting on specialist commissioning of severe asthma at 4 meetings for	Non-specific personal pecuniary	Declare and participate

Date	Item declared	Classification	Action taken
	Novartis. Presenting at 2 meetings in Denmark on severe asthma for Novartis. Attending Gulf Thoracic Society in UAE, sponsored by Novartis.		
GDG8 (8.4.14)	No change to existing declarations.	n/a	n/a
GDG9 (13.5.14)	Two presentations to primary care on the use of Flutiform in asthma, sponsored by NAPP. One presentation on specialist commissioning of severe asthma services sponsored by Novartis.	Non-specific personal pecuniary	Declare and participate
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a
GDG11 (22.7.14)	I have attended one advisory board for Boehringer Ingelheim discussing the use of Tiotropium in severe asthma.	Non-specific personal pecuniary	Declare and participate
	I have received lecture fees from NAPP for talking about the use of Flutiform in asthma.	Non-specific personal pecuniary	
	I have received lecture fees from Glaxo SmithKline for talking about Real Life clinical trials and the Salford Lung Study	Non-specific personal pecuniary	
	I have received lecture fees from Chiesi for talking about the Management of Severe Asthma	Non-specific personal pecuniary	
GDG12 (2.9.14)	Filming for Boehringer Ingelheim on the use of Tiotropium in severe asthma.	Non-specific personal pecuniary	Declare and participate
GDG13 (7.10.14)	Lecture fees for a presentation on severe asthma for Boehringer Ingelheim	Non-specific personal pecuniary	Declare and participate
	Lecture fees for a pro con debate on severe asthma for Novartis		
	Lecture fees for a presentation on treatment options for severe asthma and severe asthma workshop for severe asthma for Boehringer-Ingelheim		
GDG14 (30.3.15)			

John Alexander

Date	Item declared	Classification	Action taken
GDG1 (29.7.13)	None	n/a	n/a
GDG2 (3.9.13)	No change to existing declarations.	n/a	n/a
GDG3 (8.10.13)	No change to existing declarations.	n/a	n/a
GDG4 (19.11.13)	No change to existing declarations.	n/a	n/a
GDG5&6 (27.1.14 & 28.1.14)	Received lecture fee from GSK for lecture to GPs.	Non-specific personal pecuniary – (monitoring questionnaires review) ACT and CACT developed by GSK but both are freely available (non-profit making).	Declare and participate
GDG7 (3.3.14)	No change to existing declarations.	n/a	n/a
GDG8 (8.4.14)	No change to existing declarations.	n/a	n/a
GDG9 (13.5.14)	No change to existing declarations.	n/a	n/a
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a
GDG11 (22.7.14)	Paid lecture on RSV for Abbvie.	Non-specific personal pecuniary	Declare and participate
	Paid advisory board on preventing RSV admissions by Abbvie.	Non-specific personal pecuniary	
GDG12 (2.9.14)	No change to existing declarations.	n/a	n/a
GDG13 (7.10.14)	No change to existing declarations.	n/a	n/a
GDG14 (30.3.15)			

Tara Burn

Date	Item declared	Classification	Action taken
GDG1 (29.7.13)	None	n/a	n/a
GDG2 (3.9.13)	No change to existing declarations.	n/a	n/a
GDG3 (8.10.13)	No change to existing declarations.	n/a	n/a
GDG4 (19.11.13)	No change to existing declarations.	n/a	n/a

Date	Item declared	Classification	Action taken
GDG5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GDG7 (3.3.14)	No change to existing declarations.	n/a	n/a
GDG8 (8.4.14)	No change to existing declarations.	n/a	n/a
GDG9 (13.5.14)	No change to existing declarations.	n/a	n/a
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a
GDG11 (22.7.14)	No change to existing declarations.	n/a	n/a
GDG12 (2.9.14)	No change to existing declarations.	n/a	n/a
GDG13 (7.10.14)	No change to existing declarations.	n/a	n/a
GDG14 (30.3.15)			

Erol Gaillard

Date	Item declared	Classification	Action taken
GDG1 (29.7.13)	One research grant for £3000 from Novartis.	Non-personal pecuniary	Declare and participate
	Newly appointed member to the SIGN/BTS Asthma Guideline Development Group.	Personal non-pecuniary	
GDG2 (3.9.13)	No change to existing declarations.	n/a	n/a
GDG3 (8.10.13)	No change to existing declarations.	n/a	n/a
GDG4 (19.11.13)	No change to existing declarations.	n/a	n/a
GDG5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GDG7 (3.3.14)	I have a research collaboration with MedImmune a biotech firm with links to AstraZeneca. No direct payments to either me or my research group.	Personal non-pecuniary	Declare and participate
	I am a member to the SIGN/BTS Asthma Guideline Development Group.	Personal non-pecuniary	

Date	Item declared	Classification	Action taken
GDG8 (8.4.14)	No change to existing declarations.	n/a	n/a
GDG9 (13.5.14)	No change to existing declarations.	n/a	n/a
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a
GDG11 (22.7.14)	No change to existing declarations.	n/a	n/a
GDG12 (2.9.14)	No change to existing declarations.	n/a	n/a
GDG13 (7.10.14)	No change to existing declarations.	n/a	n/a
GDG14 (30.3.15)			

Ren Gilmartin

Date	Item declared	Classification	Action taken
GDG1 (29.7.13)	<p>Paid honoraria by Teva for position on “Integrated Care advisory board” May 2013.</p> <p>Paid honoraria by British Lung Foundation for development of “Train the Trainer COPD and Self Management” programme May / June 2013.</p> <p>PCRS-UK executive and PCRS-UK Nurse committee and receive Loss of Earnings payment plus travel expenses.</p>	Non-specific personal pecuniary	Declare and participate
	<p>Pending fee from British Lung Foundation for providing COPD training to GPs and Nurses in Hertfordshire.</p> <p>Honoraria received from TEVA for attending advisory meeting.</p> <p>Honoraria received from Almirall for attending nurse group meeting.</p> <p>Pending fee from RTA training for asthma update presentation for school nurses.</p>	Non-specific personal pecuniary	Declare and participate
GDG2 (3.9.13)	No change to existing declarations.	n/a	n/a
GDG3 (8.10.13)	No change to existing declarations.	n/a	n/a

Date	Item declared	Classification	Action taken
GDG4 (19.11.13)	No change to existing declarations.	n/a	n/a
GDG5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GDG7 (3.3.14)	No change to existing declarations.	n/a	n/a
GDG8 (8.4.14)	No change to existing declarations.	n/a	n/a
GDG9 (13.5.14)	No change to existing declarations.	n/a	n/a
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a
GDG11 (22.7.14)	No change to existing declarations.	n/a	n/a
GDG12 (2.9.14)	No change to existing declarations.	n/a	n/a
GDG13 (7.10.14)	No change to existing declarations.	n/a	n/a
GDG14 (30.3.15)			

Val Hudson

Date	Item declared	Classification	Action taken
GDG1 (29.7.13)	None	n/a	n/a
GDG2 (3.9.13)	Last year my husband was commissioned by North Durham Clinical Commissioning Group (in shadow form) to carry out a piece of work on developing public and patient involvement in the CCG. This has now finished.	Personal family interest	Declare and participate
GDG3 (8.10.13)	No change to existing declarations.	n/a	n/a
GDG4 (19.11.13)	No change to existing declarations.	n/a	n/a
GDG5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GDG7 (3.3.14)	No change to existing declarations.	n/a	n/a
GDG8 (8.4.14)	On the 2nd April I attended a Boehringer Ingelheim training event for their medical and marketing staff in Berlin. The company wanted their staff to understand what it was like for someone 'living with asthma.' I was interviewed by a GP and we both then fielded questions from the audience. The session lasted one hour. I received accommodation and travel expenses but no other	Reasonable travel expenses	Declare and participate

Date	Item declared	Classification	Action taken
	reimbursements		
GDG9 (13.5.14)	No change to existing declarations.	n/a	n/a
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a
GDG11 (22.7.14)	No change to existing declarations.	n/a	n/a
GDG12 (2.9.14)	No change to existing declarations.	n/a	n/a
GDG13 (7.10.14)	No change to existing declarations.	n/a	n/a
GDG14 (30.3.15)			

Angela Key

Date	Item declared	Classification	Action taken
GDG1 (29.7.13)	None	n/a	n/a
GDG2 (3.9.13)	No change to existing declarations.	n/a	n/a
GDG3 (8.10.13)	No change to existing declarations.	n/a	n/a
GDG4 (19.11.13)	No change to existing declarations.	n/a	n/a
GDG5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GDG7 (3.3.14)	No change to existing declarations.	n/a	n/a
GDG8 (8.4.14)	No change to existing declarations.	n/a	n/a
GDG9 (13.5.14)	No change to existing declarations.	n/a	n/a
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a
GDG11 (22.7.14)	No change to existing declarations.	n/a	n/a
GDG12 (2.9.14)	No change to existing declarations.	n/a	n/a
GDG13 (7.10.14)	No change to existing declarations.	n/a	n/a
GDG14 (30.3.15)			

Matthew Masoli

Date	Item declared	Classification	Action taken
GDG1 (29.7.13)	None	n/a	n/a
GDG2 (3.9.13)	I have received support from GSK to attend the EACCI conference in Milan (June 2013) and with Novartis for the ERS annual conference (Sept 2012). Support included registration and accommodation. In June 2013 I was paid by GSK to do a talk on 'asthma control' as part of an allergy study day for GP's and practice nurses.	Non-specific personal pecuniary – (monitoring questionnaires review) ACT and CACT developed by GSK but both are freely available (non-profit making).	Declare and participate
GDG3 (8.10.13)	No change to existing declarations.	n/a	n/a
GDG4 (19.11.13)	No change to existing declarations.	n/a	n/a
GDG5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GDG7 (3.3.14)	No change to existing declarations.	n/a	n/a
GDG8 (8.4.14)	Speaker fee for an educational talk and workshop to healthcare professionals on 'reducing emergency asthma admissions' for a severe asthma study day sponsored by Novartis. March 2014.	Non-specific personal pecuniary	Declare and participate
GDG9 (13.5.14)	Spoken presentation at a severe asthma symposium sponsored by Novartis in March 2014.	Non-specific personal pecuniary	Declare and participate
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a
GDG11 (22.7.14)	No change to existing declarations.	n/a	n/a
GDG12 (2.9.14)	No change to existing declarations.	n/a	n/a
GDG13 (7.10.14)	No change to existing declarations.	n/a	n/a
GDG14 (30.3.15)			

Melanie McFeeters

Date	Item declared	Classification	Action taken
GDG1 (29.7.13)	I have received speaker fees, expenses and hospitality from the pharmaceutical industry for both speaking & attending meetings that have taken place in the last	Non-specific personal pecuniary – (monitoring questionnaires	Declare and participate

Date	Item declared	Classification	Action taken
	<p>12 months and which are planned but have not taken place yet. This includes receiving fees for presenting educational talks to other Healthcare Professionals and hospitality for attending meetings and conferences related to the diagnosis and management of asthma. The companies include Abbott, Abbvie, AstraZeneca, GlaxoSmithKline, Novartis, Roche & Schering Plough.</p> <p>Member of the British Thoracic Society (BTS) and committee member of the BTS Nurse Advisory Group.</p> <p>Member of the BTS/SIGN 101 British Guideline on the Management of Asthma Guideline Development Group – Organisation and Delivery of Care.</p> <p>RCN Member.</p>	<p>review) ACT and CACT developed by GSK but both are freely available (non-profit making).</p> <p>Personal non-pecuniary</p>	
GDG2 (3.9.13)	No change to existing declarations.	n/a	n/a
GDG3 (8.10.13)	No change to existing declarations.	n/a	n/a
GDG4 (19.11.13)	No change to existing declarations.	n/a	n/a
GDG5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GDG7 (3.3.14)	<p>Speaker fee received for educational talk to Healthcare Professionals (GP & PN's) on 30/1/14. Meeting sponsored by GSK. Talk presented - Asthma management in children.</p> <p>Steering committee/Advisory board meeting attended on 3/2/14 for AbbVie in preparation for the EMBRACE 2014 meeting – Prophylaxis for RSV.</p>	Non-specific personal pecuniary	Declare and participate
GDG8 (8.4.14)	No change to existing declarations.	n/a	n/a
GDG9 (13.5.14)	No change to existing declarations.	n/a	n/a
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a
GDG11 (22.7.14)	No change to existing declarations.	n/a	n/a
GDG12 (2.9.14)	No change to existing declarations.	n/a	n/a
GDG13 (7.10.14)	No change to existing declarations.	n/a	n/a
GDG14 (30.3.15)			

Tahmina Siddiqui

Date	Item declared	Classification	Action taken
GDG1 (29.7.13)	None	n/a	n/a
GDG2 (3.9.13)	Member of iCOPD template development group in conjunction with PCRS UK, funded by Kendle Healthcare. Attended ERS in September 2102, also to attend a iCOPD meeting funded by Kendle Healthcare. Lead GP for COPD in Milton Keynes. Long term intervention team (LIT) chairperson Milton Keynes.	Non-specific personal non-pecuniary Non-specific personal pecuniary Non-specific personal non-pecuniary	Declare and participate
GDG3 (8.10.13)	No change to existing declarations.	n/a	n/a
GDG4 (19.11.13)	Chaired a GP study day COPD Master class on September 2013 sponsored by Almirral. Attended 1 st COPD world Summit conference in Lisbon Sponsored by Almirral.	Non-specific personal pecuniary	Declare and participate
GDG5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GDG7 (3.3.14)	No change to existing declarations.	n/a	n/a
GDG8 (8.4.14)	No change to existing declarations.	n/a	n/a
GDG9 (13.5.14)	No change to existing declarations.	n/a	n/a
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a
GDG11 (22.7.14)	No change to existing declarations.	n/a	n/a
GDG12 (2.9.14)	No change to existing declarations.	n/a	n/a
GDG13 (7.10.14)	No change to existing declarations.	n/a	n/a
GDG14 (30.3.15)			

Mike Thomas

Date	Item declared	Classification	Action taken
GDG1 (29.7.13)	<p>I have received honoraria for attending advisory panels from the following companies manufacturing respiratory products in the last 12 months: GlaxoSmithKline Almirall Novartis.</p> <p>I received sponsorship to attend the European Respiratory Society meeting from Napp (standard travel and hotel).</p> <p>I have a research study funded by GSK.</p>	<p>Non-specific personal pecuniary – (monitoring questionnaires review) ACT and CACT developed by GSK but both are freely available (non-profit making).</p> <p>Non-specific non-personal pecuniary</p>	<p>Declare and participate</p>
	<p>I received an honorarium for speaking at the ERS at the Aerocrine sponsored symposium.</p>	<p>Specific personal pecuniary</p>	<p>Declare and withdraw for FeNO</p>
	<p>In the last 3 years I have received speaker’s honoraria for speaking at sponsored meetings from the following companies marketing respiratory and allergy products: Aerocrine, Astra Zeneca, Boehringer Ingelheim, GSK, MSD, Napp, Schering-Plough, Teva.</p> <p>I have received honoraria for attending advisory panels with; Aerocrine, Almirall, Astra Zeneca, BI, Chiesi, GSK, MSD, Merck Respiratory, Schering-Plough, Teva, Novartis.</p> <p>I have received sponsorship to attend international scientific meetings from: GSK, MSD, Astra Zeneca, Mundipharma.</p> <p>I have received funding for research projects from: GSK, Almirall.</p> <p>I am chief medical adviser to the charity Asthma UK, a member of the BTS SIGN Asthma guideline group. I am a member of the EPOS Rhinosinusitis guideline</p>	<p>Specific personal pecuniary</p> <p>Non-specific non-personal pecuniary</p> <p>Personal non-pecuniary</p>	<p>Declare and withdraw for FeNO</p>

Date	Item declared	Classification	Action taken
	group. I have spoken at the ERS on the use of exhaled nitric oxide in the diagnosis and management of asthma and spoke to the NICE team on this topic as an expert witness.		
	My department has received an honorarium for me speaking at the ERS at the Aerocrine sponsored symposium and my department has received honoraria for me attending an advisory board and for giving a talk at a GP educational meeting. My department has received honoraria for producing a research study protocol for Novartis.	Specific non-personal pecuniary interest Non-specific non-personal pecuniary	Declare and withdraw for FeNO and the HE model but can answer questions on request by the Chair.
GDG2 (3.9.13)	No change to existing declarations.	n/a	n/a
GDG3 (8.10.13)	No change to existing declarations.	n/a	n/a
GDG4 (19.11.13)	No change to existing declarations.	n/a	n/a
GDG5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GDG7 (3.3.14)	No change to existing declarations.	n/a	n/a
GDG8 (8.4.14)	No change to existing declarations.	n/a	n/a
GDG9 (13.5.14)	No change to existing declarations.	n/a	n/a
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a
GDG11 (22.7.14)	My department has received an honorarium from Aerocrine (makers of a FENO monitor) for my attendance at an advisory meeting to discuss research needs in the FENO evidence and we are discussing a possible Horizon 2020 grant application for a multinational collaborative EU-Industry funded project. In addition, my department has received funding from GSK as I am the Chief Investigator and chair of the steering committee of an international study investigating inhaler device errors.	Specific non-personal pecuniary interest Non-specific non-personal pecuniary	Declare and withdraw for FeNO and the HE model but can answer questions on request by the Chair.

Date	Item declared	Classification	Action taken
	I have received an honorarium from Boehringer Ingelheim for attendance at a meeting organising a collaborative project with the University of Nottingham/PRIMIS to create an asthma electronic audit tool for use in general practice, and from Novartis for speaking at meeting on COPD.	Non-specific personal pecuniary	
GDG12 (2.9.14)	No change to existing declarations.	n/a	n/a
GDG13 (7.10.14)	No change to existing declarations.	n/a	n/a
GDG14 (30.3.15)			

NCGC team

Date	Item declared	Classification	Action taken
GDG1 (29.7.13)	In receipt of NICE commissions.	n/a	n/a
GDG2 (3.9.13)	No change to existing declarations.	n/a	n/a
GDG3 (8.10.13)	No change to existing declarations.	n/a	n/a
GDG4 (19.11.13)	No change to existing declarations.	n/a	n/a
GDG5&6 (27.1.14 & 28.1.14)	No change to existing declarations.	n/a	n/a
GDG7 (3.3.14)	No change to existing declarations.	n/a	n/a
GDG8 (8.4.14)	No change to existing declarations.	n/a	n/a
GDG9 (13.5.14)	No change to existing declarations.	n/a	n/a
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a
GDG11 (22.7.14)	No change to existing declarations.	n/a	n/a
GDG12 (2.9.14)	No change to existing declarations.	n/a	n/a
GDG13 (7.10.14)	No change to existing declarations.	n/a	n/a
GDG14 (30.3.15)			

Cochrane team

Date	Item declared	Classification	Action taken
Initial declaration (Dec 13)	None	n/a	n/a
GDG10 (16.6.14)	No change to existing declarations.	n/a	n/a

NIHR team

Date	Item declared	Classification	Action taken
Initial declaration (May 14)	None	n/a	n/a
GDG12 (2.9.14)	No change to existing declarations.	n/a	n/a

1 Appendix C: Review protocols

2 C.1 Diagnosis: Signs and symptoms

3 **Table 1: Review protocol: Signs and symptoms for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic accuracy of each of the following signs and symptoms? <ul style="list-style-type: none"> • wheezing • cough • breathlessness • nocturnal symptoms • diurnal and seasonal variations
Objectives	To evaluate the diagnostic accuracy of signs and symptoms in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups: <ul style="list-style-type: none"> • Children (1-<5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Signs and symptoms of asthma Each of the following symptoms alone or in combination: <ul style="list-style-type: none"> • Wheezing (current or persistent or triggered) • Cough (including nocturnal cough) • Breathlessness • Nocturnal symptoms • Diurnal and seasonal variations
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: <ul style="list-style-type: none"> • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p>

	In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.
Outcomes	<ul style="list-style-type: none"> Diagnostic accuracy (sensitivity and specificity)
Other exclusions	<ul style="list-style-type: none"> Not looking at occupational asthma /allergens Not looking at factors which influence signs/symptoms Due to anticipation of there being a large amount of studies retrieved from the search, the inclusion criteria was limited to studies which only look at populations in the UK, USA, Australia, Canada, New Zealand and Western Europe*. These countries were expected to be similar to the UK in terms of how people report symptoms and the impact of language. If relevant studies were identified from other review questions reporting populations outside these countries then these were included. *Western Europe = Austria, Belgium, France, Germany, Liechtenstein, Luxembourg, Monaco, Netherlands, Switzerland
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<ul style="list-style-type: none"> Different test thresholds Different reference standards Combinations of symptoms

1 C.2 Diagnosis: History of atopic disorders

2 **Table 2: Review protocol: History of atopic disorders for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic accuracy of taking a personal/family history of atopic disorders?
Objectives	To evaluate the diagnostic test value of taking a personal/family history of atopic disorders in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	<p>People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups:</p> <ul style="list-style-type: none"> Children (1-<5 years old) Children/young people (5-16 years old) Adults (>16 years old)
Setting	Primary, secondary and community care settings

<p>Index test</p>	<p>Personal/family history of atopic disorders.</p> <ul style="list-style-type: none"> This is likely to be ascertained by a questionnaire. <p>NOTE: personal history is defined as an individual who has had one of the atopic disorders listed below</p> <p>NOTE: family history is defined as: 1st degree relatives.</p> <p>NOTE: atopic disorders are defined as: eczema, hay fever, allergic rhinitis, food allergy, asthma.</p>
<p>Reference standard</p>	<p>Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following:</p> <ul style="list-style-type: none"> peak flow variability (cut-off value of more than 20% variability as indication of a positive test); bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p> <p>In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.</p>
<p>Outcomes</p>	<ul style="list-style-type: none"> Diagnostic accuracy (sensitivity and specificity)
<p>Other exclusions</p>	<ul style="list-style-type: none"> Not looking at occupational asthma /allergens Not looking at other factors which influence this
<p>Search Strategy</p>	<p>The database to be searched are Medline, Embase, The Cochrane Library</p>
<p>Review Strategy</p>	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) Move to GDG consensus
<p>Analysis-subgroups to investigate heterogeneity</p>	<ul style="list-style-type: none"> Different reference standards

1 C.3 Diagnosis: Symptoms after exercise

2 **Table 3: Review protocol: Symptoms after exercise for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic accuracy of a clinical history of symptoms in response to exercise?
Objectives	To evaluate the diagnostic test value of taking a clinical history of symptoms in response to exercise in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups: <ul style="list-style-type: none"> • Children (1- <5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Clinical history of symptoms in response to exercise. NOTE: symptoms would be a combination of the following, or individual symptoms – wheezing, cough, breathlessness
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: <ul style="list-style-type: none"> • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p> <p>In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.</p>
Statistical measures	Diagnostic accuracy (sensitivity, specificity)
Other exclusions	<ul style="list-style-type: none"> • Not occupational asthma /allergens • Not looking at other factors which influence signs/symptoms (this includes seasonal variation) • Not looking at tests in athletes or professional / specialist sports • Not looking at validation studies, or studies comparing different methods of measuring clinical history of symptoms after exercise.

	Not looking at 'case-control' type studies where the index test is applied in people with confirmed asthma and healthy controls, and where there is no uncertainty about whether the patient has asthma or not. Such studies only include a spectrum of the disease and non-diseased patients and the diagnostic test accuracy may not be applicable to the clinical question.
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality <ul style="list-style-type: none"> The methodological quality of each study will be assessed using the QUADAS-II checklist. Synthesis of data <ul style="list-style-type: none"> Diagnostic meta-analysis will be conducted where appropriate. If no/insufficient evidence is found we will (in order of preference): <ul style="list-style-type: none"> Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	None

1 C.4 Diagnosis: Symptoms after drugs

2 **Table 4: Review protocol: Symptoms after drugs for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic accuracy of a clinical history of symptoms after taking the following drugs: a) in adults - beta blockers, aspirin, or other NSAIDs b) in children – ibuprofen?
Objectives	To evaluate the diagnostic test value of taking a clinical history of worsening asthma symptoms after taking drugs (aspirin or other NSAIDs and beta blockers)?
Study Design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population/Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups: <ul style="list-style-type: none"> Children (1-<5 years old) - for ibuprofen only Children/young people (5-16 years old) – for ibuprofen only Adults (>16 years old) – for beta blockers, aspirin or other NSAIDs
Setting	Primary, secondary and community care settings
Index test	Clinical history of symptoms after taking drugs. NOTE: drugs of interest for the adult population are aspirin and NSAIDs, beta blockers. For children – ibuprofen. NOTE: symptoms would be a combination of the following, or individual symptoms – wheezing, cough, breathlessness, nocturnal symptoms, diurnal and seasonal variations.
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: <ul style="list-style-type: none"> peak flow variability (cut-off value of more than 20% variability as indication of a positive test); bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test);

Component	Description
	<ul style="list-style-type: none"> • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p>
Outcomes	Diagnostic accuracy (sensitivity, specificity)
Other exclusions	Not occupational asthma /allergens Not looking at other factors which influence signs/symptoms
Search strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review strategy	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	None

1 C.5 Diagnosis: Occupational asthma

2 **Table 5: Review protocol: Occupational asthma diagnosis**

Component	Description
Review question	In adults under investigation for occupational asthma, what is the diagnostic accuracy for case identification, of asking whether their symptoms are better away from work?
Objectives	To evaluate the diagnostic test value (for identifying occupational asthma), of asking whether symptoms are better away from work?
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	Adults (>16 years old) with suspected occupational asthma.
Setting	Primary, secondary and community care settings
Index test	Symptoms are better away from work. NOTE: symptoms are defined as – wheezing, cough, breathlessness, nocturnal symptoms, diurnal variations
Reference standard	Physician’s diagnosis of occupational asthma supported by an objective test (e.g. specific inhalation challenge)

Outcomes	Diagnostic accuracy (sensitivity, specificity)
Other exclusions	
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information)
Review Strategy	<ul style="list-style-type: none"> • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	Occupational differences (different causal agents)

1 C.6 Diagnosis: Spirometry

2 **Table 6: Review protocol: Spirometry for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of spirometry / flow volume loop measures?
Objectives	To evaluate the diagnostic test value of spirometry / flow volume loop measures in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: <ul style="list-style-type: none"> • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	<p>Spirometry measures (report separately)</p> <ul style="list-style-type: none"> • FEV1/FVC ratio (<70%) • Flow volume loop (graph) • FEV1 (<80%) – if limited evidence from the above two measures <p>Pre bronchodilator values (applies for all above measures) FEV1 and FVC should be performed using the following criteria:</p> <ul style="list-style-type: none"> • Forced expiratory volume (FEV1) - patients perform manoeuvre until 3 readings are within 5% of each other (maximum 8 attempts) the measured value being the best of these 3 readings. • Forced vital capacity (FVC) - patients perform manoeuvre until 3 readings are within 5% of each other (maximum 8 attempts) the measured value being the best of these 3 readings.
Reference standard	<p>Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following:</p> <ul style="list-style-type: none"> • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p>
Outcomes	<ul style="list-style-type: none"> • Diagnostic accuracy (sensitivity and specificity)

Other exclusions	<ul style="list-style-type: none"> • Not looking at occupational asthma /allergens • Not looking at validation studies, or studies comparing different spirometry or flow volume loop measures • Not looking at factors which influence measurements
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<ul style="list-style-type: none"> • Different reference standards

1 C.7 Diagnosis: Bronchodilator reversibility

2 **Table 7: Review protocol: Bronchodilator reversibility for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of bronchodilator response (using PEF or FEV1)?
Objectives	To evaluate the diagnostic test value of bronchodilator response (using PEF or FEV1) in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 groups: <ul style="list-style-type: none"> • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Bronchodilator response, measured using the following <ul style="list-style-type: none"> • PEF • FEV1 <ul style="list-style-type: none"> ○ change in FEV1 % initial and change in FEV1 litres <p>Exclusions:</p> <ul style="list-style-type: none"> • Change in FEV1 % initial alone • Change in absolute litres alone • Change in FEV1 % predicted (ΔFEV1 %pred) • Standardised residual (SR)-FEV1 • Change in FEV1 % of possible maximal response (ΔFEV1 %max)
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: <ul style="list-style-type: none"> • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p>
Outcomes	<ul style="list-style-type: none"> • Diagnostic accuracy (sensitivity and specificity)
Other exclusions	<ul style="list-style-type: none"> • Not occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring the same test

	<ul style="list-style-type: none"> • Not looking at factors which influence measurements
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<ul style="list-style-type: none"> • Different test thresholds • Different reference standards

1 C.8 Diagnosis: PEF variability

2 **Table 8: Review protocol: Peak expiratory flow (PEF) variability for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of peak expiratory flow (PEF) variability?
Objectives	To evaluate the diagnostic test value of PEF variability in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	<p>People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 2 different groups:</p> <ul style="list-style-type: none"> • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	PEF variability (diurnal variability usually expressed as amplitude (highest – lowest reading) as a percentage of the mean or the highest reading). PEFv values should be recorded as the mean over a period of at least 3 days)
Reference standard	<p>Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following:</p> <ul style="list-style-type: none"> • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an</p>

	<p>objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p>
Outcomes	<ul style="list-style-type: none"> • Diagnostic accuracy (sensitivity, specificity)
Other exclusions	<ul style="list-style-type: none"> • Not occupational asthma /allergens • Not looking at validation studies, or studies comparing different PEF measures • Not looking at factors which influence measurements
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<ul style="list-style-type: none"> • Different test thresholds • Different reference standards

1 C.9 Diagnosis: Skin prick tests

2 **Table 9: Review protocol: Skin prick tests for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of skin prick tests?
Objectives	To evaluate the diagnostic test value of skin prick tests in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	<p>People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups:</p> <ul style="list-style-type: none"> • Children (1-<5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	<p>Skin prick tests for the most common allergens (reported separately)</p> <ul style="list-style-type: none"> • House dust mites • Cat • Dog • Grass pollen* (native UK grasses) • Tree pollen* (native UK trees)

	<ul style="list-style-type: none"> • Mixed pollens* (native UK species) • <i>Aspergillus</i> • <i>Alternaria</i> • <i>Cladosporium</i> <p>Cut off values: 3mm WHEAL (skin reaction) greater than the negative control in the presence of a positive control</p> <p>* Mainland Europe (including Denmark; excluding Norway, Sweden, Finland, Iceland, Russia, Greece), North America (USA + Canada), Australia, New Zealand (as trees/grasses/pollen similar to UK in included countries but not in other countries)</p>
Reference standard	<p>Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following:</p> <ul style="list-style-type: none"> • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p> <p>In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.</p>
Outcomes	<ul style="list-style-type: none"> • Diagnostic accuracy (Sensitivity and specificity)
Other exclusions	<ul style="list-style-type: none"> • Not occupational asthma /allergens • Not looking at validation studies, or studies comparing different skin prick methods • Not looking at factors which influence skin prick measurements • Studies in which we are unable to calculate sensitivity and specificity (unless sensitivity/specificity has been reported by the study).
Search Strategy	<p>The database to be searched are Medline, Embase, The Cochrane Library</p>
Search terms	
Review Strategy	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information)

	<ul style="list-style-type: none"> • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<ul style="list-style-type: none"> • Different test thresholds • Different reference standards • Age groups • People with eczema • Personal or family history of atopy

1C.10 Diagnosis: IgE

2 **Table 10: Review protocol: Serum IgE for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of total and specific serum IgE measures?
Objectives	To evaluate the diagnostic test value of serum IgE in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	<p>People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups:</p> <ul style="list-style-type: none"> • Children (1-<5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	<p>Serum IgE</p> <ul style="list-style-type: none"> • Total IgE • Specific IgE* (including RAST test) <p>*Reported separately for the most common aero-allergens (dust mites, grass pollen, tree pollen, dog, cat, <i>Aspergillus</i>, <i>Alternaria</i>, <i>Cladosporium</i>).</p> <p>NOTE: serum IgE must have been assessed using ELISA (apart from RAST) as other techniques are not current/no longer used.</p>
Reference standard	<p>Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following:</p> <ul style="list-style-type: none"> • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p>

	In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.
Outcomes	<ul style="list-style-type: none"> • Diagnostic accuracy (Sensitivity and specificity)
Other exclusions	<ul style="list-style-type: none"> • POPULATION: <ul style="list-style-type: none"> ○ Occupational asthma /allergens ○ Mixed populations of asthma with other groups such as rhinitis (unless the results for the subgroup of asthma patients have been reported separately). • TESTS: <ul style="list-style-type: none"> ○ Validation studies, or studies comparing different methods of measuring IgE. ○ Studies that do not use ELISA for determining presence of IgE. • ANALYSIS/RESULTS: <ul style="list-style-type: none"> ○ Studies that look at levels of IgE ○ Studies that assess factors that may influence IgE measurements (eg. smoking, age, gender) ○ Studies that use IgE predict the development of asthma at a later follow-up time ○ Studies that look at correlations or agreement between tests, but not numbers of patients who were positive and negative ○ Studies that look at IgE to in relation to asthma severity • STUDY TYPES: <ul style="list-style-type: none"> ○ Case-control studies will be excluded if there are few 'true' diagnostic studies
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<ul style="list-style-type: none"> • Different test thresholds • Different reference standards

1C.11 Diagnosis: FeNO

2 **Table 11: Review protocol: FeNO for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of fractional exhaled nitric oxide (FeNO) measures?
Objectives	To evaluate the diagnostic test value of FeNO in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses) Case-control studies were included for the comparison of FeNO levels only
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups: <ul style="list-style-type: none"> • Children (1-<5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Fractional exhaled nitric oxide (FeNO) with a cut-off threshold between 20-50ppb and a flow rate of 50ml/s or equivalent
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: <ul style="list-style-type: none"> • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p> <p>In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.</p>
Outcomes	<ul style="list-style-type: none"> • Diagnostic accuracy (Sensitivity and specificity) • FeNO levels
Other exclusions	<ul style="list-style-type: none"> • Studies in which >50% of people are on corticosteroid treatment • Not looking at occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring FeNO. • Cross-sectional studies were included if they reported sensitivity or specificity, or the sensitivity and specificity could be calculated. • Case-control studies were only included if they reported levels of FeNO, but they had to have a sample size of N>50.

Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<p>Are there any subgroups to consider?</p> <ul style="list-style-type: none"> Different test thresholds Sequence step of the test (eg, first test, second test etc) Commercially available meters

1C.12 Diagnosis: Peripheral blood eosinophils

2 **Table 12: Review protocol: Peripheral blood eosinophil count for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of eosinophil blood count measures?
Objectives	To evaluate the diagnostic test value of eosinophil blood count in diagnosing asthma
Study design	<p>Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)</p> <p>Case-control studies were included for the comparison of blood eosinophil levels only</p>
Population / Target condition	<p>People with suspected asthma (presenting with respiratory symptoms). All ages, stratified into the following 3 different groups:</p> <ul style="list-style-type: none"> Children (1- <5 years old) Children/young people (5-16 years old) Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	Peripheral blood eosinophil count (may be part of FBC)
Reference standard	<p>Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following:</p> <ul style="list-style-type: none"> peak flow variability (cut-off value of more than 20% variability as indication of a positive test); bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p>

	<p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p> <p>In children 1-<5 years, objective tests cannot be performed so the reference standard will be physician diagnosis based on recurrent and persistent wheezing.</p>
Outcomes	<ul style="list-style-type: none"> • Diagnostic accuracy (sensitivity, specificity) • Eosinophil levels
Other exclusions	<ul style="list-style-type: none"> • Not looking at occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring eosinophil blood counts. • Not looking at factors which influence eosinophil measurements • Cross-sectional studies were included if they reported sensitivity or specificity, or the sensitivity and specificity could be calculated. If they reported levels of blood eosinophils, then they were excluded. • Case-control studies were only included if they reported levels of blood eosinophils, but they had to have a sample size of N>50.
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<ul style="list-style-type: none"> • Different test thresholds • Different reference standards • Sequence step of the test (eg, first test, second test etc) • Eosinophil counts: >1, 0.4-0.9, 0.2-0.4

1C.13 Diagnosis: Histamine and methacholine

2 **Table 13: Review protocol: Histamine and methacholine challenge tests for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of airway hyper-reactivity (non-specific bronchial challenge) with histamine and methacholine?
Objectives	To evaluate the diagnostic test value of histamine and methacholine PC20 in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 different groups: <ul style="list-style-type: none"> • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	<ul style="list-style-type: none"> • Histamine PC20 and PD20 • Methacholine PC20 and PD20 Cut-off threshold of 8mg/ml or a cut-off threshold identified from a ROC curve
Reference standard	Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following: <ul style="list-style-type: none"> • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test). <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p>
Statistical measures	<ul style="list-style-type: none"> • Diagnostic accuracy (sensitivity and specificity)
Other exclusions	<ul style="list-style-type: none"> • Not occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring the same test • Not looking at factors which influence measurements • Not looking at 'case-control' type studies where the index test is applied in people with confirmed asthma and healthy controls, and where there is no uncertainty about whether the patient has asthma or not. Such studies only include a spectrum of the disease and non-diseased patients and the diagnostic test accuracy may not be applicable to the clinical question.
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	Appraisal of methodological quality <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using the QUADAS-II

	<p>checklist.</p> <p>Synthesis of data</p> <ul style="list-style-type: none"> • Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GDG consensus
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1C.14 Diagnosis: Mannitol

2 **Table 14: Review protocol: Mannitol challenge test for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic test accuracy and cost-effectiveness of airway hyper-reactivity (non-specific bronchial challenge) with mannitol?
Objectives	To evaluate the diagnostic test value of mannitol in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	<p>People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 different groups:</p> <ul style="list-style-type: none"> • Children/young people (5-16 years old) • Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	<ul style="list-style-type: none"> • Mannitol
Reference standard	<p>Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following:</p> <ul style="list-style-type: none"> • peak flow variability (cut-off value of more than 20% variability as indication of a positive test); • bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); • bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test) <p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p>
Statistical measures	Diagnostic accuracy (sensitivity, specificity)
Other exclusions	<ul style="list-style-type: none"> • Not occupational asthma /allergens • Not looking at validation studies, or studies comparing different methods of measuring the same test • Not looking at factors which influence measurements

Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> Analyse mannitol challenge methods and kits separately (split) Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<ul style="list-style-type: none"> Different test thresholds Different reference standards

1C.15 Diagnosis: Exercise challenge test

2 **Table 15: Review protocol: Exercise challenge test for asthma diagnosis**

Component	Description
Review question	In people under investigation for asthma, what is the diagnostic accuracy of bronchoconstriction in response to an exercise challenge?
Objectives	To evaluate the diagnostic test value of bronchoconstriction in response to an exercise challenge, in diagnosing asthma
Study design	Cross sectional studies, cohort studies, case series (including both retrospective and prospective analyses)
Population / Target condition	<p>People with suspected asthma (presenting with respiratory symptoms). Ages stratified into the following 2 different groups:</p> <ul style="list-style-type: none"> Children/young people (5-16 years old) Adults (>16 years old)
Setting	Primary, secondary and community care settings
Index test	<p>Exercise challenge test (>10% FEV1 bronchoconstriction in response to exercise – within 15 mins)</p> <ol style="list-style-type: none"> Change in FEV1 \geq10% post-exercise If the study has used a cut-off based on performing a ROC <p>NOTE: usually this is a 6 minute exercise challenge test.</p>
Reference standard	<p>Physician diagnosis of asthma based on symptoms plus an objective test from any one of the following:</p> <ul style="list-style-type: none"> peak flow variability (cut-off value of more than 20% variability as indication of a positive test); bronchodilator reversibility (cut-off value of an improvement in FEV1 of more than or equal to 12%, and an increase in volume of more than or equal to 200mls as indication of a positive test); bronchial hyper-responsiveness (histamine or methacholine challenge test, cut-off value of PC20 less than or equal to 8mg/ml as indication of a positive test)

	<p>Where no evidence is available using the cut-off values specified above, evidence will be included from studies using a reference standard of physician diagnosis with an objective test using an alternative threshold.</p> <p>Where no evidence is available from studies using physician diagnosis and an objective test, evidence will be included from studies using physician diagnosis based on symptoms alone, or patient report of a previous physician diagnosis.</p>
Outcomes	<ul style="list-style-type: none"> • Diagnostic accuracy (sensitivity and specificity)
Other exclusions	<ul style="list-style-type: none"> • Not occupational asthma /allergens • Not looking at tests in athletes • Not looking at other factors which influence signs/symptoms
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using the QUADAS-II checklist. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Diagnostic meta-analysis will be conducted where appropriate. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<ul style="list-style-type: none"> • Different test thresholds • Different reference standards

1C.16 Monitoring: Questionnaires

2 **Table 16: Review protocol: Symptom scores/diaries or validated questionnaires to monitor**
3 **asthma control**

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of using symptom scores / diaries or validated questionnaires measuring symptom control (eg ACT, ACQ, CACT, RCP 3 questions) and/or health related quality of life (eg AQLQ, PAQLQ) to monitor asthma?
Objectives	To evaluate the clinical and cost-effectiveness of using symptom scores / diaries or validated questionnaires that measure symptoms or HRQoL to monitor asthma? Questionnaires that measure current disease impact and future risk of exacerbation; does measuring symptom control and QoL in asthma patients, improve patient outcomes?
Study design	<ul style="list-style-type: none"> • RCTs • Validation studies (in different age groups) – summarise these narratively.
Population / Target condition	<p>People with asthma (defined as physician Dx with objective test or recurrent persistent wheeze in <5 years). If insufficient evidence is found we will consider evidence from studies where asthma is defined as physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma.</p> <p>All ages, stratified into the following 3 different groups:</p> <ul style="list-style-type: none"> • Children (1-<5 years old)

	<ul style="list-style-type: none"> • Children/young people (5-16 years old) • Adults (>16 years old)
Intervention	<p>Monitoring the following, and using the outcomes of scores/questionnaires to adjust management/therapy according to physician decision or personalised treatment plan (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring):</p> <ul style="list-style-type: none"> • Symptom scores or diaries • Symptom/control questionnaires <ul style="list-style-type: none"> ○ Asthma Control Test, ACT (including caregivers or paediatric version, CACT) ○ Asthma Control Questionnaire, ACQ (including mini ACQ or paediatric ACQ) ○ RCP 3 questions • Quality of life questionnaires (asthma specific) <ul style="list-style-type: none"> ○ HS QoL ○ Asthma Quality of Life Questionnaire, AQLQ (including paedics version, PAQLQ)
Comparison	<p>Comparison of adjustment of asthma therapy based on symptom scores or questionnaires to:</p> <ul style="list-style-type: none"> • Usual care: eg clinical symptoms (with/without spirometry/PEF) according to guidelines (including BTS/SIGN, GINA) <p>Comparison of adjustment of asthma therapy based on:</p> <ul style="list-style-type: none"> • Symptom scores or diaries vs questionnaires • Control questionnaire vs other control questionnaire • QoL questionnaire vs control questionnaire
Outcomes	<p>Critical outcomes:</p> <ul style="list-style-type: none"> • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) <p>Important outcomes:</p> <ul style="list-style-type: none"> • Lung function (FEV1, PEF) • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	<ul style="list-style-type: none"> • Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Stratify by age group</p> <p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points:

	<ul style="list-style-type: none"> ○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) <p>Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes</p> <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<ul style="list-style-type: none"> • Ethnic groups (e.g. south Asians, African Americans, Hispanics) • Education levels • Language (non English speaking)

1C.17 Monitoring: Lung function tests

2 **Table 17: Review protocol: Lung function tests to monitor asthma control**

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of using measures of pulmonary function assessing asthma control (for example, spirometry and peak expiratory flow) to monitor asthma?
Objectives	To evaluate the clinical and cost-effectiveness of using measures of pulmonary function assessing asthma control (for example, spirometry and peak expiratory flow) to monitor asthma.
Study design	<ul style="list-style-type: none"> • RCTs
Population / Target condition	<p>People with asthma (defined as physician Dx with objective test). If insufficient evidence is found we will consider evidence from studies where asthma is defined as physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma.</p> <p>All ages, stratified into the following 2 different groups:</p> <ul style="list-style-type: none"> • Children/young people (5-16 years old) • Adults (>16 years old)
Intervention	<p>Monitoring lung function using the following tests, and using the outcomes to adjust management/therapy according to physician decision or personalised treatment plan (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring):</p> <ul style="list-style-type: none"> • Spirometry (FEV1; FEV1/FVC; Flow loop measures) • PEF
Comparison	<p>Comparison of adjustment of asthma therapy based on lung function tests to:</p> <ul style="list-style-type: none"> • Usual care: eg clinical symptoms according to guidelines (including BTS/SIGN, GINA) • Asthma control or QOL questionnaires <p>Comparison of adjustment of asthma therapy based on:</p> <ul style="list-style-type: none"> • Spirometry versus PEF
Outcomes	<p>Critical outcomes:</p> <ul style="list-style-type: none"> • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of

	<p>hours or walk-in centre)</p> <ul style="list-style-type: none"> • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) <p>Important outcomes:</p> <ul style="list-style-type: none"> • Lung function (FEV1, PEF) • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	<ul style="list-style-type: none"> • Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Stratify by age group</p> <p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points: <ul style="list-style-type: none"> ○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) <p>Default MIDAs will be used where no MIDAs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes</p> <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GDG consensus
Analysis-subgroups	
Key papers	

1C.18 Monitoring: FeNO

2 **Table 18: Review protocol: FeNO to monitor asthma control**

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of using fractional exhaled nitric oxide (FeNO) measures for monitoring asthma control?
Objectives	To evaluate the clinical and cost-effectiveness of using fractional exhaled nitric oxide (FeNO) for monitoring asthma control?
Study design	<ul style="list-style-type: none"> • RCTs
Population / Target condition	People with asthma (defined as physician Dx with objective test). If insufficient evidence is found we will consider evidence from studies where asthma is defined as

	<p>physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma.</p> <p>All ages, stratified into the following 2 different groups:</p> <ul style="list-style-type: none"> • Children/young people (5-16 years old) • Adults (>16 years old) <p>The following groups will be included/combined in the analysis (do not subgroup, would not make separate recommendations for these groups):</p> <ul style="list-style-type: none"> • Smokers • Atopic asthma
Intervention	<p>Monitoring FeNO and adjustment of management/therapy according to physician decision or personalised treatment plan (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring)</p> <p>Only use validated methods of measuring FeNO (eg 50ml/s flow rate).</p>
Comparison	<p>Comparison of adjustment of asthma therapy based on FeNO to:</p> <ul style="list-style-type: none"> • Usual care: eg clinical symptoms (with or without PEF) according to guidelines (including BTS/SIGN, GINA) • Asthma control questionnaires or QOL questionnaires • Lung function tests (spirometry or PEFv) • Blood eosinophils • Challenge tests <p>Comparison of different frequencies of monitoring using FeNO.</p>
Outcomes	<p>Critical outcomes:</p> <ul style="list-style-type: none"> • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) <p>Important outcomes:</p> <ul style="list-style-type: none"> • Lung function (FEV1, PEF) • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	<ul style="list-style-type: none"> • Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Stratify by age group</p> <p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points:

	<ul style="list-style-type: none"> ○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) <p>Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes</p> <p>Sensitivity analysis:</p> <ul style="list-style-type: none"> ● SUBGROUP: if heterogeneity, subgroup according to the aim of the treatment in the study. Would expect different directions of effect in studies aiming to decrease ICS in controlled patients and studies aiming to increase ICS in uncontrolled patients. <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> ● Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) ● Consider observational studies and NRS ● Consider prognostic studies ● Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<ul style="list-style-type: none"> ● SUBGROUP: if heterogeneity, subgroup according to the aim of the treatment in the study. Would expect different directions of effect in studies aiming to decrease ICS in controlled patients and studies aiming to increase ICS in uncontrolled patients.
Key papers	

1C.19 Monitoring: Peripheral blood eosinophils

2 **Table 19: Review protocol: Peripheral blood eosinophils to monitor asthma control**

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of using the peripheral blood eosinophil count for monitoring asthma control?
Objectives	To evaluate the clinical and cost-effectiveness of using peripheral blood eosinophil count for monitoring asthma control?
Study design	<ul style="list-style-type: none"> ● RCTs
Population / Target condition	<p>People with asthma (defined as physician Dx with objective test or recurrent persistent wheeze in <5 years). If insufficient evidence is found we will consider evidence from studies where asthma is defined as physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma.</p> <p>All ages, stratified into the following 3 different groups:</p> <ul style="list-style-type: none"> ● Children (1-<5 years old) ● Children/young people (5-16 years old) ● Adults (>16 years old) <p>The following groups will be included/combined in the analysis (do not subgroup, would not make separate recommendations for these groups):</p> <ul style="list-style-type: none"> ● Smokers ● Atopic asthma
Intervention	Monitoring peripheral blood eosinophil count and adjustment of management/therapy according to physician decision or personalised treatment plan (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring).

Comparison	<p>Comparison of adjustment of asthma therapy based on peripheral blood eosinophil count to:</p> <ul style="list-style-type: none"> • Usual care: eg clinical symptoms (with or without PEF) according to guidelines (including BTS/SIGN, GINA) • Asthma control questionnaires or QOL questionnaires • Lung function tests (spirometry or PEFv) • Challenge tests <p>Comparison of different frequencies of monitoring using blood eosinophil count.</p>
Outcomes	<p>Critical outcomes:</p> <ul style="list-style-type: none"> • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George’s respiratory questionnaire) <p>Important outcomes:</p> <ul style="list-style-type: none"> • Lung function (FEV1, PEF) • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	<ul style="list-style-type: none"> • Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	<p>The database to be searched are Medline, Embase, The Cochrane Library</p>
Review Strategy	<p>Stratify by age group</p> <p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points: <ul style="list-style-type: none"> ○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) <p>Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes</p> <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GDG consensus
Analysis-subgroups to	

investigate heterogeneity	
Key papers	

1C.20 Monitoring: Challenge tests

2 **Table 20: Review protocol: Challenge tests to monitor asthma control**

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of using indirect challenge tests with mannitol or direct challenge tests with histamine or methacholine for monitoring asthma control?
Objectives	To evaluate the clinical and cost-effectiveness of using indirect challenge tests with mannitol, or direct challenge tests with histamine or methacholine PC20 for monitoring asthma control?
Study design	<ul style="list-style-type: none"> • RCTs
Population / Target condition	<p>People with asthma (defined as physician Dx with objective test). If insufficient evidence is found we will consider evidence from studies where asthma is defined as physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma.</p> <p>All ages, stratified into the following 2 different groups:</p> <ul style="list-style-type: none"> • Children/young people (5-16 years old) • Adults (>16 years old)
Intervention	<p>Monitoring using indirect or direct challenge tests and using the outcomes to adjust management/therapy according to physician decision or personalised treatment plan (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring):</p> <ul style="list-style-type: none"> • Indirect challenge test with mannitol • Direct challenge test with methacholine or histamine
Comparison	<p>Comparison of adjustment of asthma therapy based on indirect or direct challenge tests to:</p> <ul style="list-style-type: none"> • Usual care: eg clinical symptoms according to guidelines (including BTS/SIGN, GINA) • Asthma control questionnaires or QOL questionnaires • Lung function tests (spirometry or PEFv) <p>Comparison of adjustment of asthma therapy based on:</p> <ul style="list-style-type: none"> • Indirect vs direct challenge tests • Comparison of different frequencies of monitoring using challenge tests
Outcomes	<p>Critical outcomes:</p> <ul style="list-style-type: none"> • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) <p>Important outcomes:</p> <ul style="list-style-type: none"> • Lung function (FEV1, PEF) • Symptoms (annual symptom free days)

	<ul style="list-style-type: none"> • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	<ul style="list-style-type: none"> • Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Stratify by age group</p> <p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points: <ul style="list-style-type: none"> ○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) <p>Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes</p> <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	
Key papers	

1C.21 Monitoring: Adherence to treatment

2 **Table 21: Review protocol: Monitoring adherence to treatment**

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of monitoring adherence to treatment?
Objectives	To evaluate the clinical and cost-effectiveness of monitoring adherence to treatment? Adherence with repeat therapies
Study design	<ul style="list-style-type: none"> • RCTs
Population / Target condition	<p>People with asthma (defined as physician Dx with objective test or recurrent persistent wheeze in <5 years). If insufficient evidence is found we will consider evidence from studies where asthma is defined as physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma.</p> <p>All ages, stratified into the following 3 different groups:</p> <ul style="list-style-type: none"> • Children (1-<5 years old) • Children/young people (5-16 years old)

	<ul style="list-style-type: none"> • Adults (>16 years old)
Intervention	<p>Monitoring adherence/compliance/concordance using the following methods and provide patient feedback or intervention to improve adherence (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring):</p> <ul style="list-style-type: none"> • Adherence with repeat therapy (using prescription and refill data) • Electronic monitoring inhalers (to monitor inhaler use) • Prednisolone levels (serum and urine – when on prednisolone) • MARS questionnaire (medication adherence rating scale) • FeNO levels (comes down if patients are taking their inhalers) • Theophylline levels (when on theophylline)
Comparison	<ul style="list-style-type: none"> • No monitoring of adherence • Usual care • Comparison of different frequencies of monitoring adherence
Outcomes	<p>Critical outcomes:</p> <ul style="list-style-type: none"> • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George’s respiratory questionnaire) • Adherence <p>Important outcomes:</p> <ul style="list-style-type: none"> • Lung function (FEV1, PEF) • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	<ul style="list-style-type: none"> • Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Search terms	<ul style="list-style-type: none"> • Adherence • Compliance • Concordance
Review Strategy	<p>Stratify by age group</p> <p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points: <ul style="list-style-type: none"> ○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) <p>Default MIDAs will be used where no MIDAs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes</p> <p>If no/insufficient evidence is found we will (in order of preference):</p>

	<ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	<ul style="list-style-type: none"> • Socio economic disadvantage • Cognitive function • Some ethnic groups • Disability (esp. use of inhalers) • Near fatal asthma attacks (associated with psychological effects etc)

1C.22 Monitoring: Inhaler technique

2 **Table 22: Review protocol: Monitoring inhaler technique**

Component	Description
Review question	In people with asthma, what is the optimal frequency and method for monitoring inhaler technique?
Objectives	To evaluate the clinical and cost-effectiveness of the optimal frequency and method for monitoring inhaler technique?
Study design	<ul style="list-style-type: none"> • RCTs
Population / Target condition	<p>People with asthma (defined as physician Dx with objective test or recurrent persistent wheeze in <5 years). If insufficient evidence is found we will consider evidence from studies where asthma is defined as physician Dx only or on asthma treatment (give details of how Dx was made). Not including severe asthma.</p> <p>All ages, stratified into the following 3 different groups:</p> <ul style="list-style-type: none"> • Children (1-<5 years old) • Children/young people (5-16 years old) • Adults (>16 years old)
Intervention	<p>Monitoring inhaler technique using the following methods and provide patient feedback or intervention to improve inhaler technique (use of other interventions to be included if equal access in each group, eg both groups receive education in addition to monitoring):</p> <ul style="list-style-type: none"> • Electronic devices to monitor inhaler technique (devices check the inhaler is being used correctly but this will still be face-to-face monitoring) • Visual monitoring by doctor, nurse or pharmacist (may include use of a checklist to monitor inhaler technique)
Comparison	<ul style="list-style-type: none"> • No monitoring of inhaler technique • Comparison of different frequencies of monitoring inhaler technique • Monitoring using electronic devices vs monitoring by visual inspection
Outcomes	<p>Critical outcomes:</p> <ul style="list-style-type: none"> • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) <p>Important outcomes:</p> <ul style="list-style-type: none"> • Lung function (FEV1, PEF)

	<ul style="list-style-type: none"> • Symptoms (annual symptom free days) • Dose of regular asthma therapy / preventer medication (ICS dose) • Rescue medication (SABA use) • Time off school or work
Exclusions	<ul style="list-style-type: none"> • Exclude observational cohort studies and NRS unless limited evidence from RCTs • Studies not in English • Not occupational asthma /allergens
Search Strategy	The database to be searched are Medline, Embase, The Cochrane Library
Review Strategy	<p>Stratify by age group</p> <p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Meta-analysis will be conducted where appropriate • Outcomes will be grouped into the following categories based on time-points: <ul style="list-style-type: none"> ○ <6 months (or the one nearest to 6 months if multiple time-points are given) ○ ≥6 months (or the longest one if multiple time-points are given) <p>Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes</p> <p>If no/insufficient evidence is found we will (in order of preference):</p> <ul style="list-style-type: none"> • Consider unpublished or partially published studies (including abstracts – and contact the authors for more information) • Consider observational studies and NRS • Consider prognostic studies • Move to GDG consensus
Analysis-subgroups to investigate heterogeneity	
Key papers	

1C.23 Monitoring: Tele-healthcare

2 **Table 23: Review protocol: Tele-healthcare to monitor asthma control**

Component	Description
Review question	In people with asthma, what is the clinical and cost-effectiveness of tele-healthcare to monitor asthma control?
Objectives	To review the efficacy and effectiveness of tele-healthcare to monitor asthma control.
Study design	Full reports of randomised controlled trials which compared a tele-healthcare intervention with usual care or any other control intervention.
Population	Children and adults with clinician-diagnosed asthma. We included studies conducted in both primary and secondary care settings. We focused on studies which looked exclusively at people with asthma. There were no exclusions on the basis of age, gender, ethnicity or language spoken.
Intervention and comparison	<p>Focus on the proactive use of ICT to provide the information the health professional requires to make their decisions and then feedback of their advice to the patient. The study of technology needed to be central and its use sustained. These interventions included the following.</p> <ul style="list-style-type: none"> • Video or telephone links between patient and healthcare professionals in real time or using store-and-forward technologies. • Systems of care using Internet-based telecommunication; these could be synchronous or asynchronous (e.g. Skype®, messaging, email) with healthcare professionals. • Systems of care using both wired and wireless telemetry for monitoring of Peak Expiratory Flow (PEF), spirometry (Forced Expiratory Volume in 1 second (FEV1); Forced Vital Capacity (FVC) respiratory rate, chest movement and oxygen saturations involving feedback to the patient, which had been processed or authorised by a healthcare professional. • Other systems of remote healthcare incorporating patient self-reporting of symptoms on a questionnaire and information exchange with a professional. • Complex intervention studies, if it was possible to tease out the individual tele-healthcare elements. <p>Professional involvement in care was considered fundamentally important; we thus excluded the following types of interventions.</p> <ul style="list-style-type: none"> • Remote interventions that were merely educational and so did not include the input of a professional, e.g. electronic information provision in an emergency waiting room. Although this type of passive information provision was excluded, education could have been part of a more complex interactive intervention that might fit the inclusion criteria, e.g. if it included feedback from a professional. • Decision support which functioned without the active input of a healthcare professional. •
Outcomes	<p>Critical outcomes:</p> <ul style="list-style-type: none"> • Mortality • Unscheduled healthcare utilisation (ED/A&E visit; hospital admissions; GP out of hours or walk-in centre) • Exacerbations (defined as need for course of oral steroids) • Asthma control questionnaires (ACT; CACT; ACQ; PACQ; RCP-3) • QoL (AQLQ; pAQLQ; St George's respiratory questionnaire) <p>Important outcomes:</p> <ul style="list-style-type: none"> • Lung function (FEV1, PEF) <p>Symptoms (annual symptom free days)</p>

Search	<p>Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and hand-searching of respiratory journals and meeting abstracts. All records coded as 'asthma' were searched using the following terms:</p> <p>Telehealth* or tele-health* or telemedicine*- or tele-medicine* or internet* or computer* or web* or interactive* or telecommunication* or telephone or phone or SMS or tele-monitor* or telemonitor* or telemanagement or tele-management- or teleconsultation or tele-consultation or telecare* or tele-care* or telematic* or telepharmacy or tele-pharmacy or telenurs* or tele-nurs* or video or email or e-mail or "remote consult*" or wireless or Bluetooth or tele-homecare or telehomecare or "remote care" or tele-support or telesupport or "mobile healthcare" or "computer mediated therapy" or ehealth or e-health or mhealth or m-health</p>
Review strategy	<p>Stratify by age group</p> <p>Appraisal of methodological quality</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by GRADE for each outcome. <p>Synthesis of data</p> <ul style="list-style-type: none"> • Meta-analysis will be conducted where appropriate <p>Sources of potential heterogeneity will be assessed with subgroup analyses for device (phonecalls, SMS, email, internet software) and study length (<6 months and > 6 months), or summarised narratively where insufficient numbers of studies are found.</p> <p>Default MIDs will be used where no MIDs are established: 0.75 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes</p>

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2C.24 Health economic review protocols for all review questions

Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to the review questions set out above.
Criteria	<ul style="list-style-type: none"> • Populations, interventions and comparators must be as specified in the individual review protocols above. • Studies must be of a relevant economic study design (cost–utility analysis, cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis, comparative cost analysis). • Studies must not be an abstract only, a letter, editorial or commentary, or a review of economic evaluations.^(a) Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix F.
Review strategy	<p>Each study fulfilling the criteria above will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).¹²¹⁶</p> <p>Inclusion and exclusion criteria</p> <ul style="list-style-type: none"> • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will

usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile.

- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GDG if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix H.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden)
- OECD countries with predominantly private health insurance systems (for example, USA, Switzerland)
- non-OECD settings (always 'Not applicable').

Economic study type:

- cost–utility analysis
- other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis)
- comparative cost analysis
- non-comparative cost analyses including cost-of-illness studies (always 'Not applicable').
- Year of analysis:
 - The more recent the study, the more applicable it is.

Quality and relevance of effectiveness data used in the economic analysis:

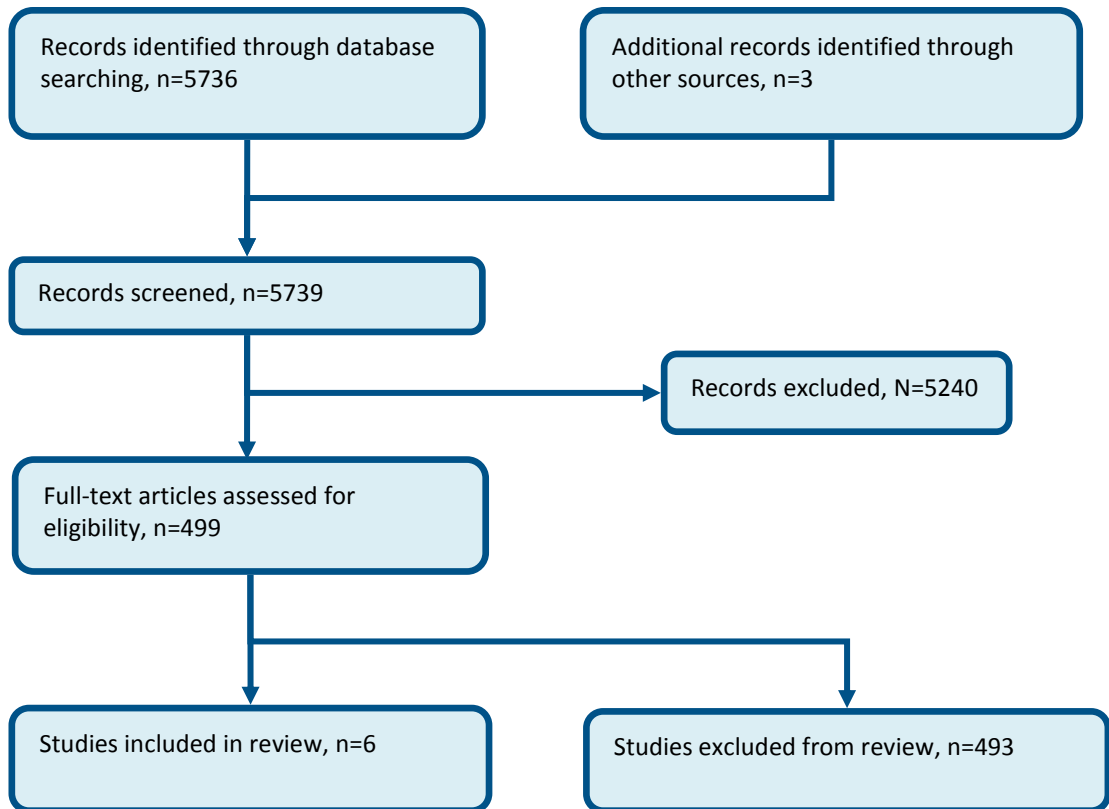
- The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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- (a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

1 Appendix D: Clinical article selection

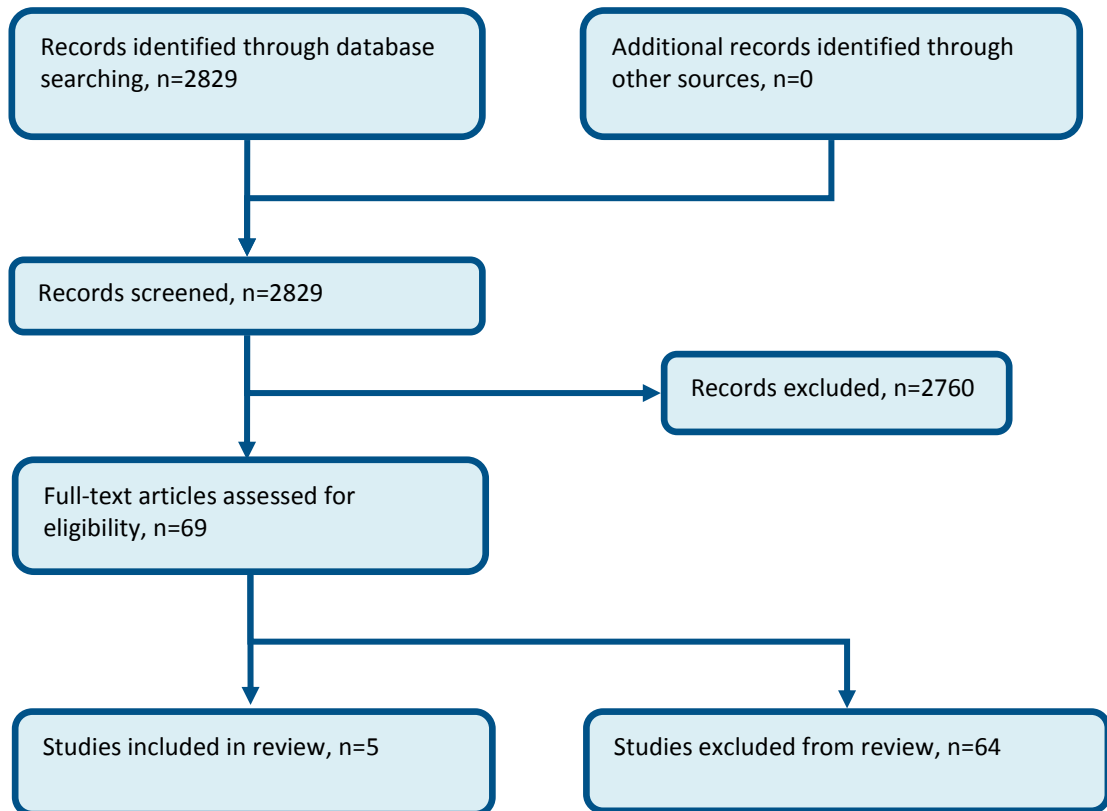
2 D.1 Diagnosis: Signs and symptoms

Figure 1: Flow diagram of article selection for the review of signs and symptoms



1 D.2 Diagnosis: History of atopic disorders

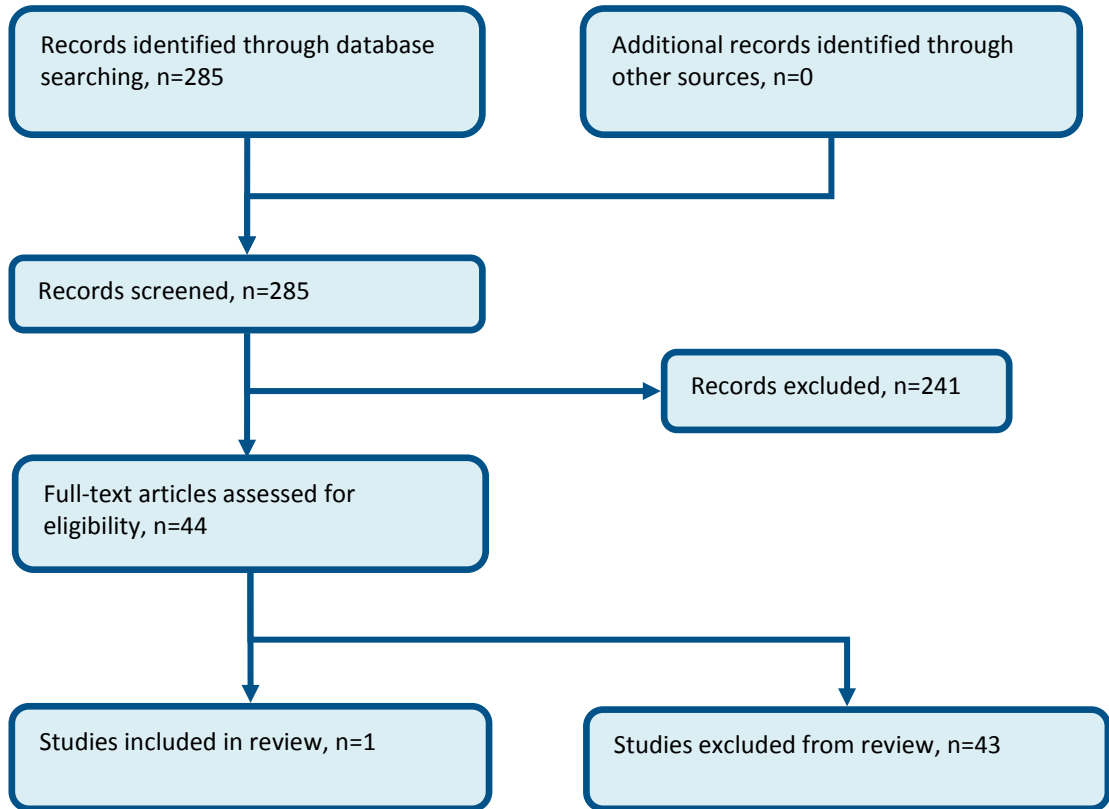
Figure 2: Flow diagram of clinical article selection for the review of history of atopic disorders



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1 D.3 Diagnosis: Symptoms after exercise

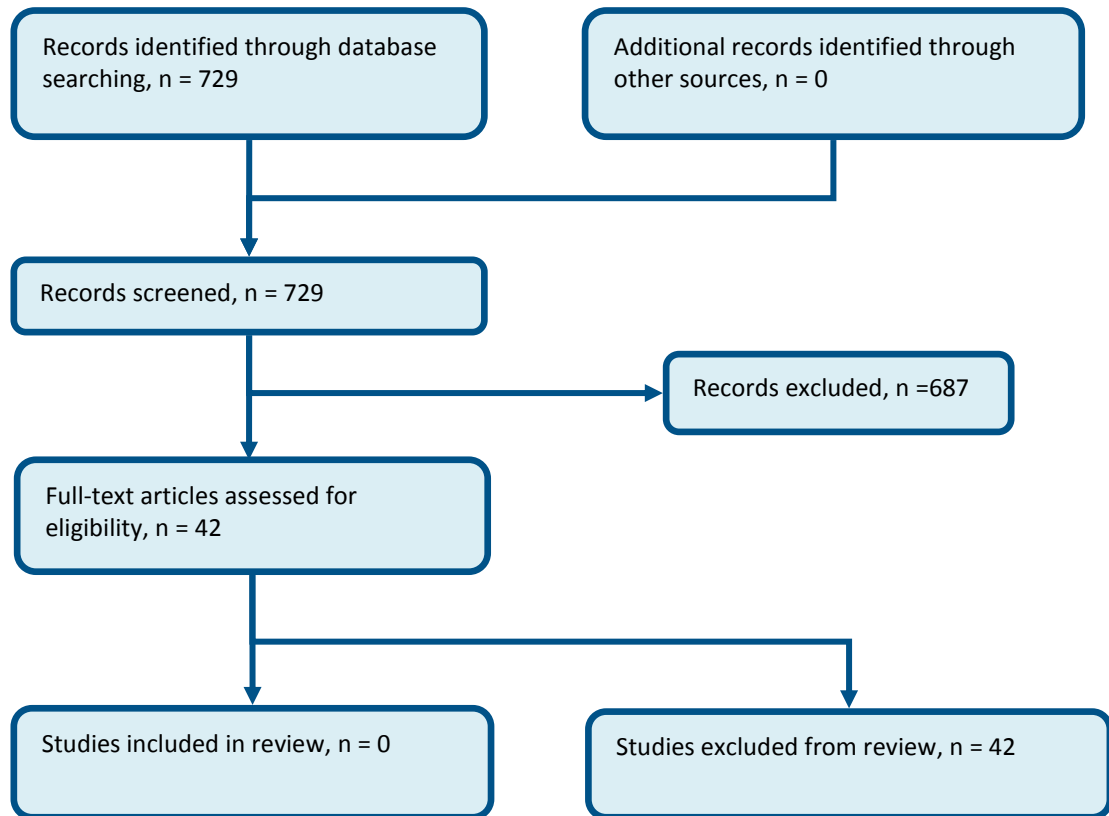
Figure 3: Flow diagram of clinical article selection for the review of symptoms after exercise



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1 D.4 Diagnosis: Symptoms after drugs

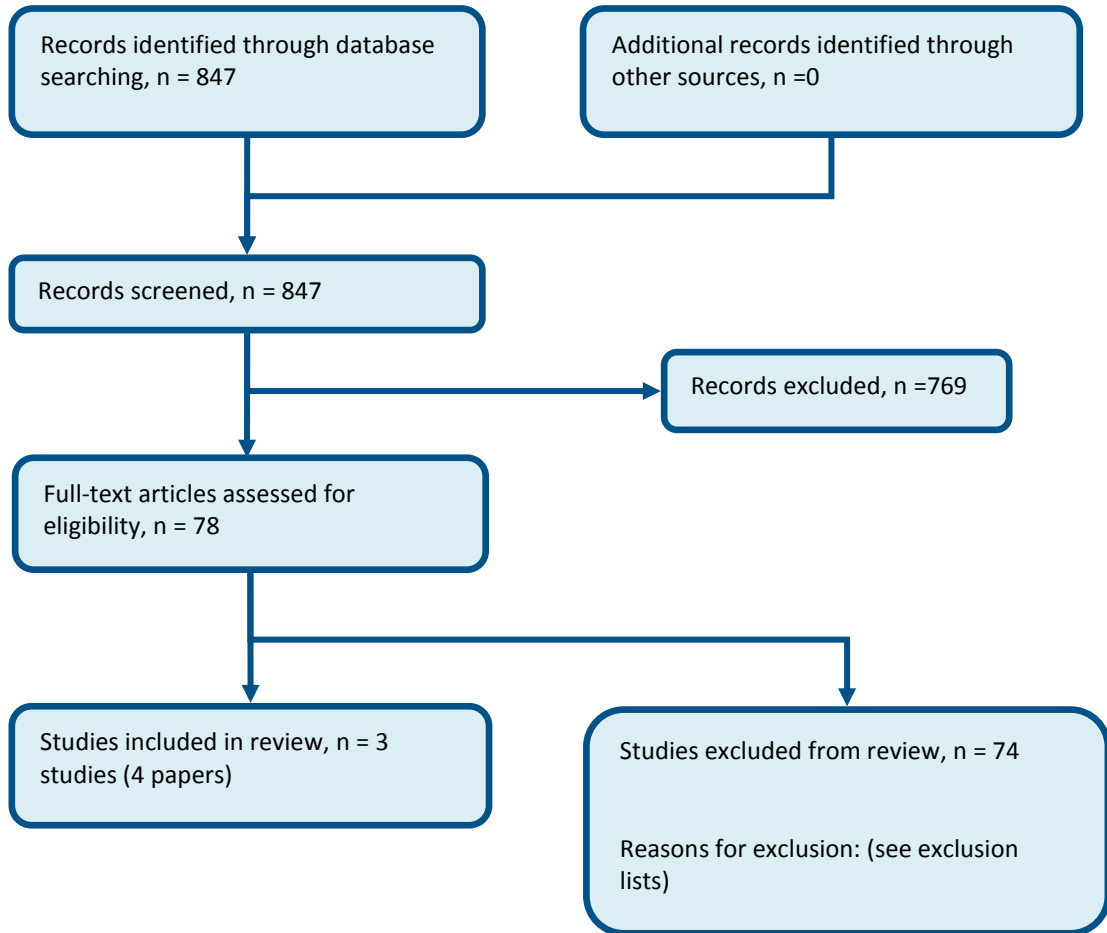
Figure 4: Flow diagram of clinical article selection for the review of symptoms after drugs



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1 D.5 Diagnosis: Occupational asthma

2 **Figure 5: Flow diagram of clinical article selection for the review of occupational asthma**

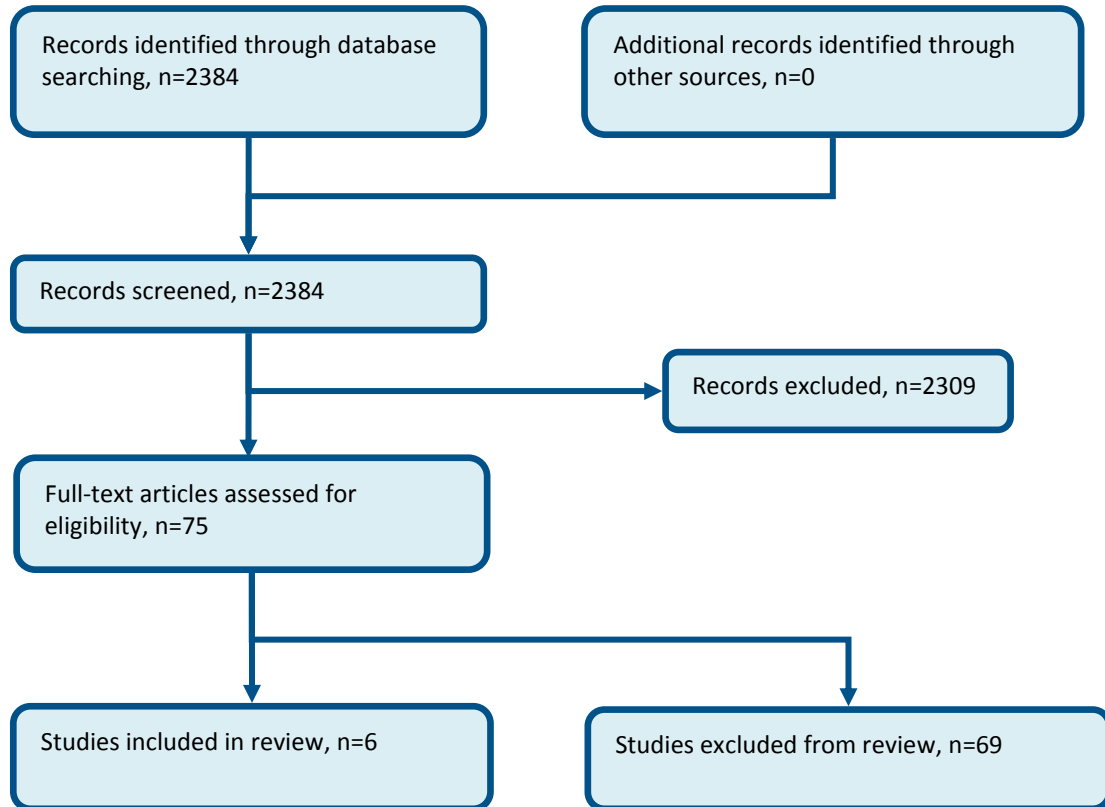


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1 D.6 Diagnosis: Spirometry

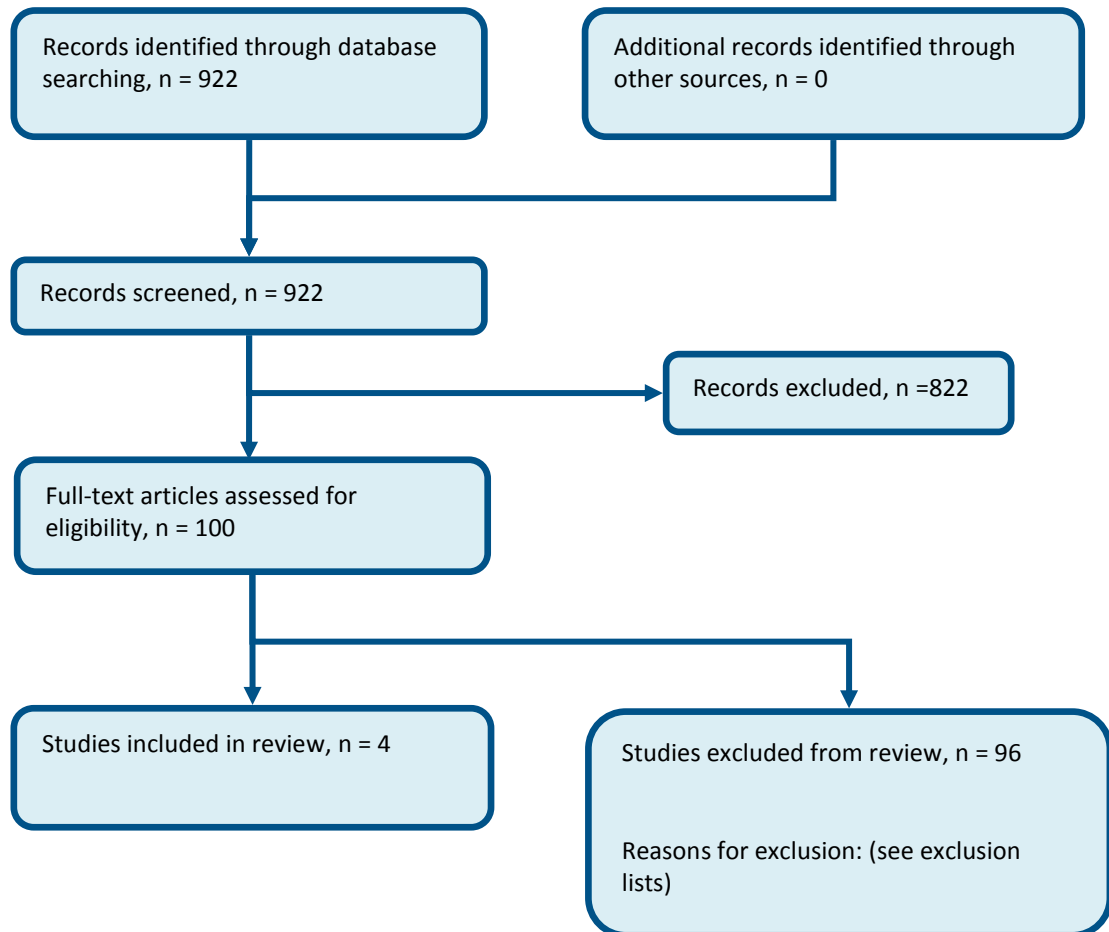
Figure 6: Flow diagram of clinical article selection for the review of spirometry



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1 D.7 Diagnosis: Bronchodilator reversibility

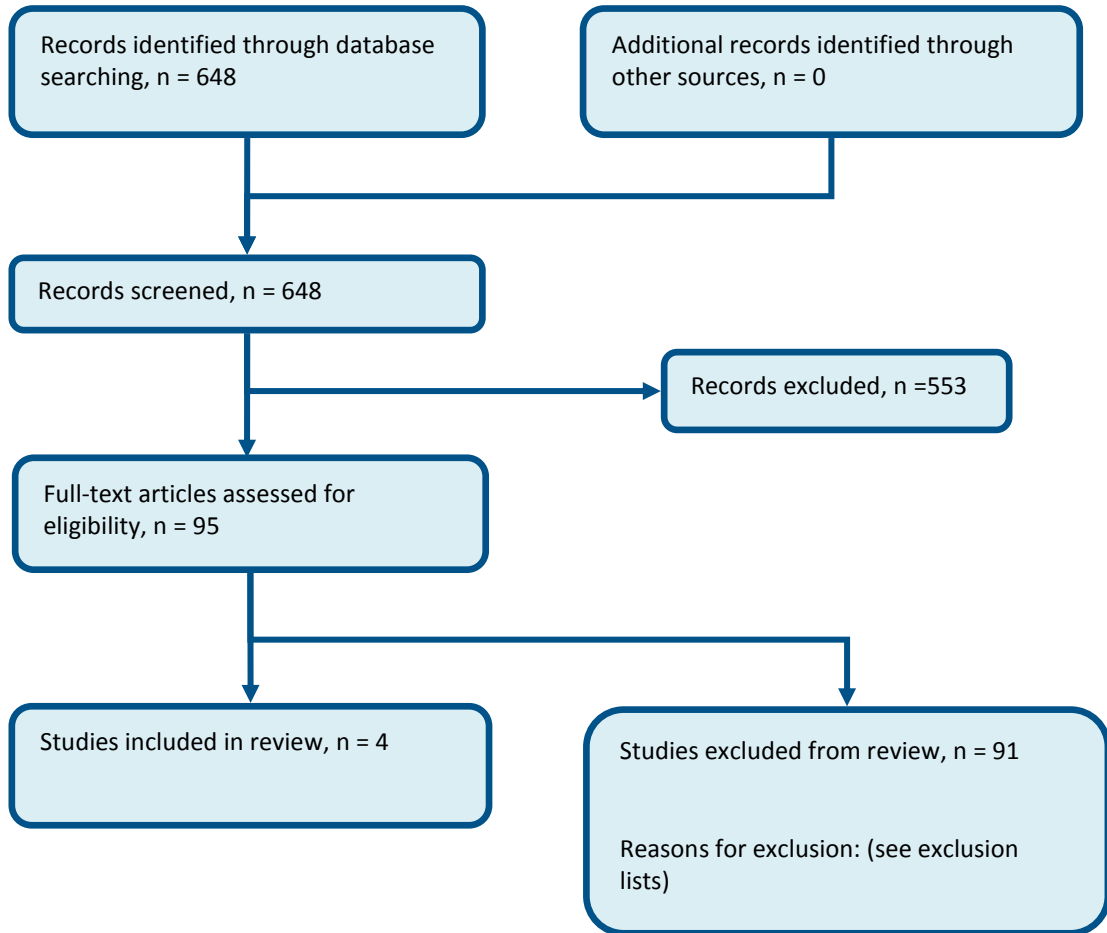
2 **Figure 7: Flow diagram of clinical article selection for the review of bronchodilator reversibility**



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1 D.8 Diagnosis: PEF variability

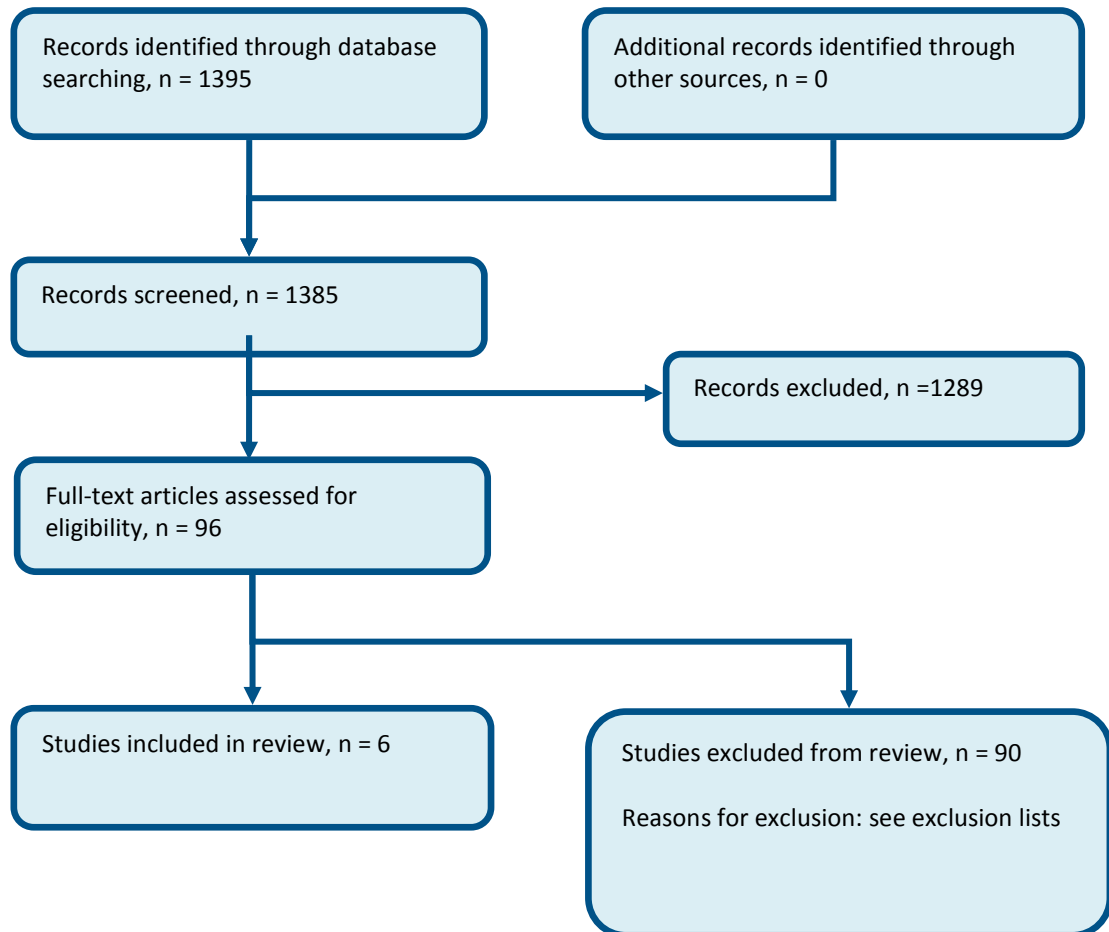
2 **Figure 8: Flow diagram of clinical article selection for the review of PEF variability**



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1 D.9 Diagnosis: Skin prick tests

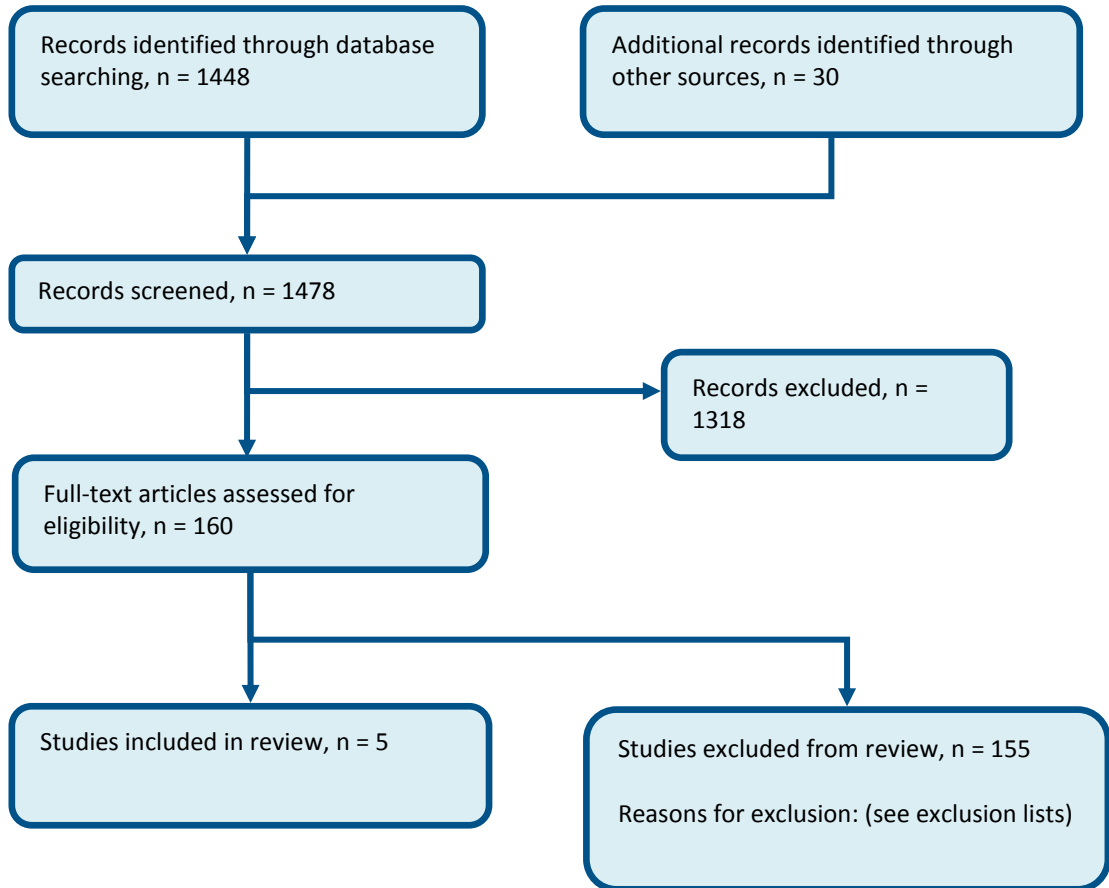
2 **Figure 9: Flow diagram of clinical article selection for the review of skin prick tests**



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4

D.10 Diagnosis: IgE

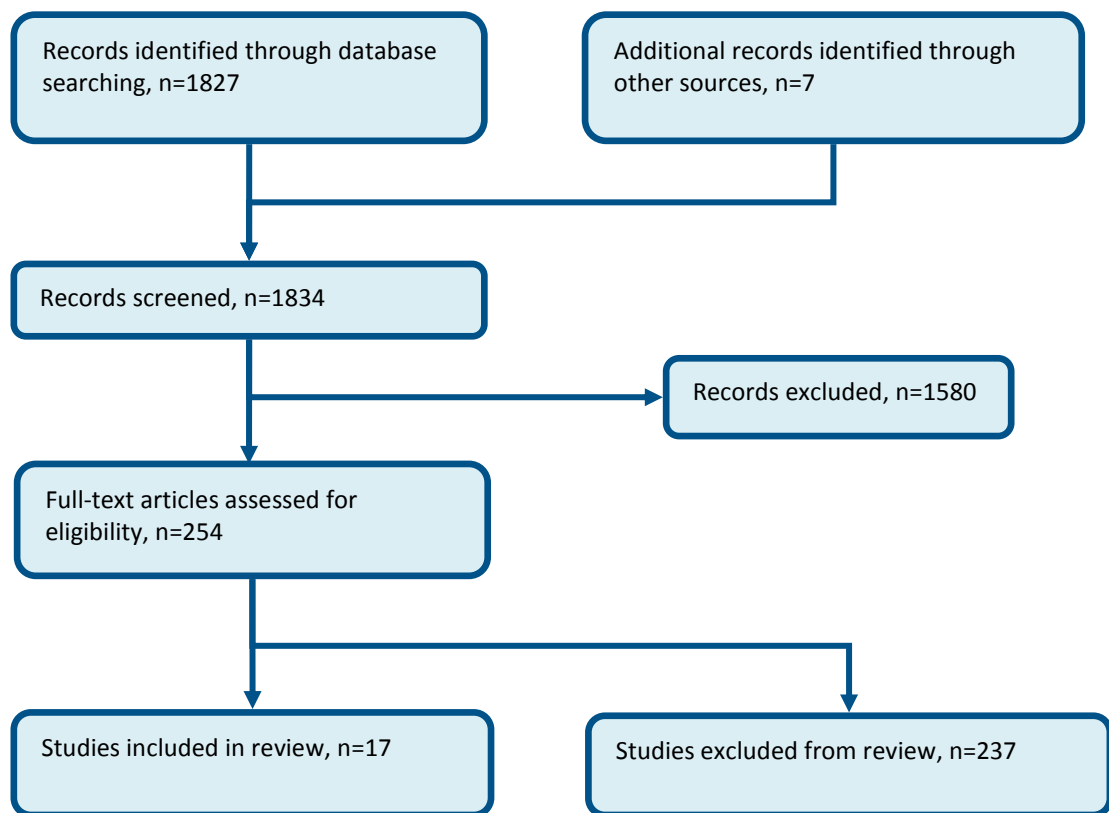
2 **Figure 10: Flow diagram of clinical article selection for the review of IgE**



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D.11 Diagnosis: FeNO

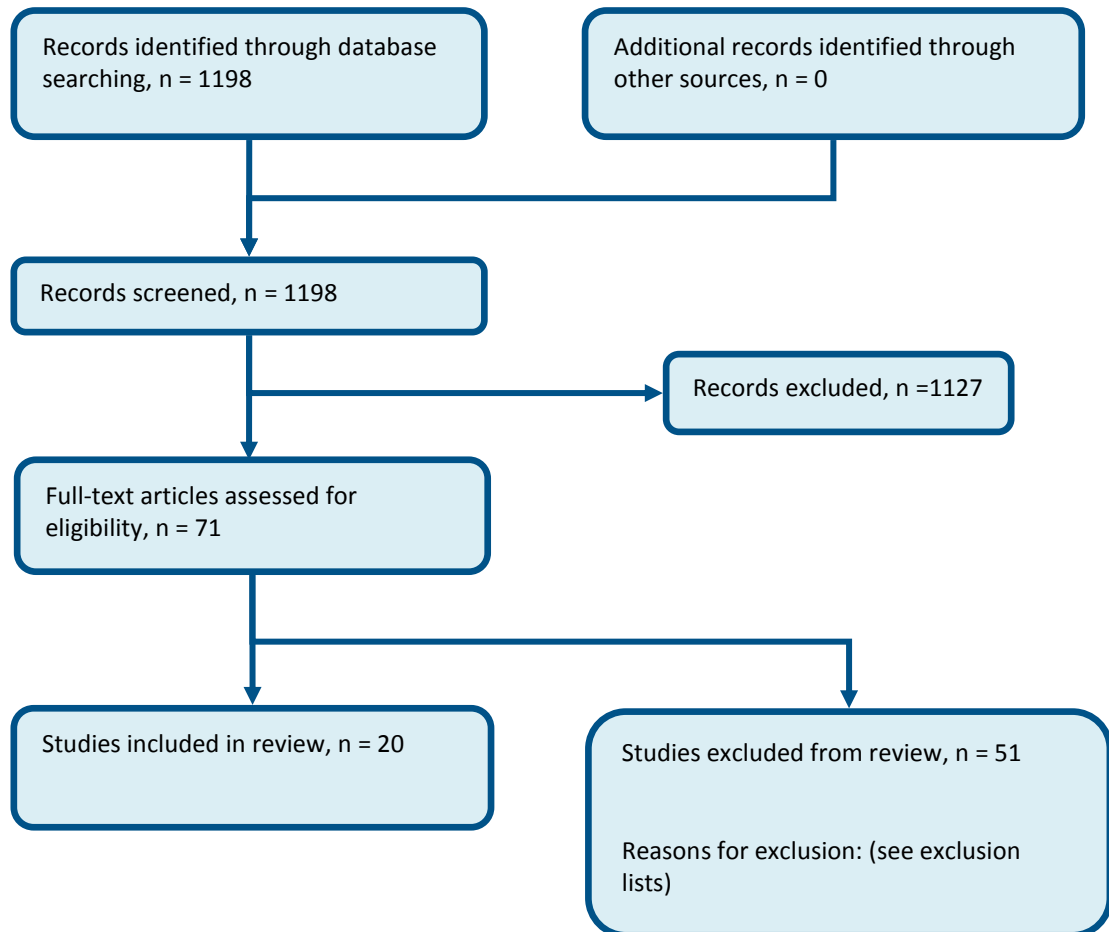
Figure 11: Flow diagram of article selection for the review of FeNO



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D.12 Diagnosis: Eosinophils

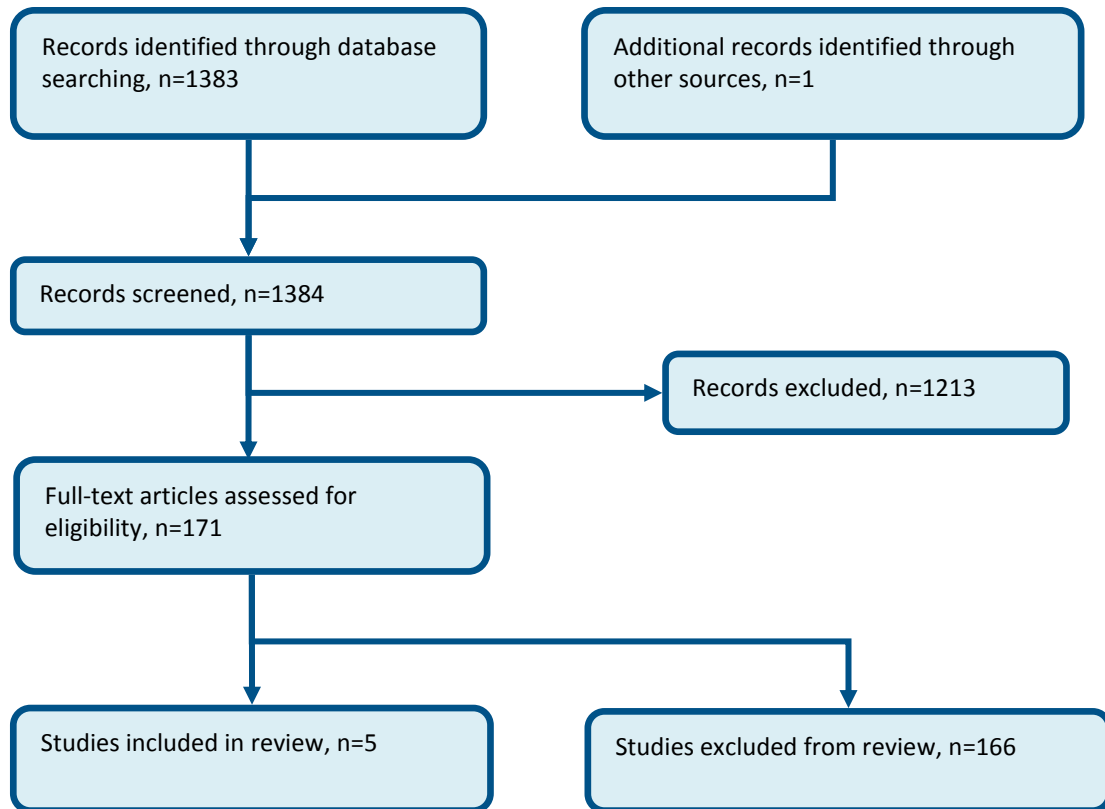
2 **Figure 12: Flow diagram of clinical article selection for the review of peripheral blood eosinophils**



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D.13 Diagnosis: Histamine and methacholine

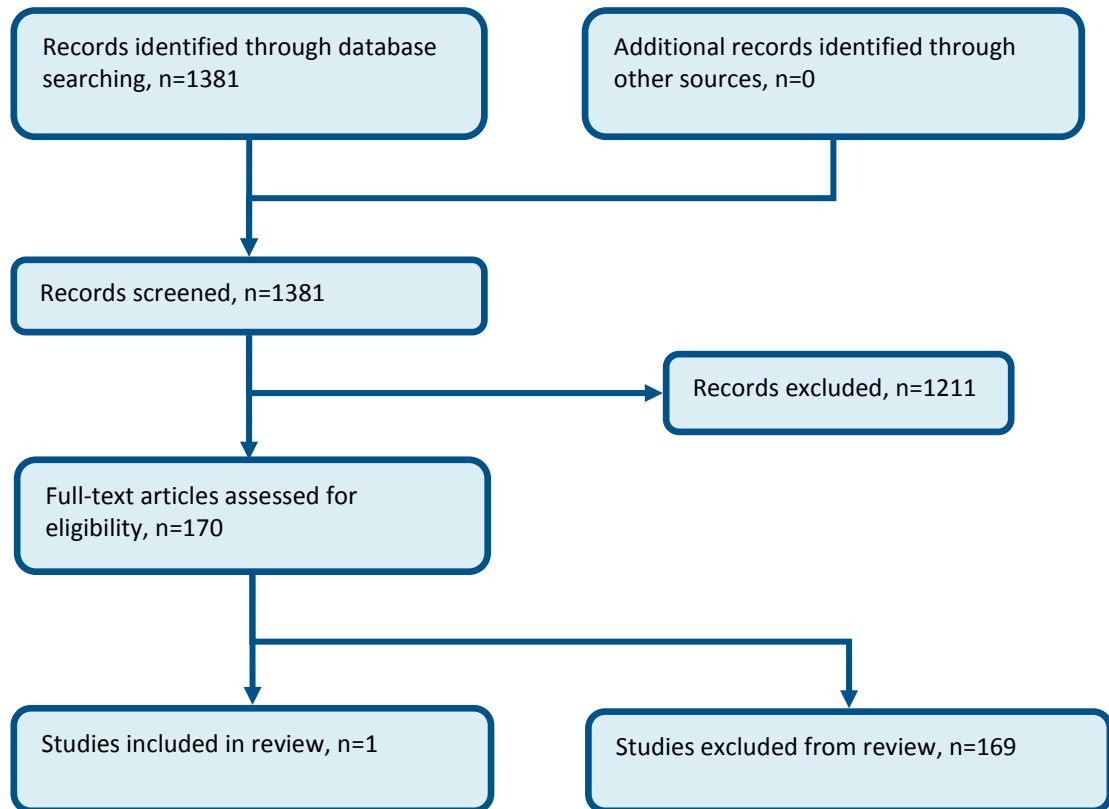
Figure 13: Flow diagram of clinical article selection for the review of histamine and methacholine challenge tests



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D.14 Diagnosis: Mannitol

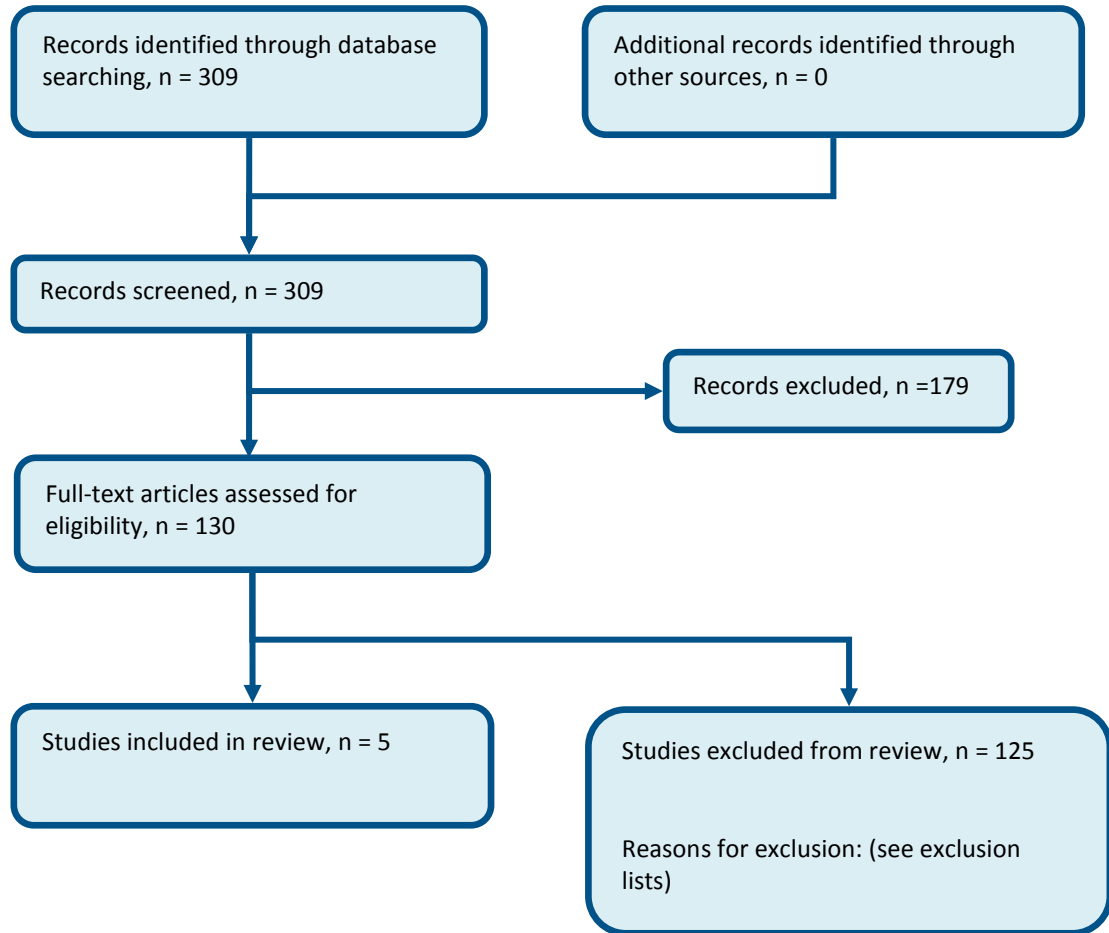
Figure 14: Flow diagram of clinical article selection for the review of mannitol challenge test



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D.15 Diagnosis: Exercise

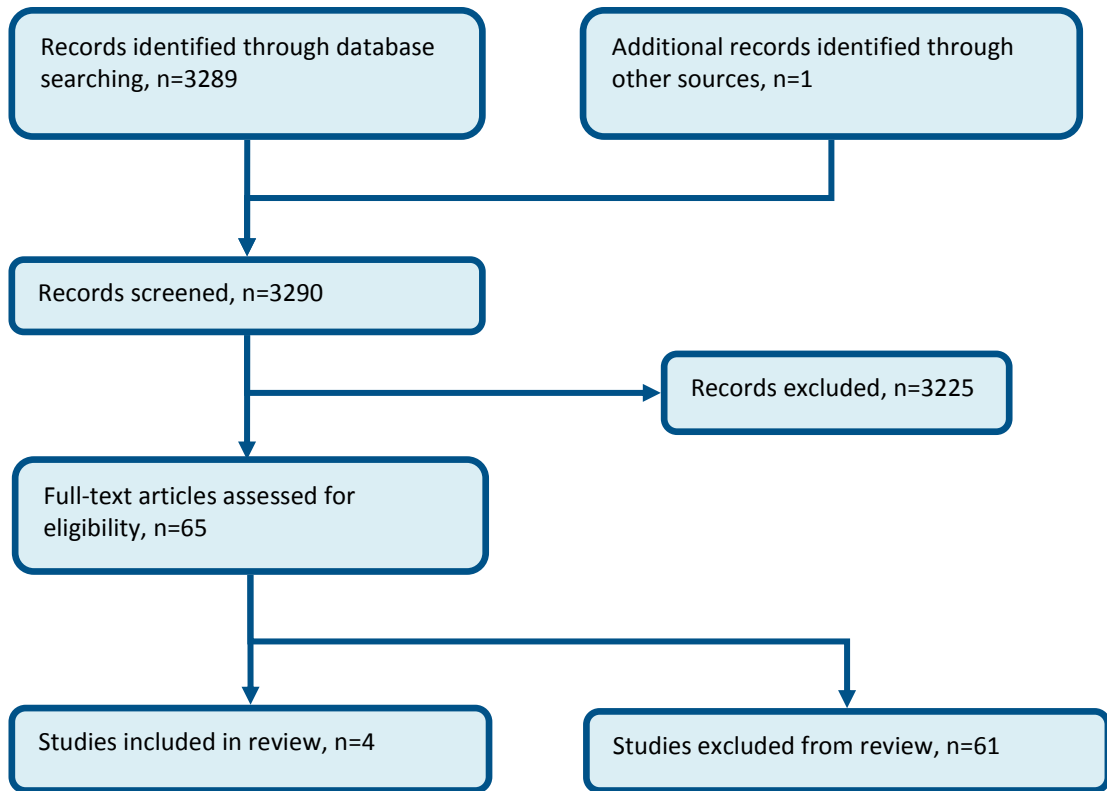
2 **Figure 15: Flow diagram of clinical article selection for the review of exercise challenge test**



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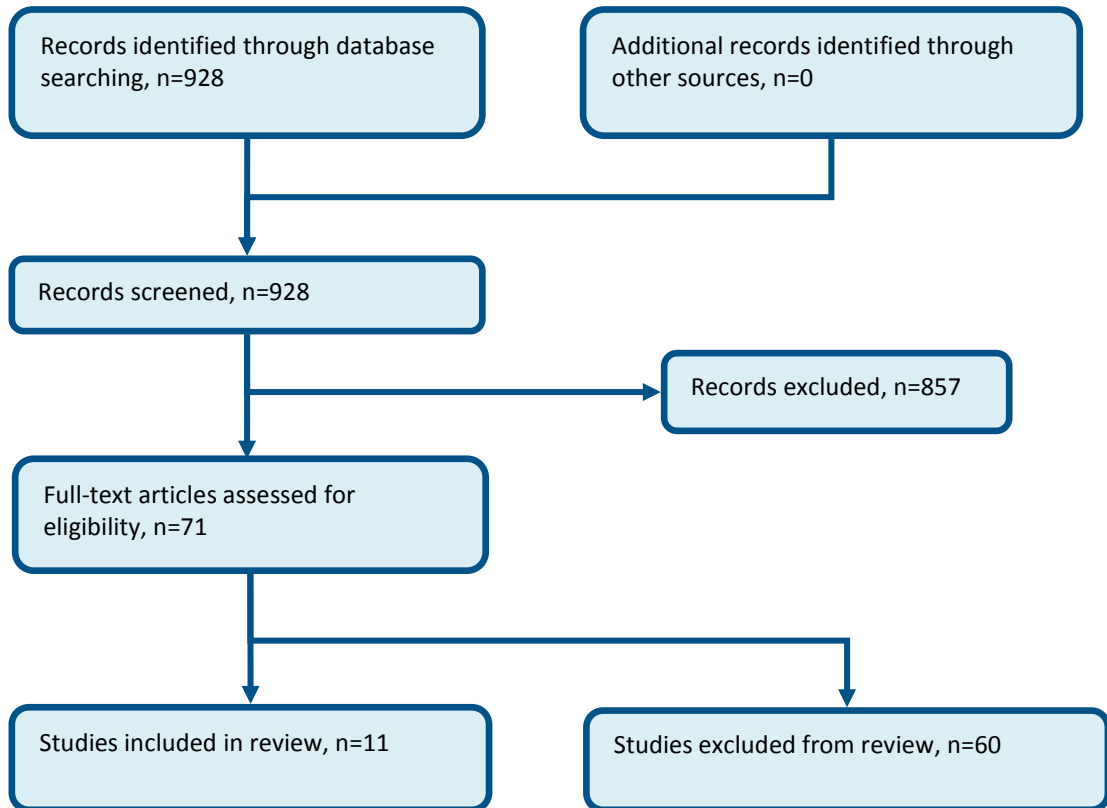
D.16 Monitoring: Questionnaires

2 **Figure 16: Flow chart of clinical article selection for the review of symptom scores/diaries or**
3 **validated questionnaires to monitor asthma control**



D.17 Monitoring: Lung function tests

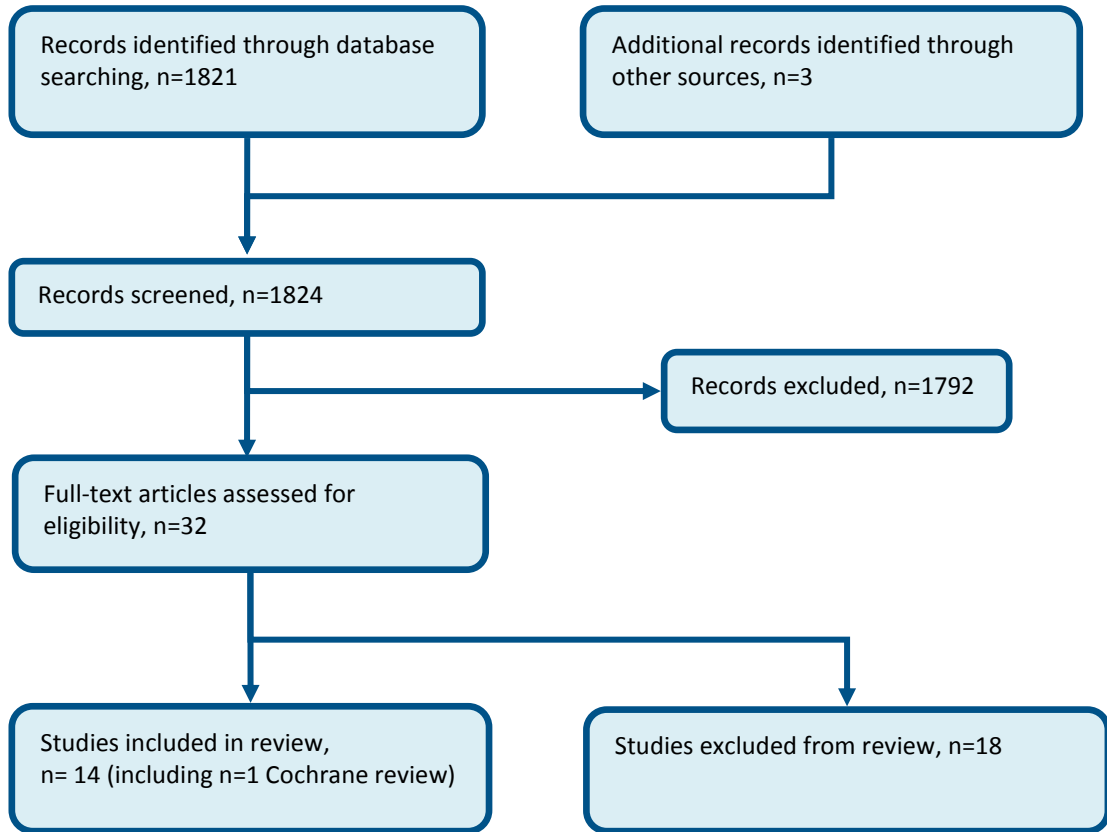
Figure 17: Flow chart of clinical article selection for the review of lung function tests to monitor asthma control



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D.18 Monitoring: FeNO

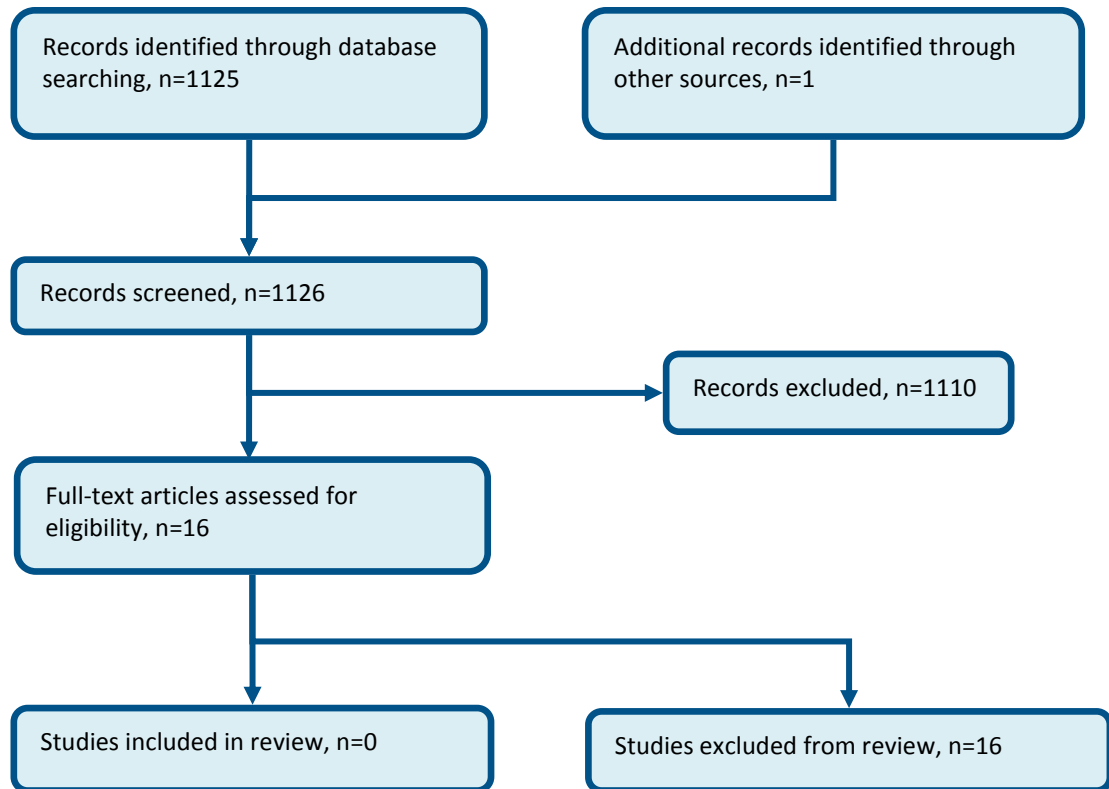
2 **Figure 18: Flow chart of clinical article selection for the review of FeNO to monitor asthma control**



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D.19 Monitoring: Peripheral blood eosinophils

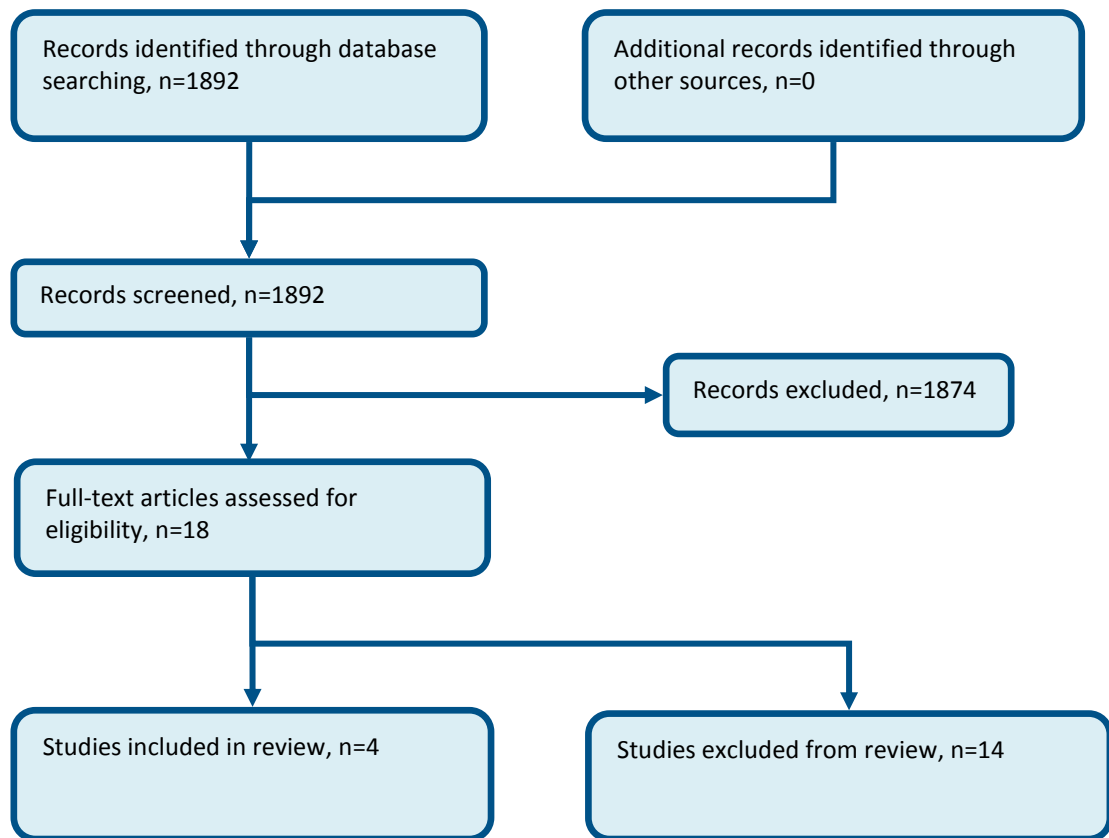
2 **Figure 19: Flow chart of clinical article selection for the review of peripheral blood eosinophils to**
3 **monitor asthma control**



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D.20 Monitoring: Challenge tests

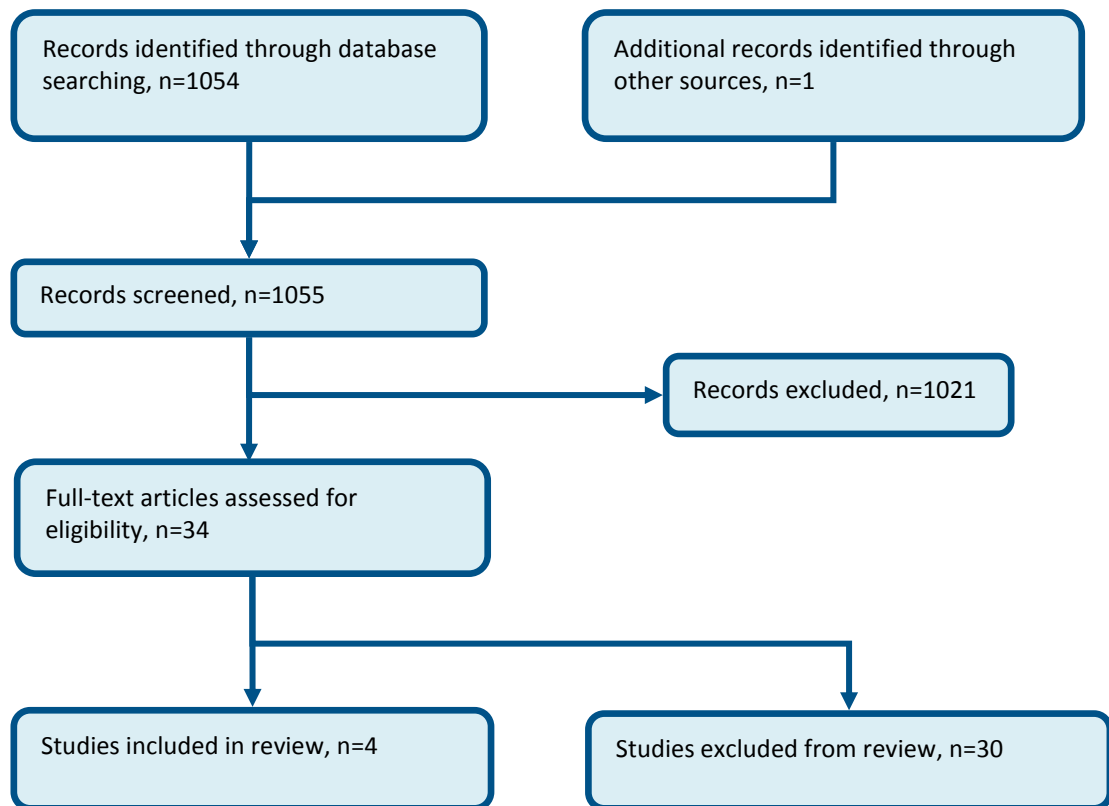
Figure 20: Flow chart of clinical article selection for the review of challenge tests to monitor asthma control



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D.21 Monitoring: Adherence to treatment

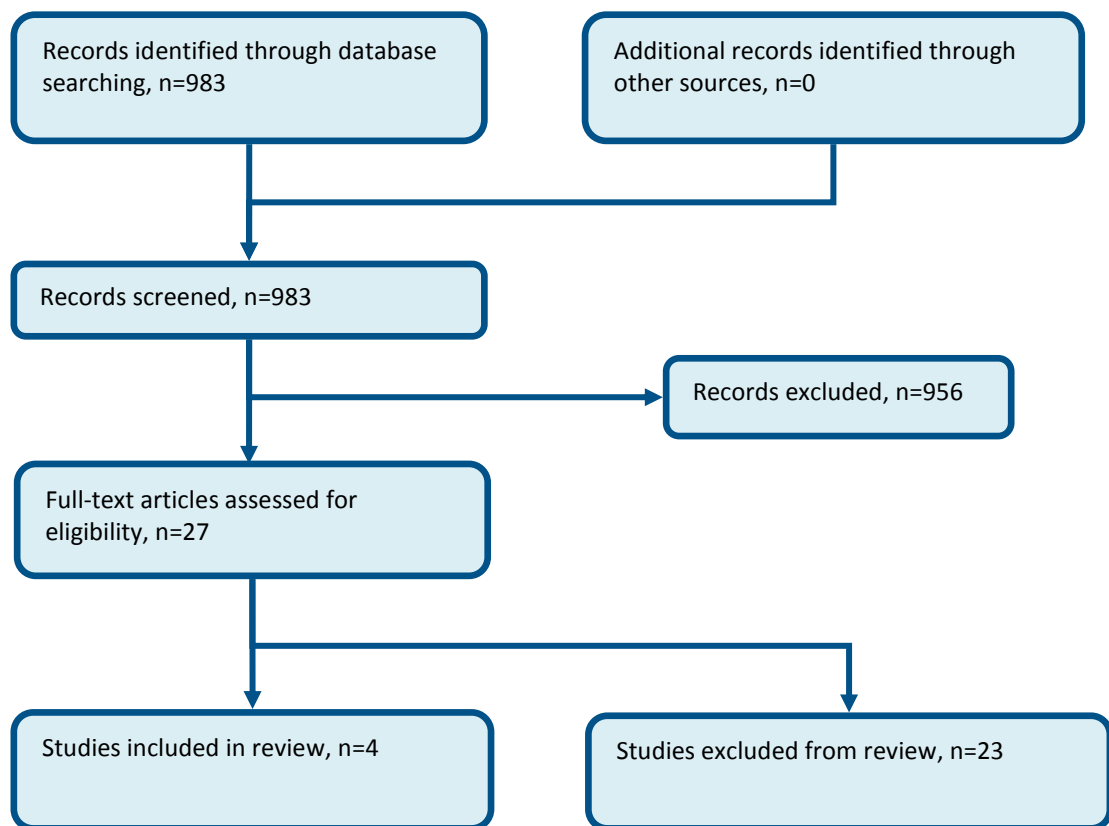
Figure 21: Flow chart of clinical article selection for the review of monitoring adherence to treatment



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D.22 Monitoring: Inhaler technique

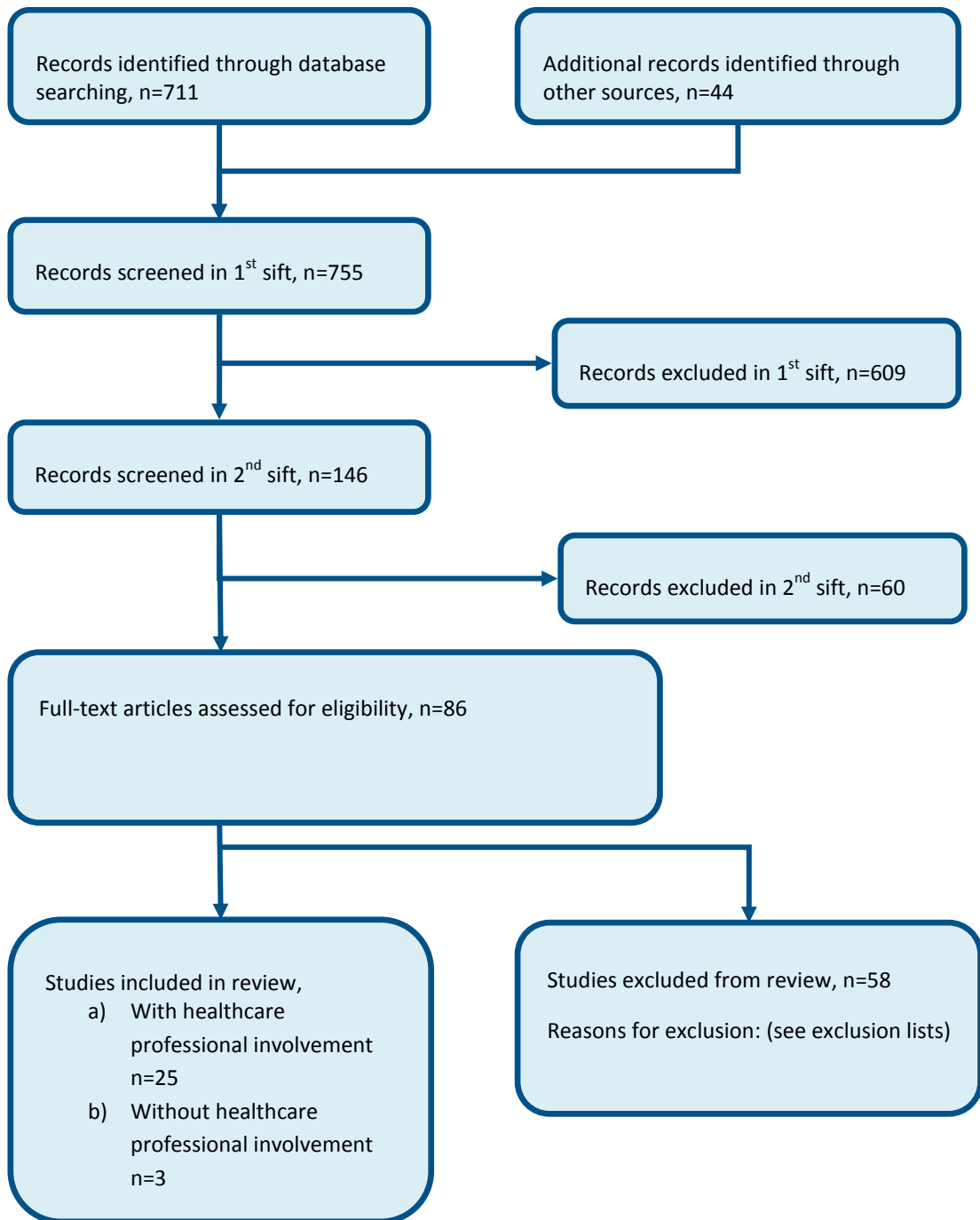
Figure 22: Flow chart of clinical article selection for the review of monitoring inhaler technique



2
3

D.23 Monitoring: Tele-healthcare

2 **Figure 23: Flow chart of clinical article selection for the review of tele-healthcare to monitor**
3 **asthma control**

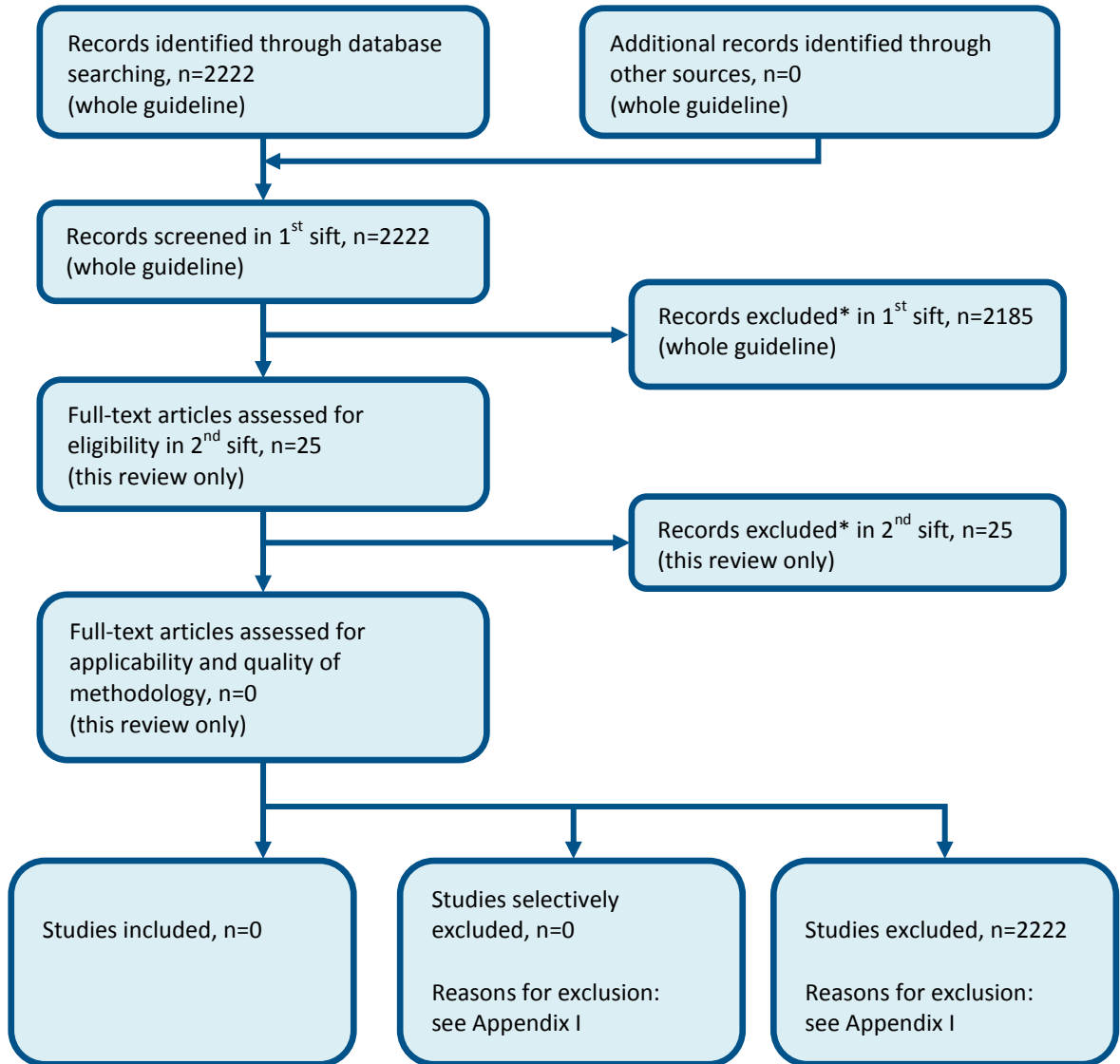


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1 Appendix E: Economic article selection

2 E.1 Diagnosis: Signs and symptoms

Figure 24: Flow chart of economic article selection for the review of signs and symptoms

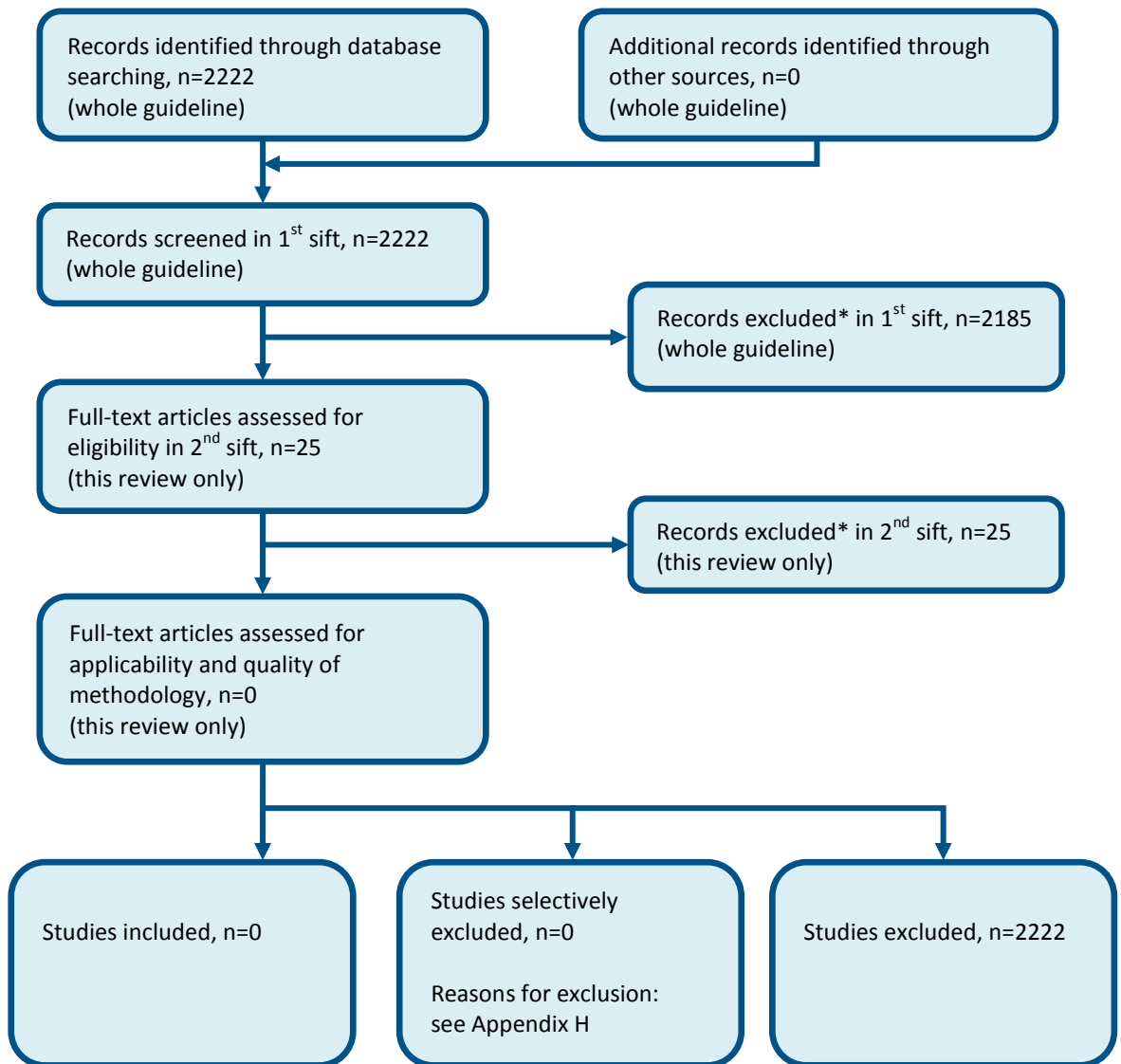


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1 E.2 Diagnosis: History of atopic disorders

Figure 25: Flow diagram of economic article selection for the review of history of atopic disorders

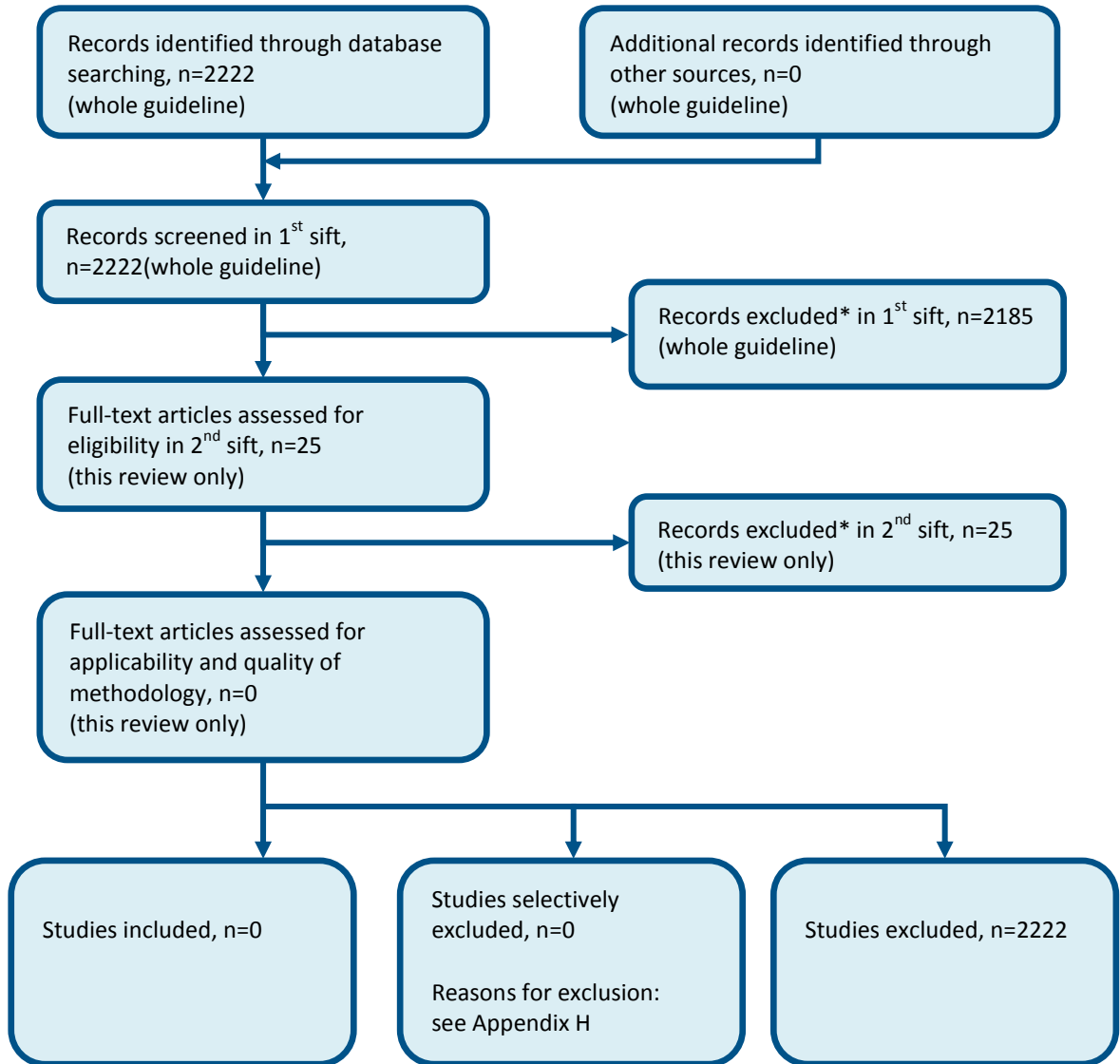


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1 E.3 Diagnosis: Symptoms after exercise

Figure 26: Flow diagram of economic article selection for the review of symptoms in response to exercise

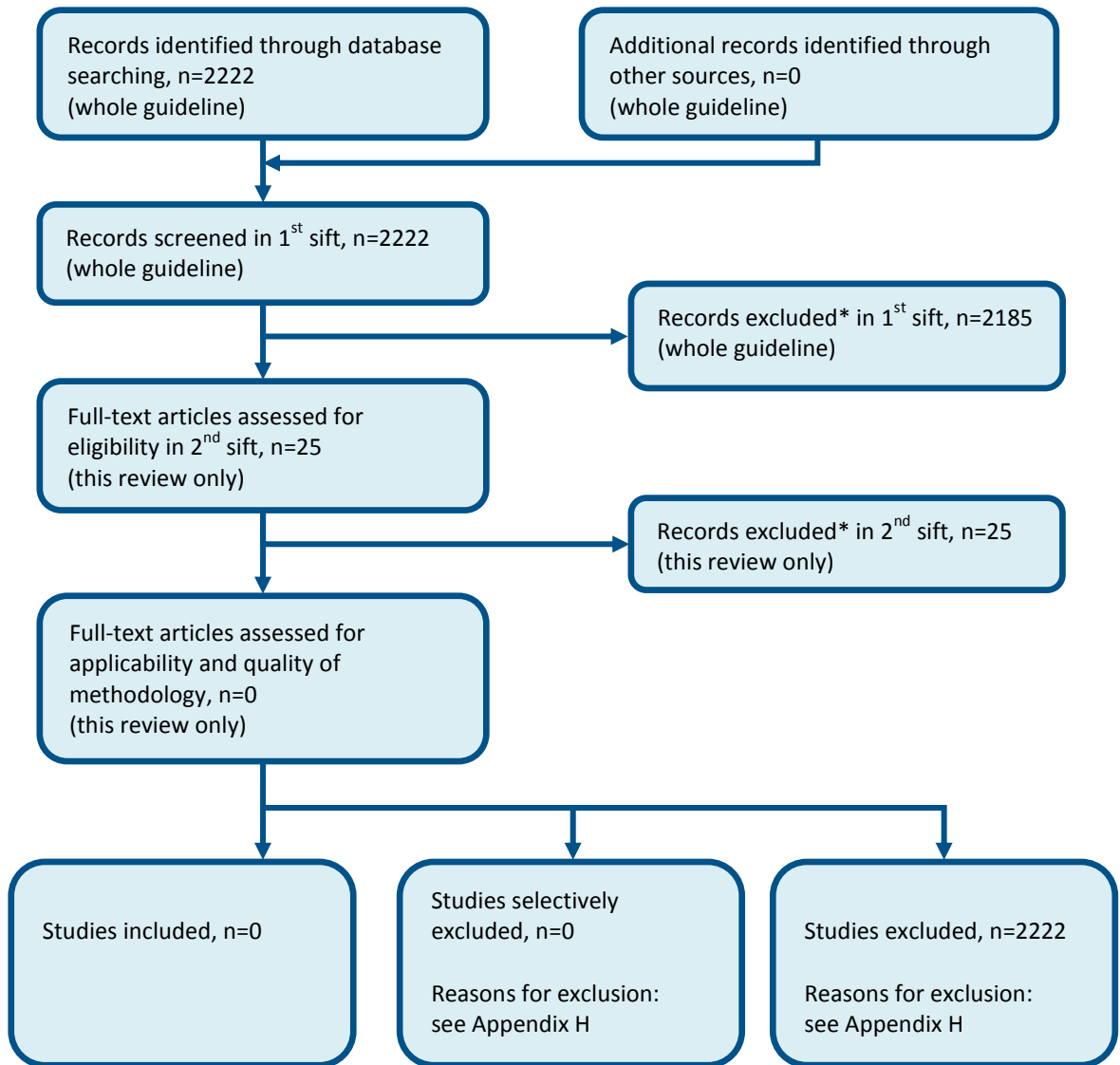


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1 E.4 Diagnosis: Symptoms after drugs

Figure 27: Flow diagram of economic article selection for the review of history of symptoms after drugs

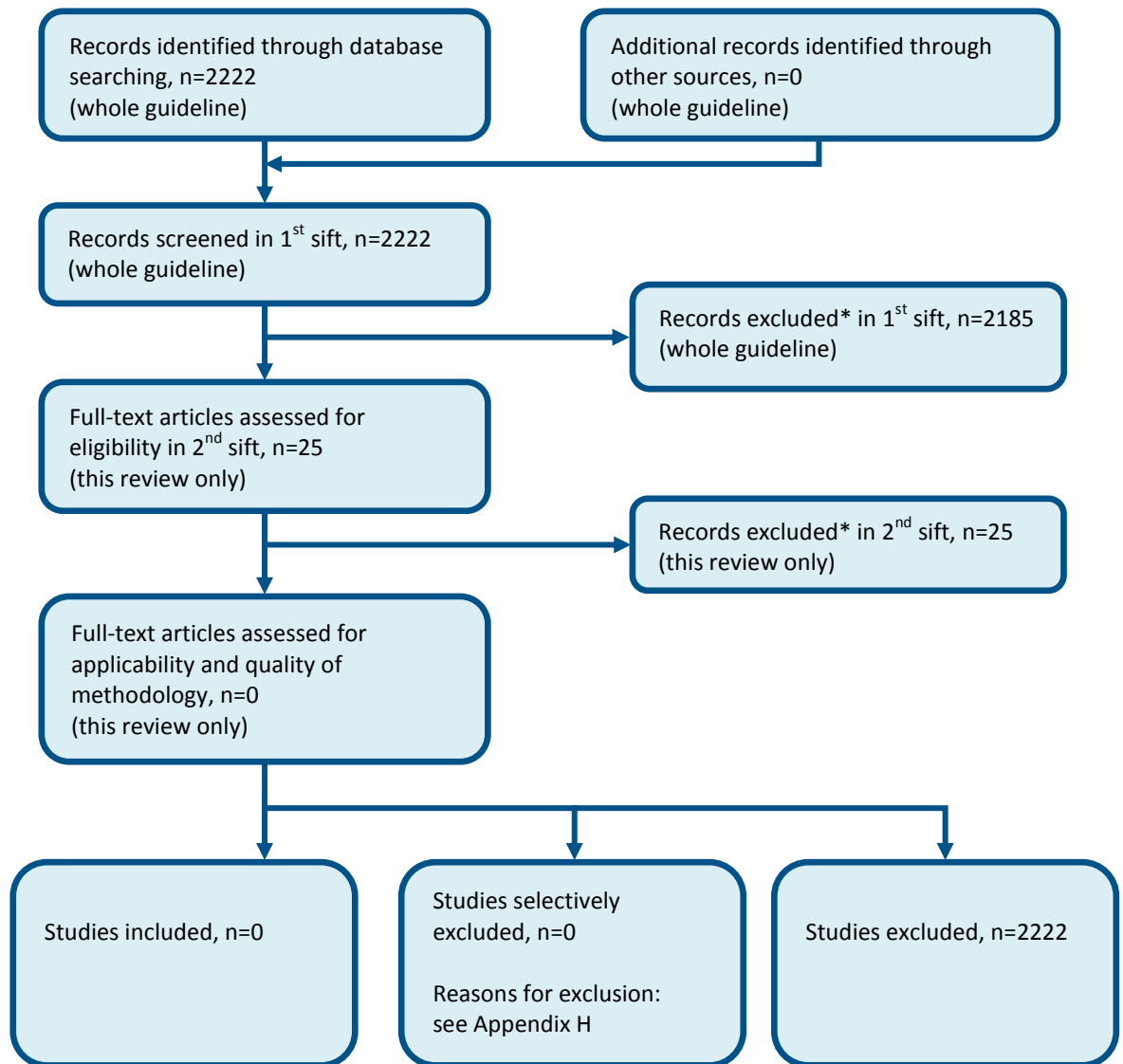


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1 E.5 Diagnosis: Occupational asthma

Figure 28: Flow diagram of economic article selection for the review of occupational asthma

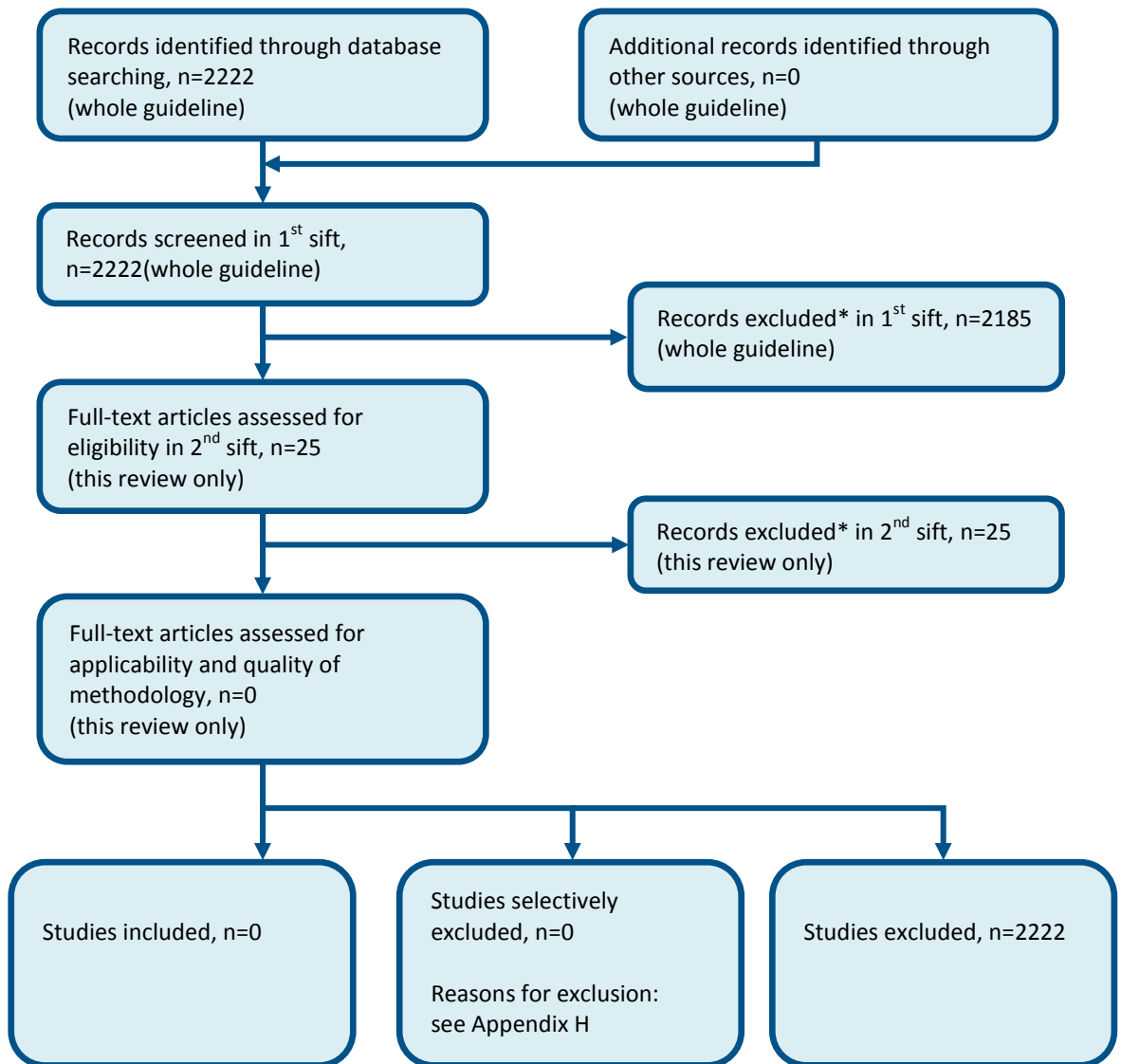


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1 E.6 Diagnosis: Spirometry

Figure 29: Flow diagram of economic article selection for the review of spirometry

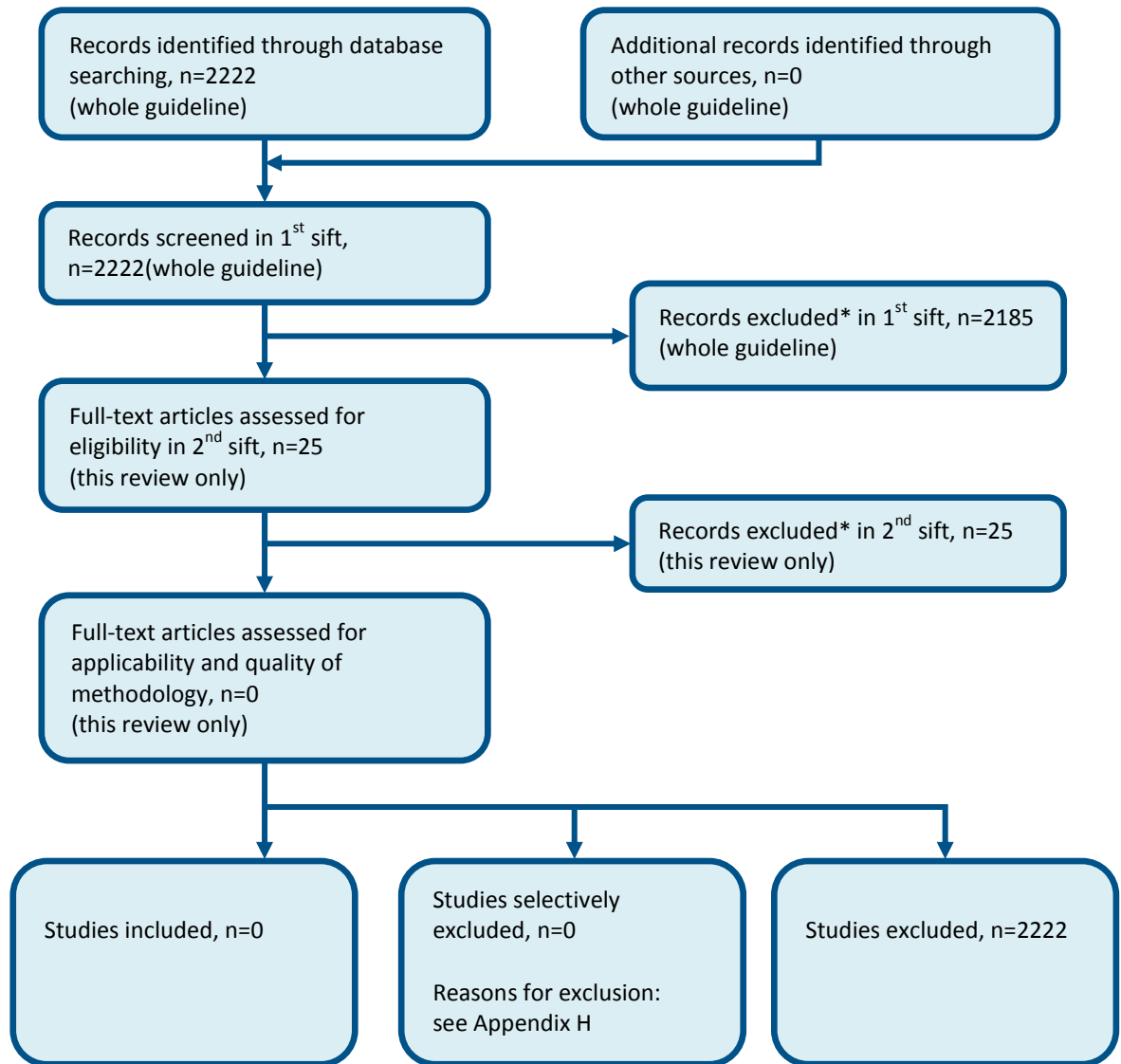


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1 E.7 Diagnosis: Bronchodilator reversibility

Figure 30: Flow diagram of economic article selection for the review of bronchodilator reversibility

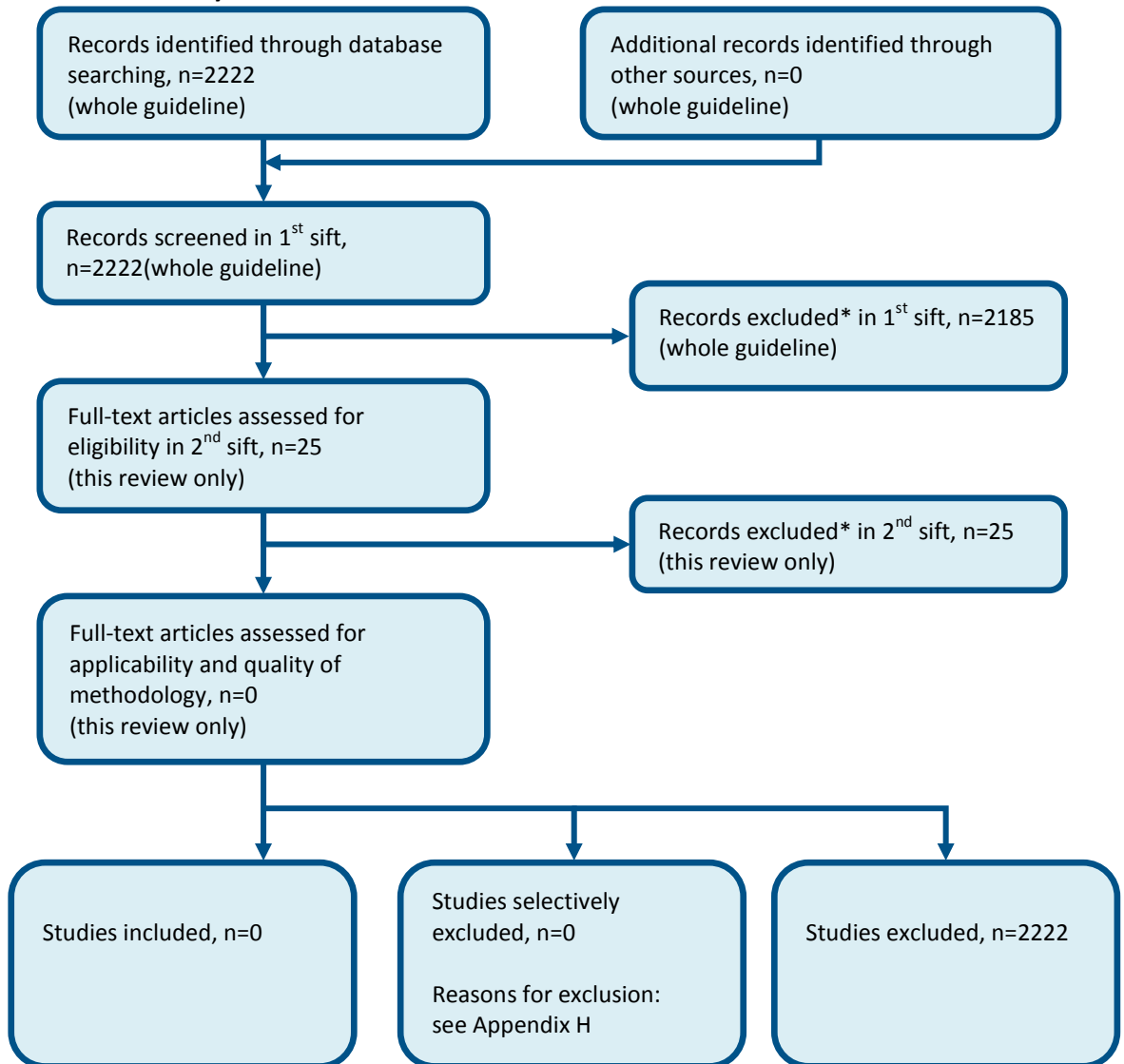


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1 E.8 Diagnosis: PEF variability

Figure 31: Flow chart of economic article selection for the review of peak expiratory flow variability

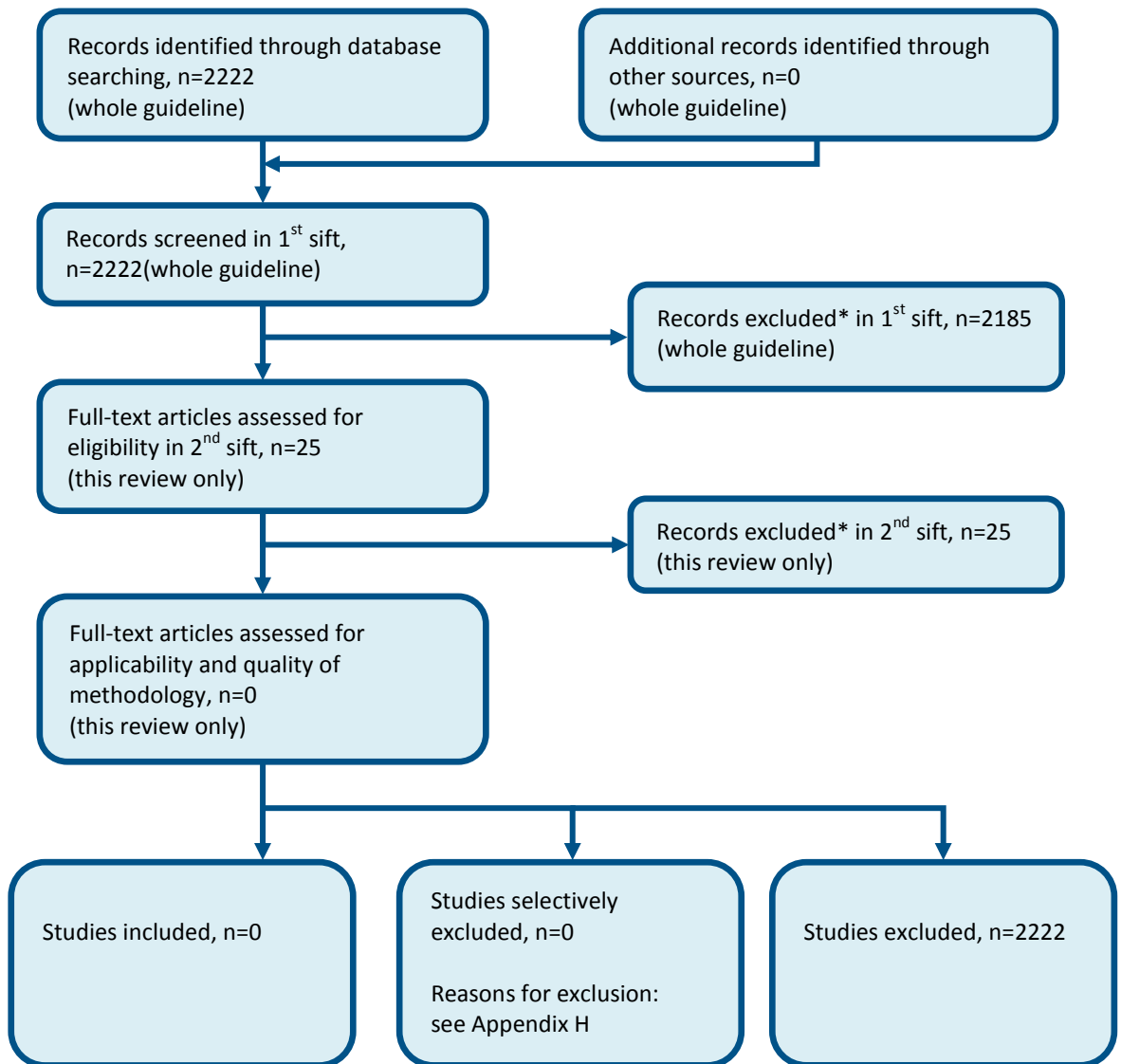


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1 E.9 Diagnosis: Skin prick tests

Figure 32: Flow diagram of economic article selection for the review of skin prick tests

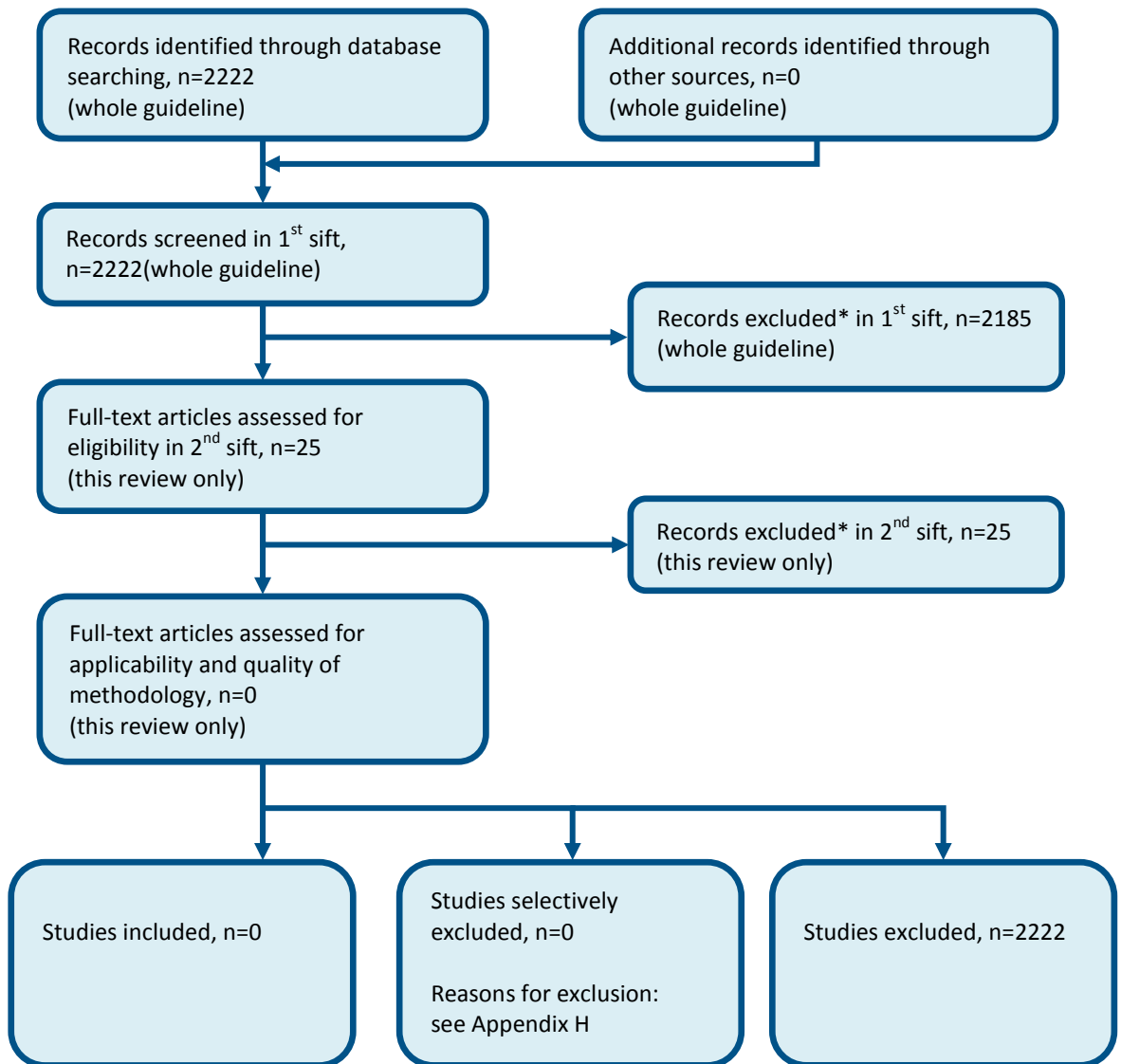


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.10 Diagnosis: IgE

Figure 33: Flow diagram of economic article selection for the review of IgE

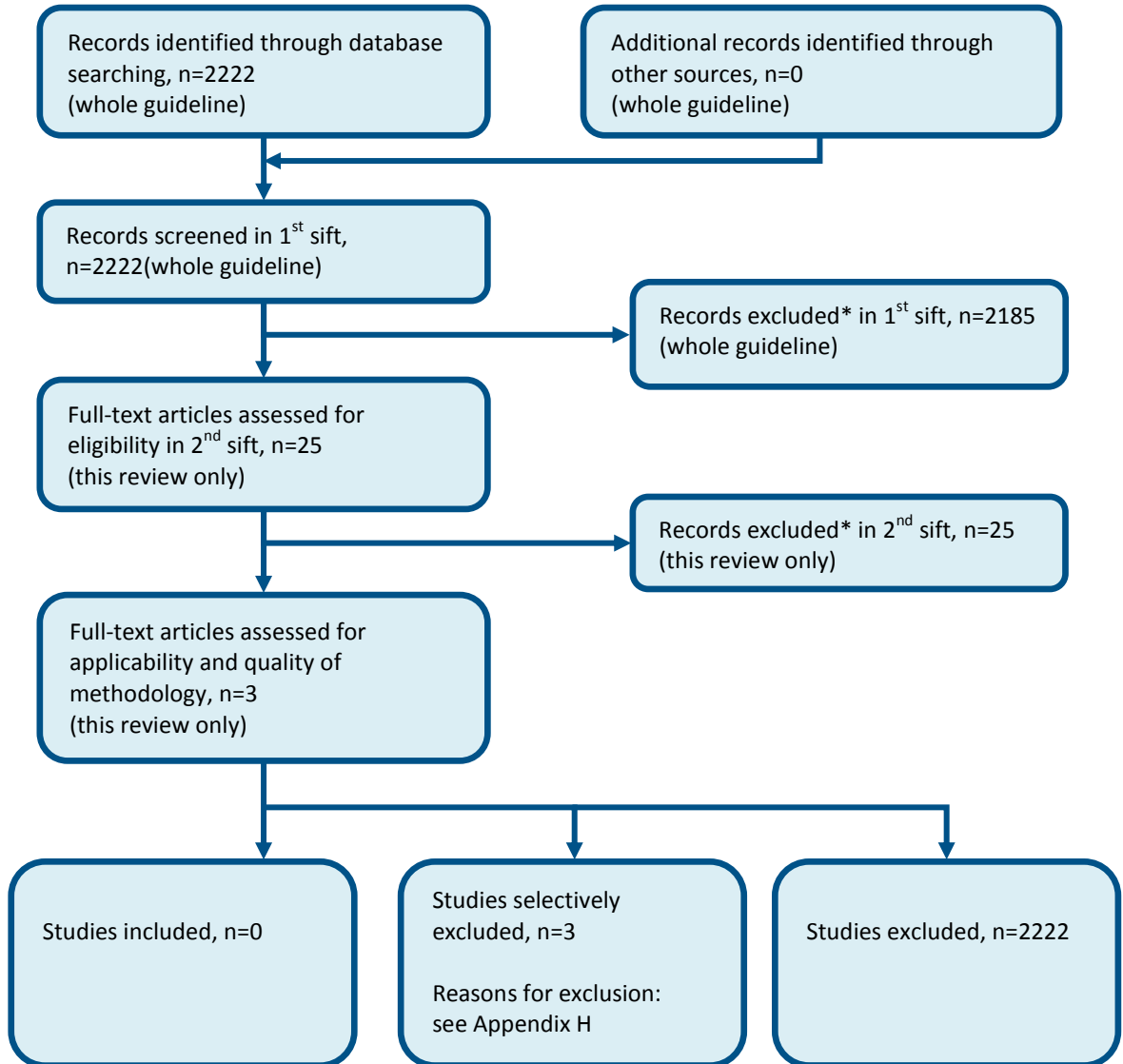


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.11 Diagnosis: FeNO

Figure 34: Flow chart of economic article selection for the review of FeNO for asthma diagnosis

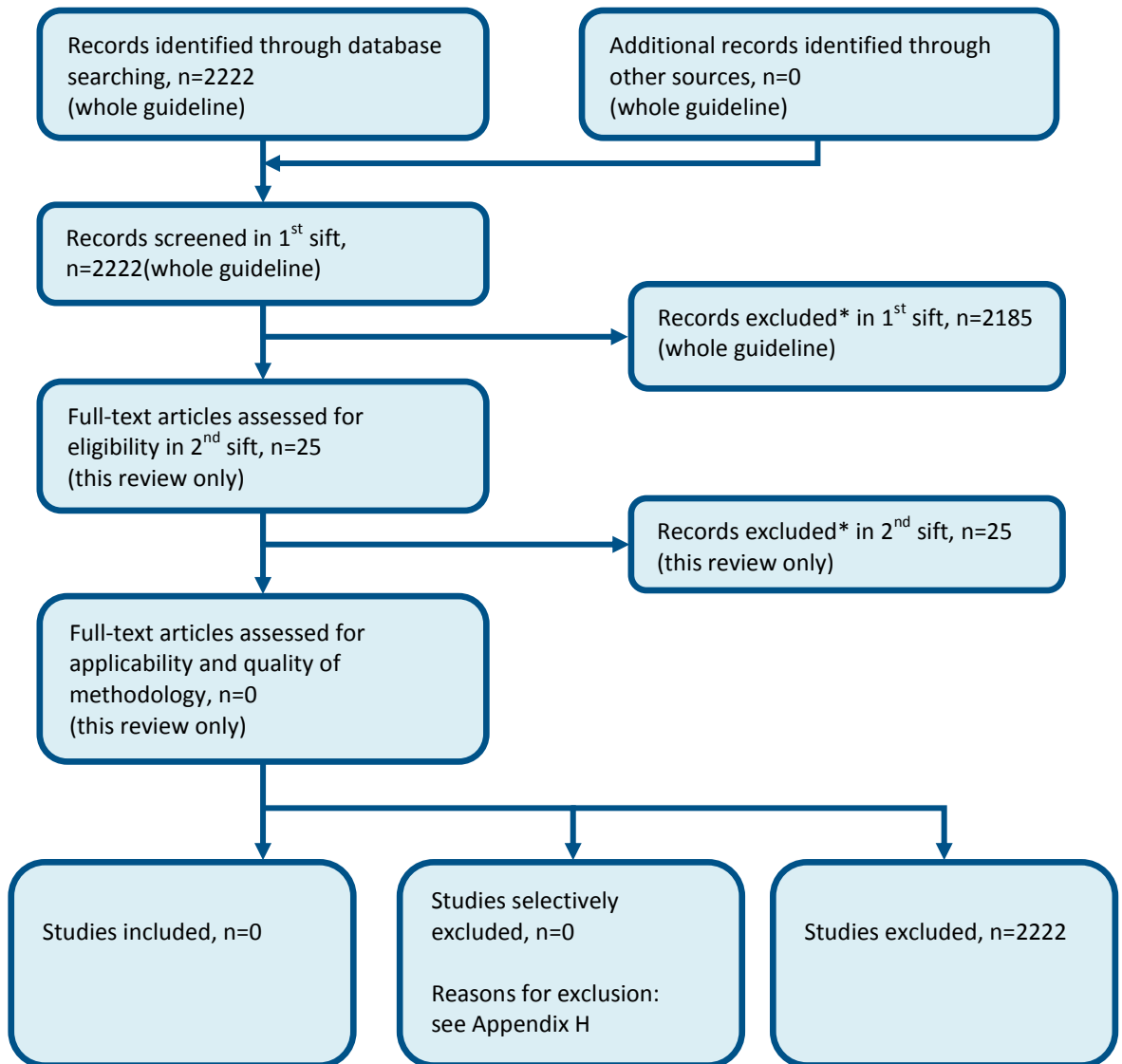


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.12 Diagnosis: Eosinophils

2 **Figure 35: Flow diagram of economic article selection for the review of eosinophils**

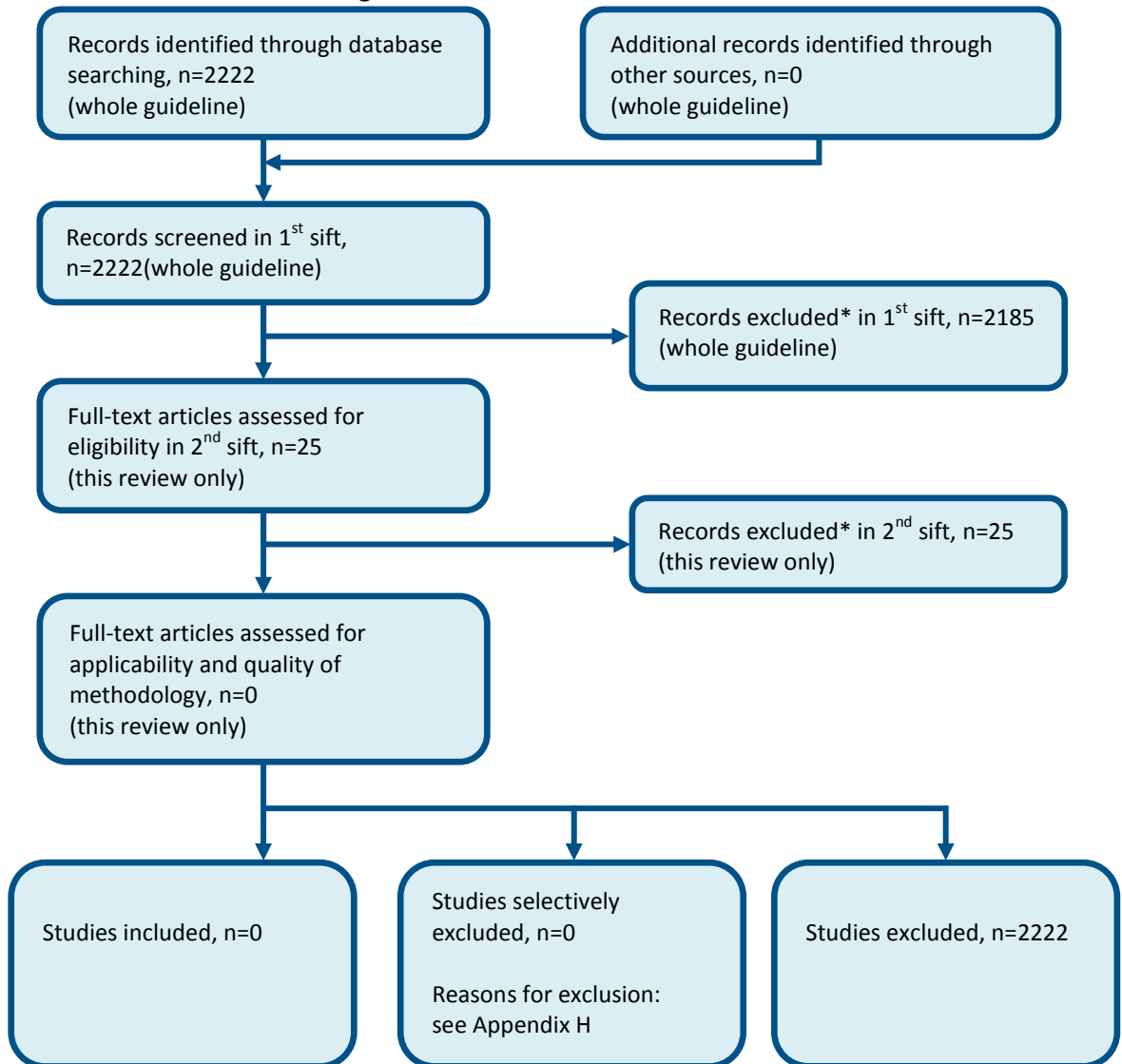


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.13 Diagnosis: Histamine and methacholine

Figure 36: Flow diagram of economic article selection for the review of histamine and methacholine challenge tests

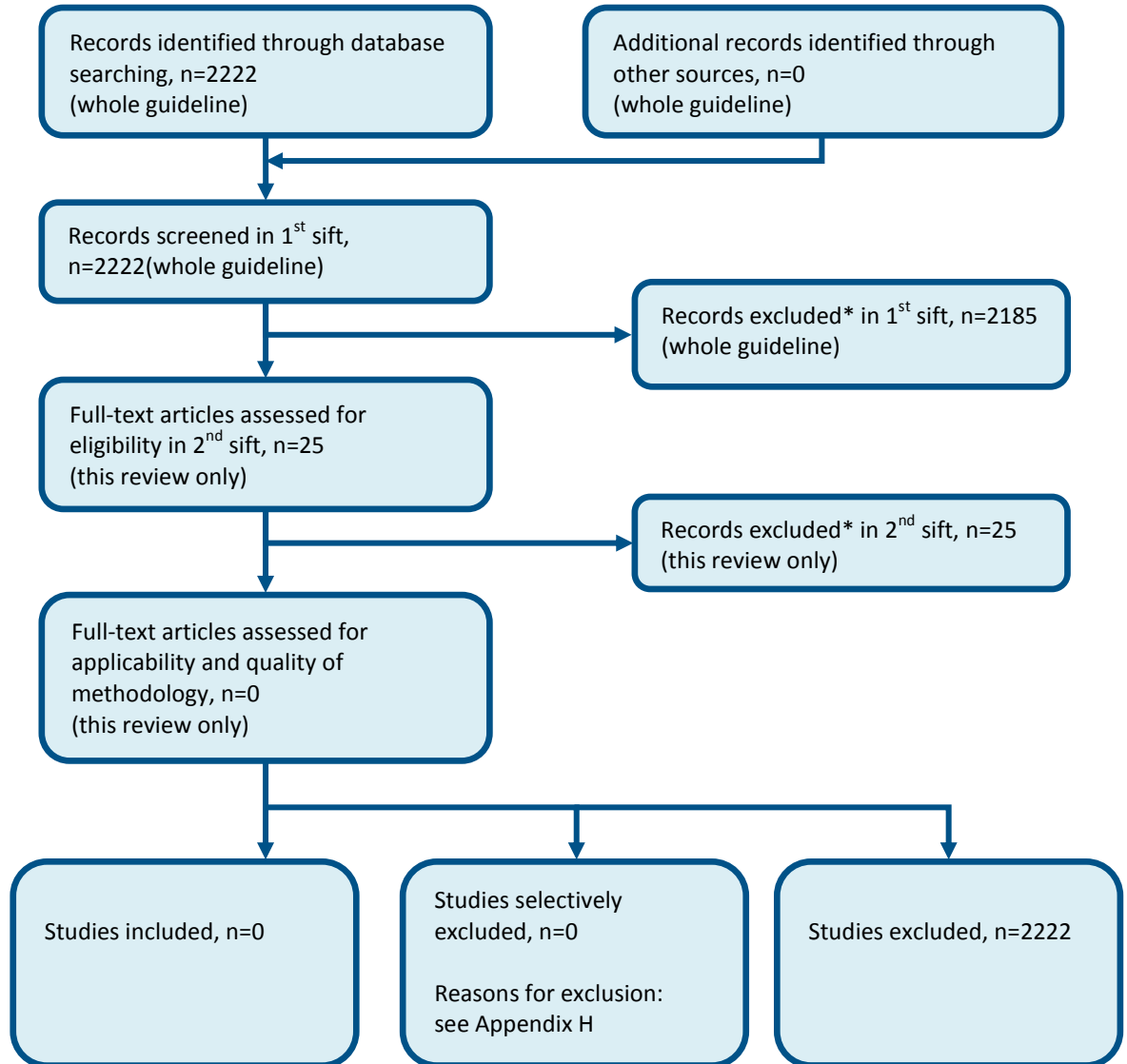


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.14 Diagnosis: Mannitol

Figure 37: Flow chart of economic article selection for the review of mannitol challenge test

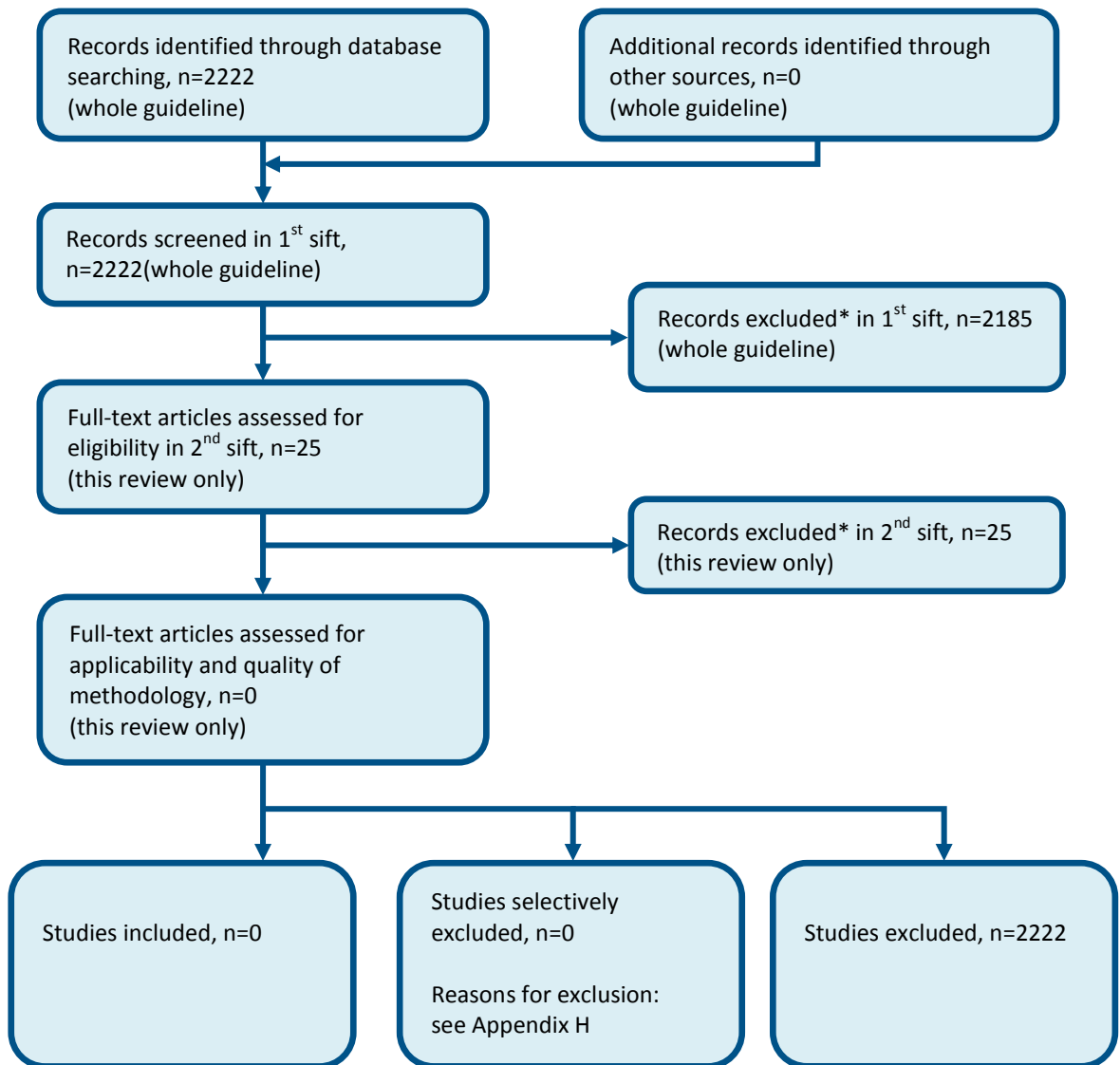


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.15 Diagnosis: Exercise challenge test

Figure 38: Flow diagram of economic article selection for the review of exercise challenge tests

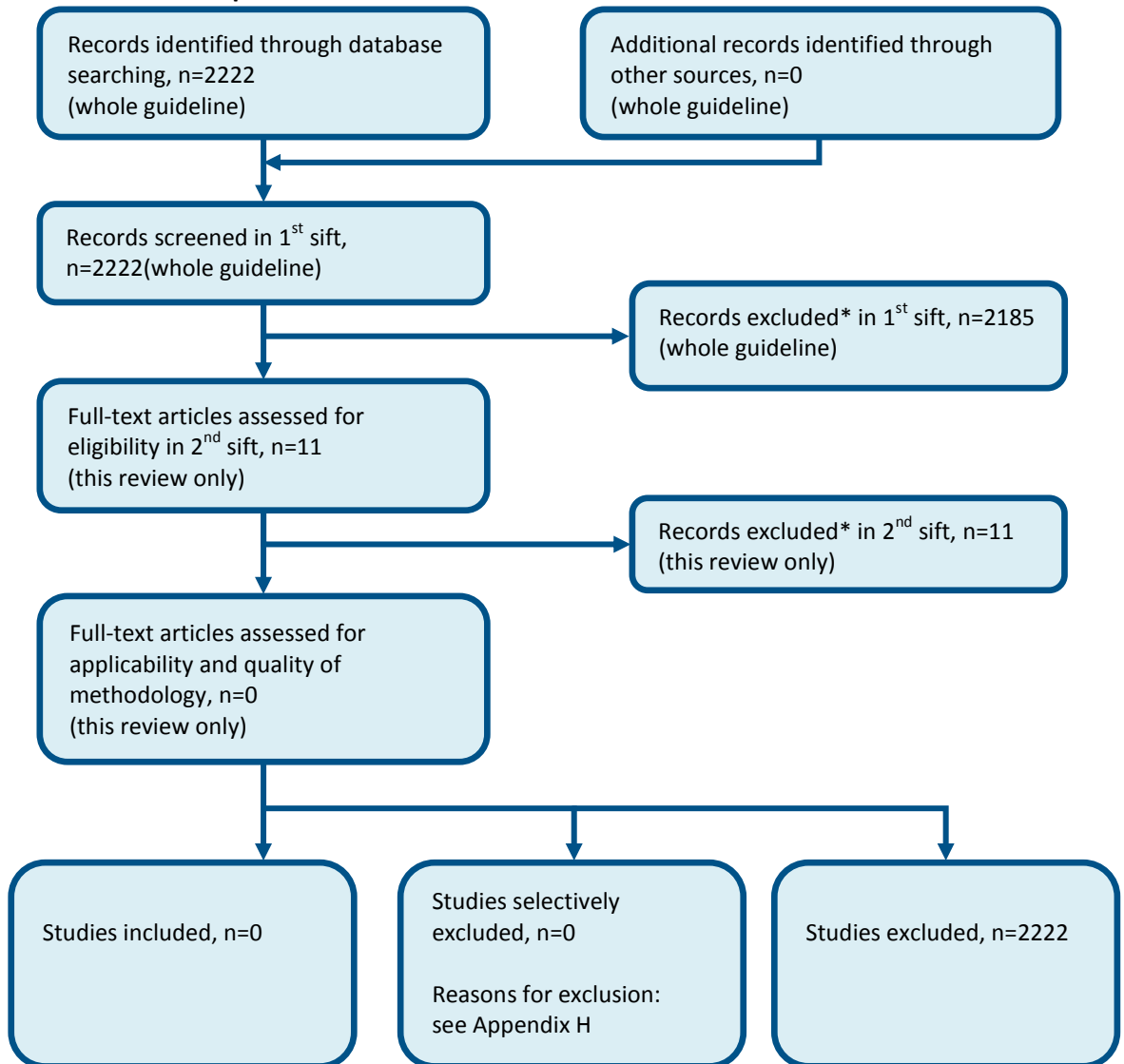


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.16 Monitoring: Questionnaires

Figure 39: Flow chart of economic article selection for the review of symptom scores/diaries or validated questionnaires to monitor asthma control

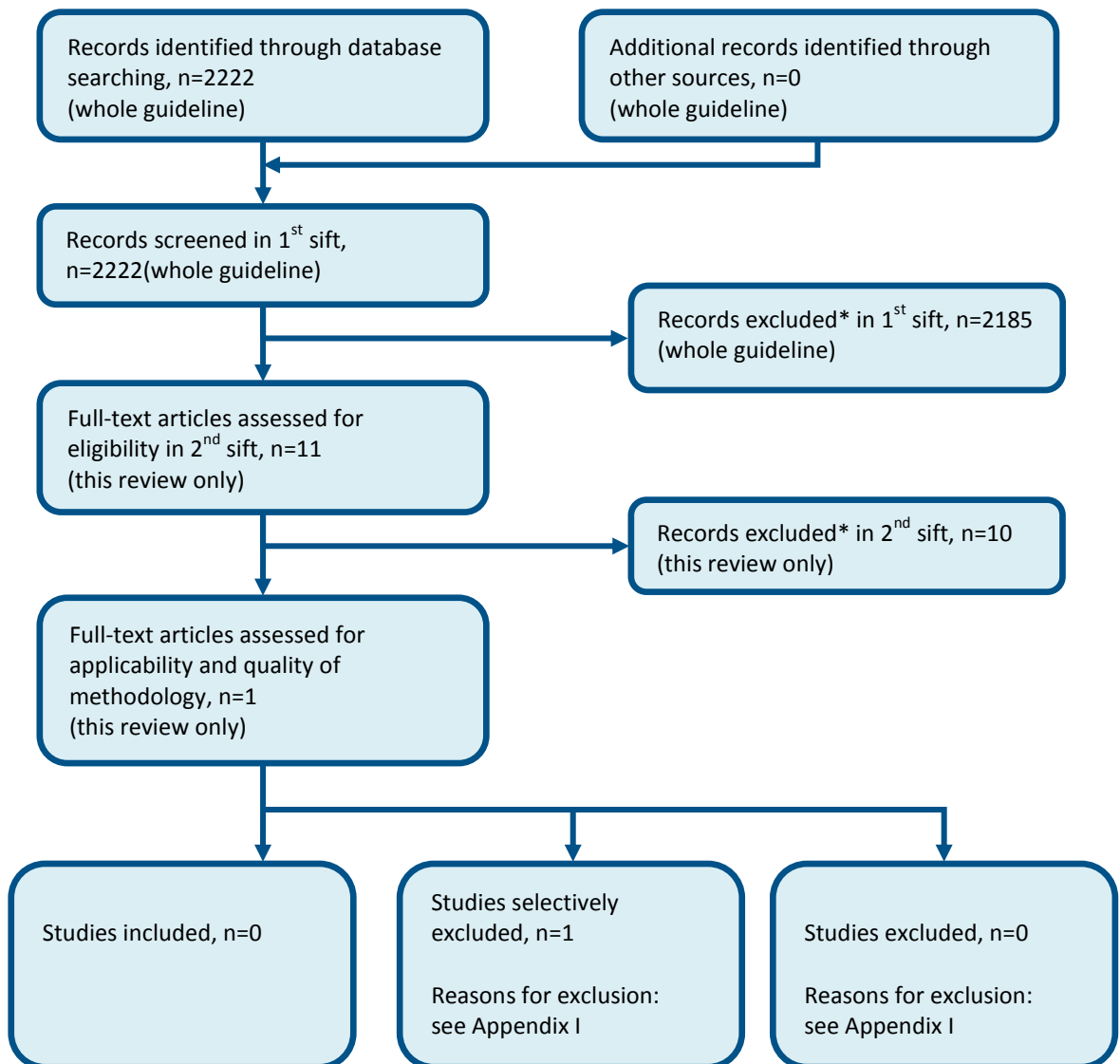


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.17 Monitoring: Lung function tests

Figure 40: Flow chart of economic article selection for the review of lung function tests to monitor asthma control

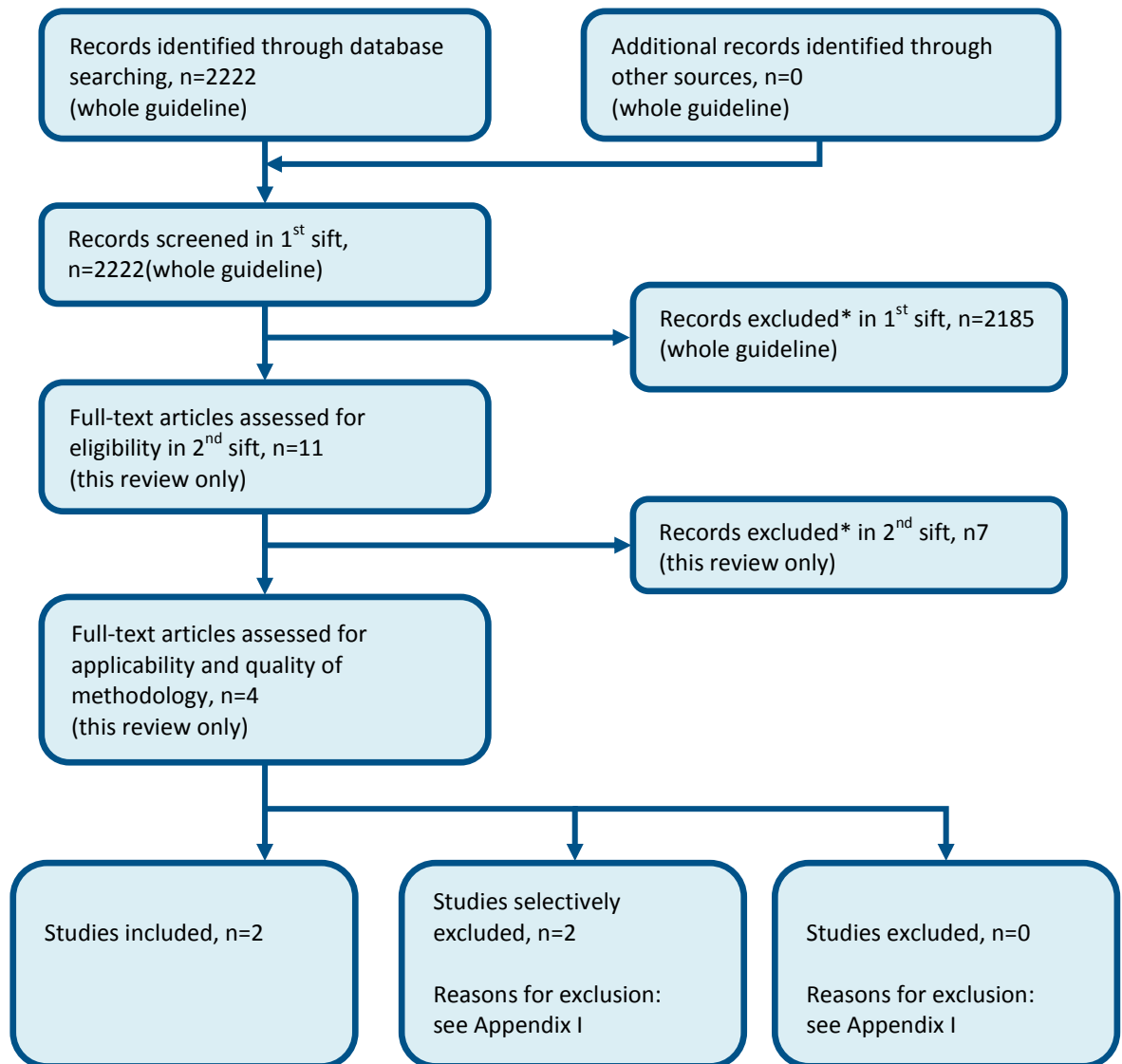


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.18 Monitoring: FeNO

Figure 41: Flow chart of economic article selection for the review of FeNO to monitor asthma control

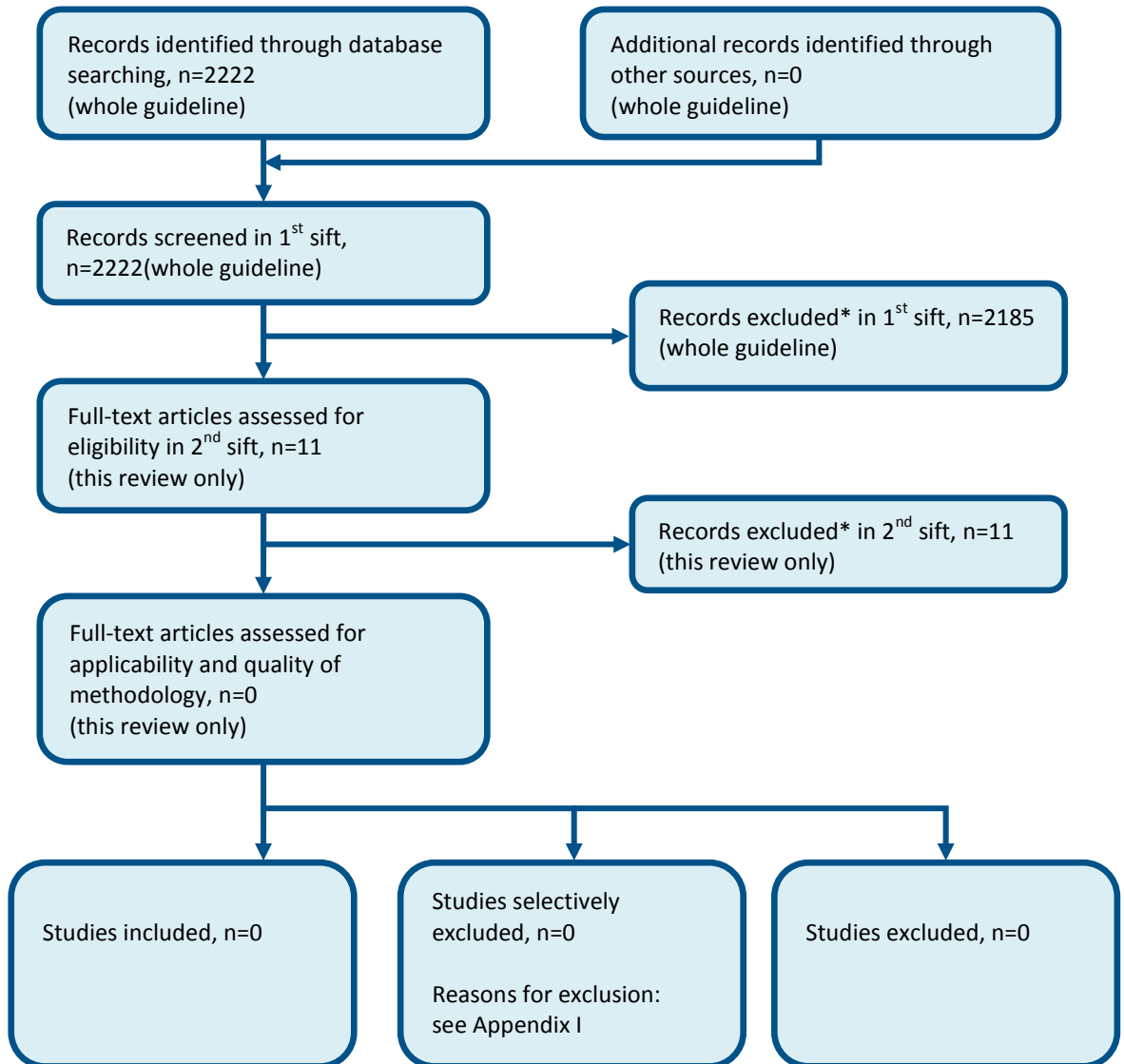


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.19 Monitoring: Peripheral blood eosinophils

Figure 42: Flow chart of economic article selection for the review of peripheral blood eosinophils to monitor asthma control

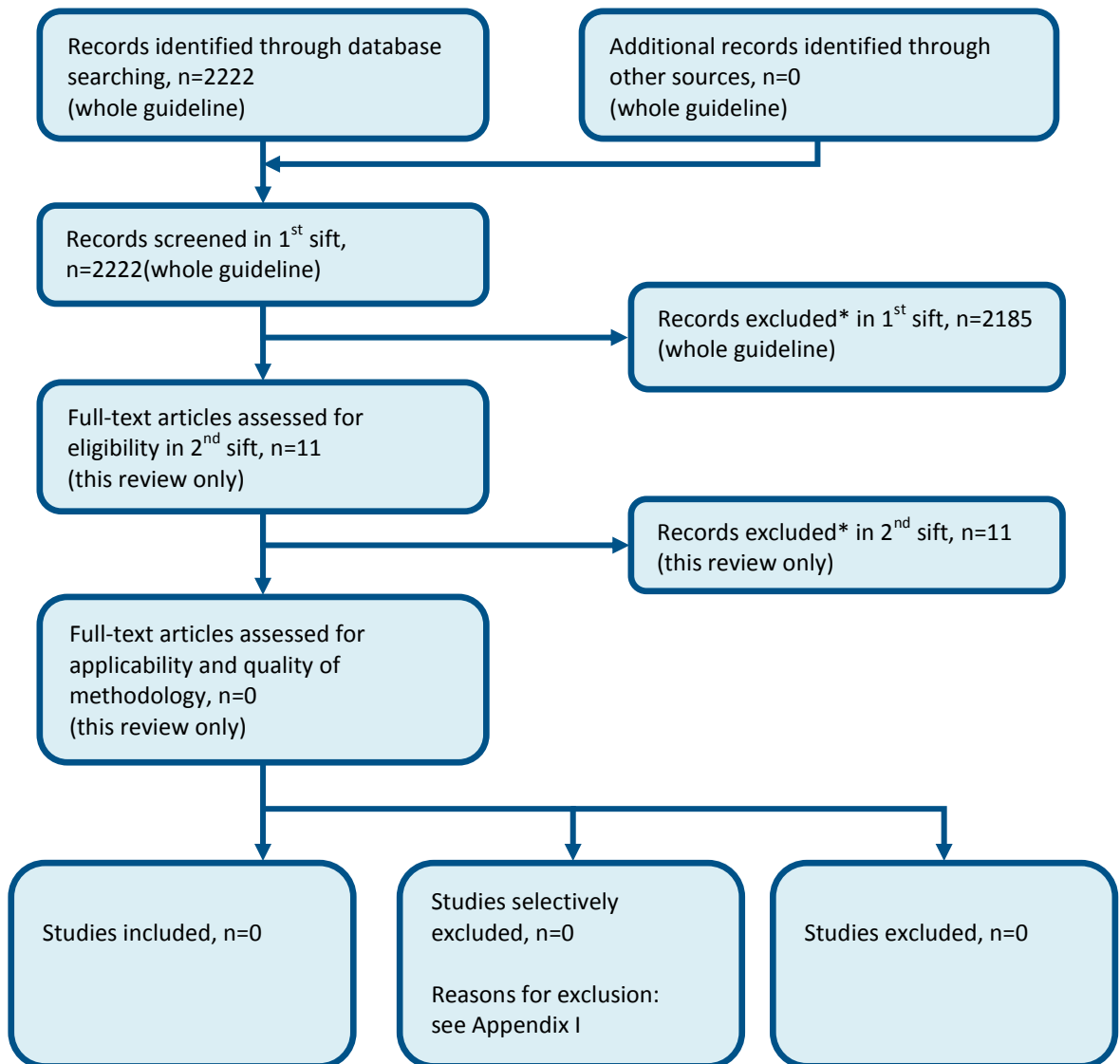


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.20 Monitoring: Challenge tests

Figure 43: Flow chart of economic article selection for the review of challenge tests to monitor asthma control

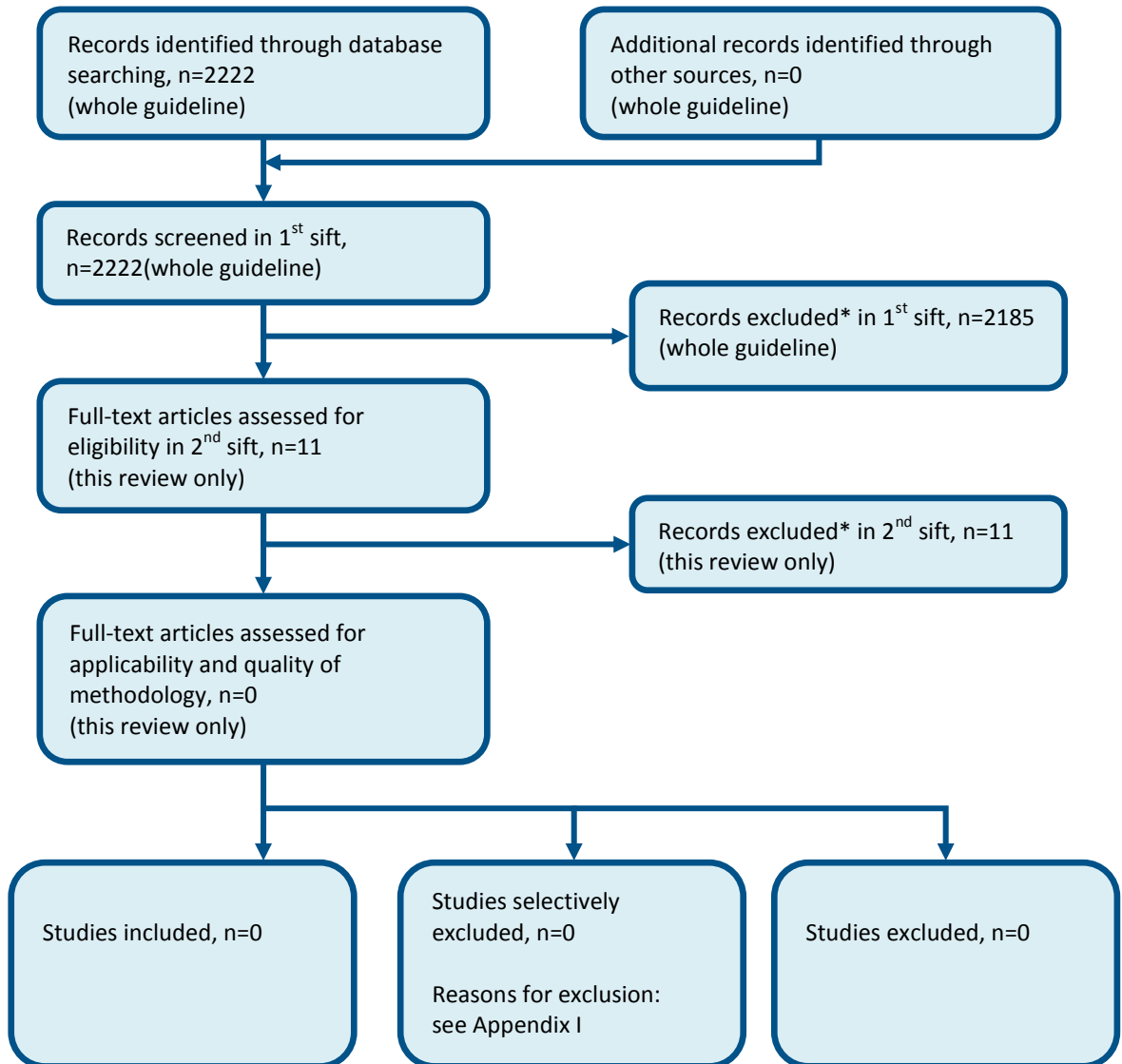


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.21 Monitoring: Adherence to treatment

Figure 44: Flow chart of economic article selection for the review of monitoring adherence to treatment

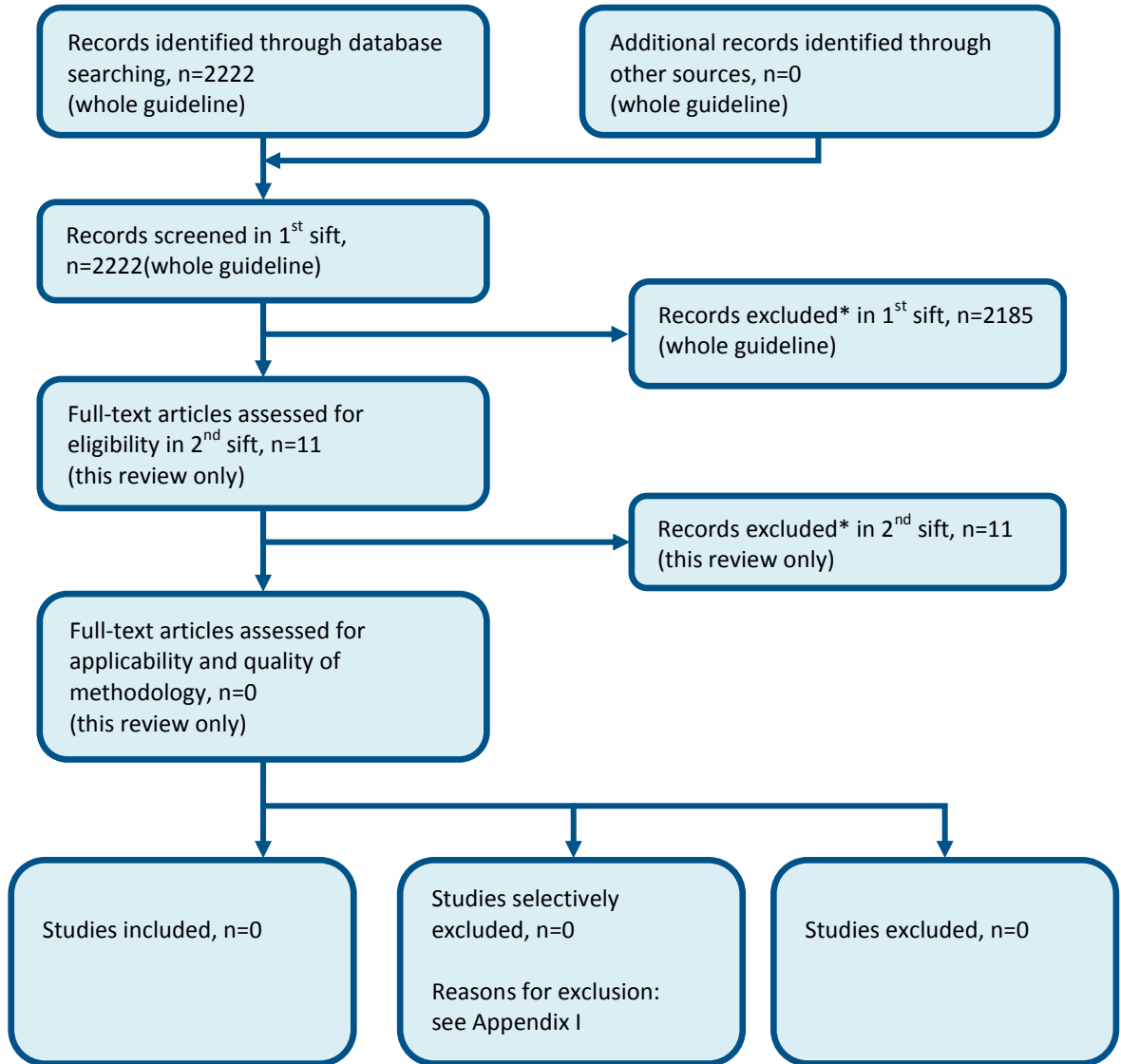


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.22 Monitoring: Inhaler technique

Figure 45: Flow chart of economic article selection for the review of monitoring inhaler technique

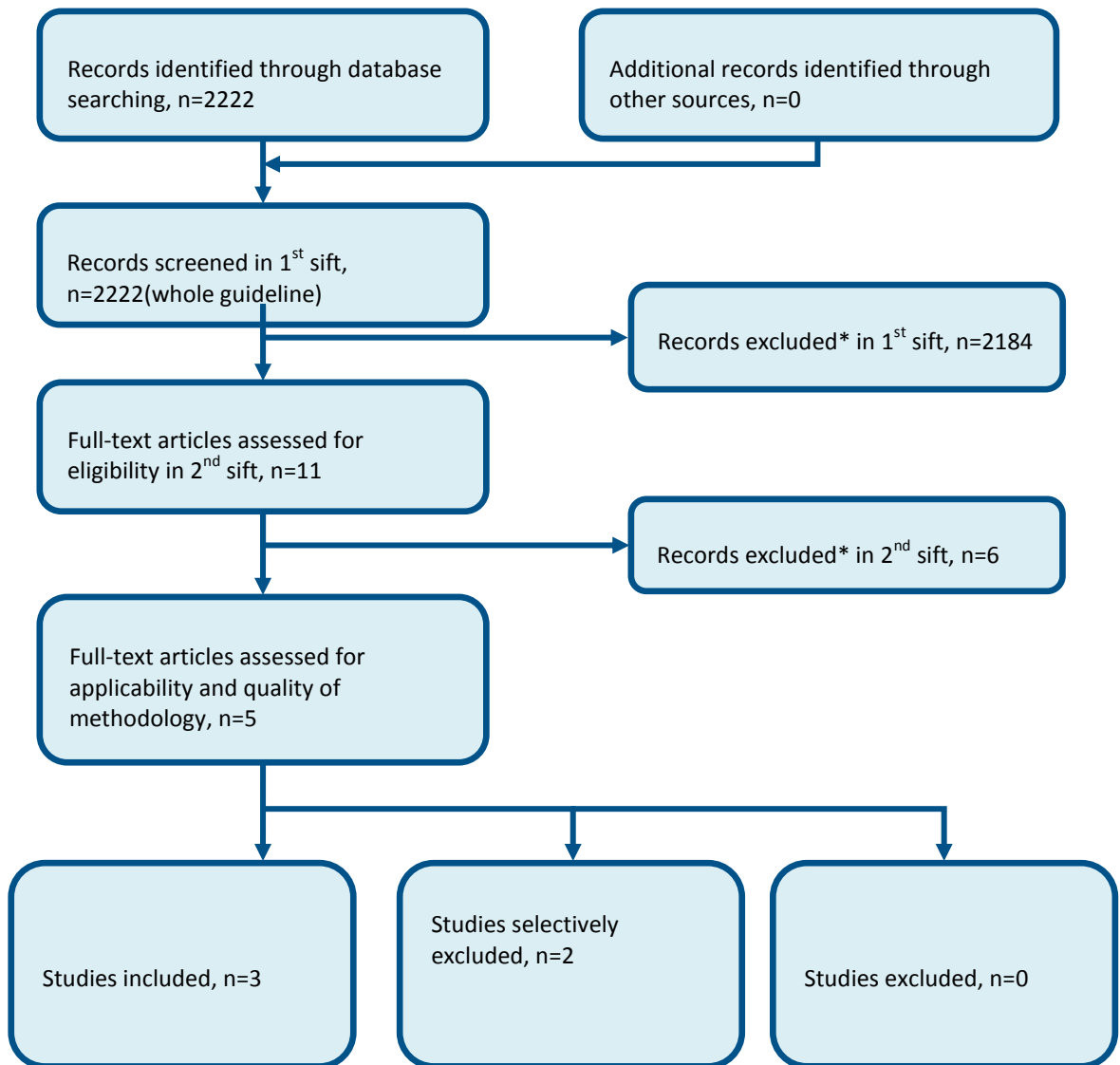


* Non-relevant population, intervention, comparison, design or setting; non-English language

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1E.23 Monitoring: Tele-healthcare

Figure 46: Flow chart of economic article selection for the review of tele-healthcare to monitor asthma control



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

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1 Appendix F: Literature search strategies

2 Contents

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F.2.2	Randomised controlled trials (RCT)
F.2.3	Observational studies (OBS)
F.2.4	Diagnostic test accuracy studies (DIAG1)
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F.2.8	Health economic studies (HE)
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Section F.4	Health economics searches
F.4.1	Health economic reviews
F.4.2	Quality of life reviews
Appendix P:	References

1 Search strategies used for the asthma guideline are outlined below and were run in accordance with
 2 the methodology in the NICE guidelines manual 2012.¹²¹⁶ All searches were run up to 1 October 2014
 3 unless otherwise stated. Any studies added to the databases after this date (even those published
 4 prior to this date) were not included unless specifically stated in the text. We do not routinely search
 5 for electronic, ahead of print or “online early” publications. Where possible searches were limited to
 6 retrieve material published in English.

7 **Table 24: Database date parameters**

Database	Dates searched
Medline	1946—1 October 2014
Embase	1980 – 1 October 2014 (week 39)
The Cochrane Library	Cochrane Reviews to 2014 Issue 10 of 12 CENTRAL to 2014 Issue 9 of 12 DARE, HTA and NHSEED to 2014 Issue 3 of 4

8 Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane
 9 Library (Wiley).

10 Searches for **intervention and diagnostic studies** were usually constructed using a PICO format
 11 where population (P) terms were combined with Intervention (I) and sometimes Comparison (C)
 12 terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used
 13 in search strategies for interventions. Search filters were also added to the search where
 14 appropriate.

15 Searches for **prognostic studies** were usually constructed combining population terms with
 16 prognostic variable terms and sometimes outcomes. Search filters were added to the search where
 17 appropriate.

18 Searches for the **health economic reviews** were run in Medline (OVID), Embase (OVID), the NHS
 19 Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and
 20 the Health Economic Evaluation Database (HEED). Searches in NHS EED and HEED were constructed
 21 using population terms only. For Medline and Embase an economic filter (instead of a study type
 22 filter) was added to the same clinical search strategy.

23 F.1 Population search strategies

24 F.1.1 Standard population

25 This population was used in all clinical questions except F.3.5 occupational asthma.

26 Medline and Embase search terms

1.	exp asthma/
2.	asthma*.ti.

3.	or/1-2
----	--------

1 **Cochrane search terms**

#1.	MeSH descriptor: [Asthma] explode all trees
#2.	asthma*:ti
#3.	{or #1-#2}

2 **F.2 Study filter search terms**

3 **F.2.1 Systematic review (SR) search terms**

4 **Medline search terms**

1.	meta-analysis/
2.	meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(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.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

5 **Embase search terms**

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(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.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

6 **F.2.2 Randomised controlled trials (RCTs) search terms**

7 **Medline search terms**

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomi#ed.ab.
4.	placebo.ab.
5.	randomly.ab.
6.	clinical trials as topic.sh.

7.	trial.ti.
8.	or/1-7

1 **Embase search terms**

1.	random*.ti,ab.
2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	crossover procedure/
7.	double blind procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

2 **F.2.3 Observational studies (OBS) search terms**

3 **Medline search terms**

1.	epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/
4.	cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

4 **Embase search terms**

1.	clinical study/
2.	exp case control study/
3.	family study/
4.	longitudinal study/
5.	retrospective study/
6.	prospective study/
7.	cross-sectional study/
8.	cohort analysis/
9.	follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.

16.	or/1-8,11-15
-----	--------------

1 **Cochrane search terms**

#1.	case control:ti,ab,kw
#2.	(cohort near/2 (study or studies or analys*)):ti,ab,kw
#3.	((follow up or observational or uncontrolled or non randomi?ed or nonrandomi?ed or epidemiologic*) near/2 (study or studies)):ti,ab,kw
#4.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)):ti,ab,kw
#5.	{or #1-#4}

2 **F.2.4 Diagnostic test accuracy studies (DIAG1) search terms**

3 **Medline search terms**

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or PPV or NPV).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	likelihood function/
7.	(ROC curve* or AUC).ti,ab.
8.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
9.	gold standard.ab.
10.	or/1-9

4 **Embase search terms**

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or PPV or NPV).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	(ROC curve* or AUC).ti,ab.
7.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
8.	diagnostic accuracy/
9.	diagnostic test accuracy study/
10.	gold standard.ab.
11.	or/1-10

5 **Cochrane search terms**

#1.	diagnos*:ti,ab,kw
#2.	(sensitivity or specificity):ti,ab,kw
#3.	((pre test or pretest or post test) near probability):ti,ab,kw
#4.	(predictive value* or PPV or NPV):ti,ab,kw
#5.	likelihood ratio*:ti,ab,kw
#6.	(ROC or AUC):ti,ab,kw
#7.	gold standard:ti,ab,kw

#8.	Any MeSH descriptor with qualifier(s): [Diagnosis - DI]
#9.	{or #1-#8}

1 F.2.5 Diagnostic studies (DIAG2) search terms

2 The following terms were added to the diagnostic test accuracy search terms in F.2.4 to create a
3 more sensitive search in Medline and Embase only.

4 Medline and Embase search terms

1.	sensitiv*.mp.
2.	diagnos*.mp.
3.	di.fs.
4.	or/1-3

5 F.2.6 Prognostic studies (PROG) search terms

6 Medline search terms

1.	predict.ti.
2.	(validat* or rule*).ti,ab.
3.	(predict* and (outcome* or risk* or model*)).ti,ab.
4.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
5.	decision*.ti,ab. and Logistic models/
6.	(decision* and (model* or clinical*)).ti,ab.
7.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
8.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
9.	ROC curve/
10.	or/1-9

7 Embase search terms

1.	predict.ti.
2.	(validat* or rule*).ti,ab.
3.	(predict* and (outcome* or risk* or model*)).ti,ab.
4.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
5.	decision*.ti,ab. and statistical model/
6.	(decision* and (model* or clinical*)).ti,ab.
7.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
8.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or auc or calibration or indices or algorithm or multivariable).ti,ab.
9.	receiver operating characteristic/
10.	or/1-9
11.	predict.ti.

8 Cochrane search terms

#1.	predict:ti,ab,kw
-----	------------------

#2.	(validat* or rule*):ti,ab,kw
#3.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (model* or decision* or identif* or prognos*)):ti,ab,kw
#4.	(decision* and (model* or clinical*)):ti,ab,kw
#5.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)):ti,ab,kw
#6.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or calibration or indices or algorithm or multivariable):ti,ab,kw
#7.	{or #1-#6}

1 F.2.7 Validation (VAL) studies search terms

2 Medline search terms

1.	validation studies/
2.	reproducibility of results/
3.	(valid* or reliab*):ti,ab.
4.	observer variation/
5.	((inter* or intra* or observer* or rater*) adj3 (bias* or variation* or agree* or concordan*)):ti,ab.
6.	or/1-5

3 Embase search terms

1.	(valid* or reliab*):ti,ab.
2.	((inter* or intra* or observer* or rater*) adj3 (bias* or variation* or agree* or concordan*)):ti,ab.
3.	validation study/
4.	exp reliability/
5.	exp reproducibility/
6.	exp observer variation/
7.	or/1-6

4 F.2.8 Health economics (HE) search terms

5 Medline search terms

1.	economics/
2.	value of life/
3.	exp "costs and cost analysis"/
4.	exp economics, hospital/
5.	exp economics, medical/
6.	economics, nursing/
7.	economics, pharmaceutical/
8.	exp "fees and charges"/
9.	exp budgets/
10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.
13.	(price* or pricing*):ti,ab.
14.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)):ab.

15.	(financ* or fee or fees).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	or/1-16

1 **Embase search terms**

1.	health economics/
2.	exp economic evaluation/
3.	exp health care cost/
4.	exp fee/
5.	budget/
6.	funding/
7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13

2 **F.2.9 Quality of life (QOL) search terms**

3 **Medline search terms**

1.	(euroqol* or eq5d* or eq 5d*).ti,ab.
----	--------------------------------------

4 **Embase search terms**

1.	(euroqol* or eq5d* or eq 5d*).ti,ab.
----	--------------------------------------

5 **F.2.10 Excluded study designs and publication types**

6 The following study designs and publication types were removed from retrieved results using the
7 NOT operator.

8 **Medline search terms**

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	exp animals, laboratory/
14.	exp animal experimentation/

15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

1 **Embase search terms**

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5
7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	animal/ not human/
10.	nonhuman/
11.	exp animal experiment/
12.	exp experimental animal/
13.	animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.
16.	or/8-15

2 **F.3 Searches for specific questions**

3 **F.3.1 Signs and Symptoms**

- 4 6. In people under investigation for asthma, what is the diagnostic accuracy of each of the following
5 signs and symptoms?
- 6 • wheezing
 - 7 • cough
 - 8 • breathlessness
 - 9 • nocturnal symptoms
 - 10 • diurnal and seasonal variations.

11 Search constructed by combining the columns in the following table using the AND Boolean operator.
12 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Signs and symptoms of asthma as listed in the question	n/a	The following filters were used in all databases: DIAG1, OBS, PROG	See Table 24 English only Exclusion filter applied in Medline and Embase

13 **Medline search terms**

1.	*respiratory sounds/
----	----------------------

2.	*cough/
3.	*dyspnea/
4.	exp *periodicity/
5.	(wheez* or rhonchi or cough* or breathless* or dyspn?ea).ti,ab.
6.	((difficult* or labo?r* or short*) adj2 breath*).ti,ab.
7.	((24h* or 24 hour* or 24 hr*) adj2 (rhythm* or varia* or change* or pattern* or symptom* or sign or signs)).ti,ab.
8.	((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.
9.	or/1-8

1 **Embase search terms**

1.	*wheezing/
2.	*irritative coughing/
3.	*chronic cough/
4.	*coughing/
5.	*dyspnea/
6.	*abnormal respiratory sound/
7.	*seasonal variation/
8.	exp *periodicity/
9.	((difficult* or labo?r* or short*) adj2 breath*).ti,ab.
10.	((24h* or 24 hour* or 24 hr*) adj2 (rhythm* or varia* or change* or pattern* or symptom* or sign or signs)).ti,ab.
11.	((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.
12.	(wheez* or rhonchi or cough* or breathless* or dyspn?ea).ti,ab.
13.	or/1-12

2 **Cochrane search terms**

#1.	MeSH descriptor: [Respiratory Sounds] this term only
#2.	MeSH descriptor: [Cough] this term only
#3.	MeSH descriptor: [Dyspnea] this term only
#4.	MeSH descriptor: [Periodicity] explode all trees
#5.	(wheez* or rhonchi or cough* or breathless* or dyspn?ea):ti,ab,kw
#6.	((difficult* or labo?r* or short*) near/2 breath*):ti,ab,kw
#7.	((24h* or 24 hour* or 24 hr*) near/2 (rhythm* or varia* or change* or pattern* or symptom* or sign or signs):ti,ab,kw
#8.	((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
#9.	{or #1-#8}

3 **F.3.2 Personal/family history of atopic disorders**

- 4 7. In people under investigation for asthma, what is the diagnostic accuracy of taking a
5 personal/family history of atopic disorders?

- 1 Search constructed by combining the columns in the following table using the AND Boolean operator.
2 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Personal/family history of atopic disorders	n/a	The following filters were used in all databases: DIAG1, PROG	See Table 24 English only Exclusion filter applied in Medline and Embase

3 **Medline search terms**

1.	medical history taking/
2.	(histories or history).ti,ab.
3.	exp questionnaires/
4.	question?aire*.ti,ab.
5.	or/1-4
6.	(atopic or atopy).ti,ab.
7.	(histor* adj2 (hypersensitiv* or allerg*)).ti,ab.
8.	((family or familial or relative? or kin or kinship or brother? or sister? or mother? or father? or son? or daughter? or parent?) adj3 (hypersensitiv* or allerg*)).ti,ab.
9.	rhinitis, allergic, seasonal/
10.	rhinitis, allergic, perennial/
11.	dermatitis, atopic/
12.	exp food hypersensitivity/
13.	((hypersensitiv* or allerg*) adj2 asthma*).ab.
14.	(hay fever or hayfever or pollinosis).ti,ab.
15.	(pollen* adj2 (sensitiv* or hypersensitiv* or allerg*)).ti,ab.
16.	allergic rhinitis.ti,ab.
17.	eczema.ti,ab.
18.	((food* or wheat or nut* or peanut* or milk or dairy or egg* or soy* or sesame or seed* or pecan* or pistachio* or walnut* or coconut* or fish or shellfish or seafood* or cereal* or gluten* or barley or corn* or maize) adj2 (sensitiv* or hypersensitiv* or allerg*)).ti,ab.
19.	or/6-18
20.	5 and 19

4 **Embase search terms**

1.	exp *anamnesis/
2.	(histories or history).ti,ab.
3.	exp *questionnaire/
4.	question?aire*.ti,ab.
5.	or/1-4
6.	(atopic or atopy).ti,ab.
7.	(histor* adj2 (hypersensitiv* or allerg*)).ti,ab.
8.	((family or familial or relative? or kin or kinship or brother? or sister? or mother? or father? or son? or daughter? or parent?) adj3 (hypersensitiv* or allerg*)).ti,ab.
9.	((hypersensitiv* or allerg*) adj2 asthma*).ab.
10.	(hay fever or hayfever or pollinosis).ti,ab.

11.	(pollen* adj2 (sensitiv* or hypersensitiv* or allerg*)).ti,ab.
12.	allergic rhinitis.ti,ab.
13.	eczema.ti,ab.
14.	((food* or wheat or nut* or peanut* or milk or dairy or egg* or soy* or sesame or seed* or pecan* or pistachio* or walnut* or coconut* or fish or shellfish or seafood* or cereal* or gluten* or barley or corn* or maize) adj2 (sensitiv* or hypersensitiv* or allerg*)).ti,ab.
15.	*atopic dermatitis/
16.	*atopy/
17.	exp *allergic rhinitis/
18.	exp *food allergy/
19.	or/6-18
20.	5 and 19

1 **Cochrane search terms**

#1.	(histories or history or question*):ti,ab,kw
#2.	(atopic or atopy):ti,ab,kw
#3.	(histor* near/2 (hypersensitiv* or allerg*)):ti,ab,kw
#4.	((family or familial or relative? or kin or kinship or brother? or sister? or mother? or father? or son? or daughter? or parent?) near/3 (hypersensitiv* or allerg*)):ti,ab,kw
#5.	((hypersensitiv* or allerg*) near/2 asthma*):ti,ab,kw
#6.	(hay fever or hayfever or pollinosis):ti,ab,kw
#7.	(pollen* near/2 (sensitiv* or hypersensitiv* or allerg*)):ti,ab,kw
#8.	allergic rhinitis:ti,ab,kw
#9.	eczema:ti,ab,kw
#10.	((food* or wheat or nut* or peanut* or milk or dairy or egg* or soy* or sesame or seed* or pecan* or pistachio* or walnut* or coconut* or fish or shellfish or seafood* or cereal* or gluten* or barley or corn* or maize) near/2 (sensitiv* or hypersensitiv* or allerg*)):ti,ab,kw
#11.	{or #2-#10}
#12.	#1 and #11

2 **F.3.3 Symptoms in response to exercise**

3 **8.** In people under investigation for asthma, what is the diagnostic accuracy of a clinical history of
4 symptoms in response to exercise?

5 Search constructed by combining the columns in the following table using the AND Boolean operator.
6 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	History of symptoms following exercise	n/a	The following filter was used in all databases: DIAG1	See Table 24 English only Exclusion filter applied in Medline and Embase

7 **Medline search terms**

1.	medical history taking/
2.	(histories or history).ti,ab.
3.	exp questionnaires/

4.	question*.ti,ab.
5.	exp "signs and symptoms, respiratory"/
6.	(symptom or symptoms).ti,ab.
7.	or/1-6
8.	exp exercise/
9.	exp sports/
10.	(exercise* or sport*).ti,ab.
11.	(physical* adj (train* or exert* or activit*)).ti,ab.
12.	or/8-11
13.	7 and 12

1 **Embase search terms**

1.	exp *anamnesis/
2.	(histories or history).ti,ab.
3.	exp *questionnaire/
4.	question*.ti,ab.
5.	(symptom or symptoms).ti,ab.
6.	exp *breathing disorder/
7.	exp *coughing/
8.	or/1-7
9.	exp *exercise/
10.	exp *sport/
11.	(exercise* or sport*).ti,ab.
12.	(physical* adj (train* or exert* or activit*)).ti,ab.
13.	or/9-12
14.	8 and 13

2 **Cochrane search terms**

#1.	(histories or history or question*):ti,ab,kw
#2.	(symptom or symptoms):ti,ab,kw
#3.	{or #1-#2}
#4.	(exercise* or sport*):ti,ab,kw
#5.	(physical* near/1 (train* or exert* or activit*)):ti,ab,kw
#6.	#4or #5
#7.	#3 and #6

3 **F.3.4 Symptoms after drugs**

4 9. In people under investigation for asthma, what is the diagnostic accuracy of a clinical history of
5 symptoms after taking the following drugs:

- 6 • in adults - beta blockers, aspirin, or other NSAIDs
7 • in children – ibuprofen?

8 Search constructed by combining the columns in the following table using the AND Boolean operator.
9 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all	Drugs as listed in	n/a	The following filter was	See Table 24

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
ages with asthma or suspected asthma	the question		used in all databases: DIAG1 The following filter was used in Medline and Embase only: DIAG2	English only Exclusion filter applied in Medline and Embase

1

Medline search terms

1.	((anti inflamm* or antiinflam* or anti-inflamm*) adj2 (non- steroid* or nonsteroid* or non-steroid*) adj2 agent*).ti,ab.
2.	((cox2 or cox-2 or coxii or cox-ii) adj2 inhibitor*).ti,ab.
3.	((cyclo-oxygenase2 or cyclo-oxygenase-2 or cyclooxygenase-2 or cyclooxygenase2) adj2 inhibitor*).ti,ab.
4.	((cyclo-oxygenase-ii or cyclo-oxygenaseii or cyclooxygenase-ii or cyclooxygenaseii) adj2 inhibitor*).ti,ab.
5.	(arcoxia or Iodine or eccoxolac or mobic or prexige).ti,ab.
6.	(diclofenac or naproxen or tolmetin or ketoprofen or aceclofenac).ti,ab.
7.	(fenbufen or tenoxicam or nabumetone or osmosin or benoxaprofen).ti,ab.
8.	(fenoprofen or azapropazone or aceclofenac or mefenamic acid or dexketoprofen).ti,ab.
9.	(ibuprofen or ibuprofen).ti,ab.
10.	(indometacin or indomethacin).ti,ab.
11.	(parecoxib or deracoxib or cimicoxib or tilmacoxib).ti,ab.
12.	(piroxicam or flurbiprofen or niflumic acid or diflunisal).ti,ab.
13.	(sulindac or meclofenamate or meclofenamic acid).ti,ab.
14.	exp anti-inflammatory agents, non-steroidal/
15.	celebrex.ti,ab.
16.	celecoxib.ti,ab.
17.	coxib*.ti,ab.
18.	etodolac.ti,ab.
19.	etoricoxib.ti,ab.
20.	exp aspirin/
21.	aspirin.ti,ab.
22.	exp cyclooxygenase 2 inhibitors/
23.	exp diclofenac/
24.	exp diflunisal/
25.	exp etodolac/
26.	exp fenoprofen/
27.	exp flurbiprofen/
28.	exp ibuprofen/
29.	exp indomethacin/
30.	exp ketoprofen/
31.	exp meclofenamic acid/
32.	exp mefenamic acid/
33.	exp naproxen/
34.	exp niflumic acid/

35.	exp piroxicam/
36.	exp sulindac/
37.	exp tolmetin/
38.	flosulide.ti,ab.
39.	iguratimod.ti,ab.
40.	meloxicam.ti,ab.
41.	nimesulide.ti,ab.
42.	nsaid*.ti,ab.
43.	tiaprofenic acid.ti,ab.
44.	(isoxicam or zomepirac or carprofen or proquazone or lornoxicam).ti,ab.
45.	(propranolol or angilol or angilol or inderal-1a or half-inalderal or inderal or bedranol or prograne or slo-pro or acebutolol or setral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevbloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
46.	(beta adj3 block*).ti,ab.
47.	(b adj3 block*).ti,ab.
48.	(beta adj2 antagonist*).ti,ab.
49.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj3 (blockade or blocker* or blocking or antagonist*).ti,ab.
50.	exp adrenergic beta-antagonists/
51.	or/1-50
52.	medical history taking/
53.	(histories or history).ti,ab.
54.	exp drug hypersensitivity/
55.	((drug or medication* or medicine*) adj2 (allerg* or hypersensitivity or sensitivity or intolerance)).ti,ab.
56.	exp questionnaires/
57.	question*.ti,ab.
58.	exp "signs and symptoms, respiratory"/
59.	(symptom or symptoms).ti,ab.
60.	or/52-59
61.	51 and 60

1

Embase search terms

1.	((anti inflamm* or antiinflamm* or anti-inflamm*) adj2 (non-steroid* or nonsteroid* or non-steroid*) adj2 agent*).ti,ab.
2.	((cox2 or cox-2 or coxii or cox-ii) adj2 inhibitor*).ti,ab.
3.	((cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase 2) adj2 inhibitor*).ti,ab.
4.	((cyclooxygenase-ii or cyclooxygenaseii or cyclooxygenase ii) adj2 inhibitor*).ti,ab.
5.	(arcoxia or lodine or eccoxolac or prexige or mobic).ti,ab.
6.	(diclofenac or naproxen or tolmetin or ketoprofen or aceclofenac).ti,ab.
7.	(fenbufen or tenoxicam or nabumetone or osmosin or benoxaprofen).ti,ab.
8.	(fenoprofen or azapropazone or aceclofenac or mefenamic acid or dexketoprofen).ti,ab.
9.	(ibuprofen or ibuprufen).ti,ab.
10.	(indometacin or indomethacin).ti,ab.

11.	(isoxicam or zomepirac or carprofen or proquazone or lornoxicam).ti,ab.
12.	(parecoxib or deracoxib or cimicoxib or tilmacoxib).ti,ab.
13.	(piroxicam or flurbiprofen or niflumic acid or diflunisal).ti,ab.
14.	(sulindac or meclofenamate or meclofenamic acid).ti,ab.
15.	celebrex.ti,ab.
16.	celecoxib.ti,ab.
17.	coxib*.ti,ab.
18.	etodolac.ti,ab.
19.	etoricoxib.ti,ab.
20.	exp *aceclofenac/
21.	exp *aspirin/
22.	exp *azapropazone/
23.	exp *benoxaprofen/
24.	exp *carprofen/
25.	exp *celecoxib/
26.	exp *cyclooxygenase 2 inhibitor/
27.	exp *dexketoprofen/
28.	exp *diclofenac/
29.	exp *diflunisal/
30.	exp *etodolac/
31.	exp *etoricoxib/
32.	exp *fenbufen/
33.	exp *fenoprofen/
34.	exp *flosulide/
35.	exp *flurbiprofen/
36.	exp *ibuprofen/
37.	exp *iguratimod/
38.	exp *indomethacin/
39.	exp *ketoprofen/
40.	exp *lornoxicam/
41.	exp *lumiracoxib/
42.	exp *meclofenamic acid/
43.	exp *mefenamic acid/
44.	exp *meloxicam/
45.	exp *nabumetone/
46.	exp *naproxen/
47.	exp *niflumic acid/
48.	exp *nimesulide/
49.	exp *parecoxib/ or exp *tilmacoxib/
50.	exp *piroxicam/
51.	exp *proquazone/
52.	exp *sulindac/
53.	exp *tenoxicam/
54.	exp *tiaprofenic acid/
55.	exp *tolmetin/

56.	exp *zomepirac/
57.	flosulide.ti,ab.
58.	iguratimod.ti,ab.
59.	lumiracoxib.ti,ab.
60.	meloxicam.ti,ab.
61.	nimesulide.ti,ab.
62.	exp *nonsteroid antiinflammatory agent/
63.	nsaid*.ti,ab.
64.	tiaprofenic acid.ti,ab.
65.	aspirin.ti,ab.
66.	exp *beta adrenergic receptor blocking agent/
67.	exp *bisoprolol/ or exp *bisoprolol fumarate/ or exp *bisoprolol fumarate plus hydrochlorothiazide/ or exp *carvedilol/ or exp *metoprolol/ or exp*metoprolol fumarate/ or exp *metoprolol succinate/ or exp *metoprolol tartrate/ or exp *nebivolol/
68.	(propranolol or angilol or angilol or inderal-la or half-inalderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevbloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
69.	(beta adj3 block*).ti,ab.
70.	(b adj3 block*).ti,ab.
71.	(beta adj2 antagonist*).ti,ab.
72.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj3 (blockade or blocker* or blocking or antagonist*).ti,ab.
73.	or/1-72
74.	exp *anamnesis/
75.	(histories or history).ti,ab.
76.	exp *questionnaire/
77.	question*.ti,ab.
78.	exp *drug hypersensitivity/
79.	((drug or medication* or medicine*) adj2 (allerg* or hypersensitivity or sensitivity or intolerance)).ti,ab.
80.	(symptom or symptoms).ti,ab.
81.	exp *breathing disorder/
82.	exp *coughing/
83.	or/74-82
84.	73 and 83

1

Cochrane search terms

#1.	((anti inflamm* or antiinflamm* or anti-inflamm*) near/2 (non- steroid* or nonsteroid* or non-steroid*)):ti,ab,kw
#2.	((cox2 or cox-2 or coxii or cox-ii) near/2 (inhibitor*)):ti,ab,kw
#3.	((cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase 2) near/2 (inhibitor*)):ti,ab,kw
#4.	((cyclo-oxygenase2 or cyclo-oxygenase-2 or cyclooxygenase-2 or cyclooxygenase2) near/2 (inhibitor*)):ti,ab,kw
#5.	((cyclooxygenase-ii or cyclooxygenaseii) near/2 (inhibitor*)):ti,ab,kw
#6.	((cyclo-oxygenase-ii or cyclo-oxygenaseii or cyclooxygenase-ii or cyclooxygenaseii) near/2

	(inhibitor*):ti,ab,kw
#7.	(aceclofenac or arcoxia or aspirin or azapropazone or benoxaprofen or carprofen or celebrex or celecoxib or cimicoxib or coxib* or deracoxib or dexketoprofen or diclofenac or diflunisal or eccoxolac or etodolac or etoricoxib or fenbufen or fenoprofen or flosulide or flurbiprofen or ibuprofen or ibuprofen or iguratimod or indometacin or indomethacin or isoxicam or ketoprofen or lodine or lornoxicam or lumiracoxib or meclofenam* or mefenamic acid or meloxicam or mobic or nabumetone or naproxen or niflumic acid or nimesulide or nsaid* or osmosin or parecoxib or piroxicam or prexige or proquazone or sulindac or tenoxicam or tiaprofenic acid or tilmacoxib or tolmetin or zomepirac):ti,ab,kw
#8.	(propranolol or angilol or angilol or inderal-1a or half-inalderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardiacor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim):ti,ab,kw
#9.	(beta or b) near/3 (block* or antagonist*):ti,ab,kw
#10.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) near/3 (blockade or blocker* or blocking or antagonist*):ti,ab,kw
#11.	{or #1-#10}
#12.	(histories or history or question*):ti,ab,kw
#13.	((drug or medication* or medicine*) near/2 (allerg* or hypersensitivity or sensitivity or intolerance):ti,ab,kw
#14.	(symptom or symptoms):ti,ab,kw
#15.	{or #12-#14}
#16.	#11 and #15

1 F.3.5 Occupational asthma

2 10. In adults under investigation for occupational asthma, what is the diagnostic accuracy for case
3 identification, of asking whether their symptoms are better away from work?

4 Search constructed by combining the columns in the following table using the AND Boolean operator.
5 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults under investigation for occupational asthma	Symptom history	n/a	The following filters were used in Medline and Embase only: DIAG1, OBS, RCT, SR	See Table 24 English only Exclusion filter applied in Medline and Embase

6 Medline search terms

1.	asthma, occupational/
2.	((occupation* or work* or job* or employ*) adj2 asthma*).ti,ab
3.	or/1-2
4.	*occupational diseases/
5.	exp asthma/
6.	4 and 5
7.	3 or 6
8.	medical history taking/
9.	(histories or history).ti,ab.

10.	questionnaires/
11.	question*.ti,ab.
12.	(holiday* or weekend* or vacation*).ti,ab.
13.	((away or absent* or leave*) adj3 (work* or job* or employ* or occupation*)).ti,ab.
14.	or/8-13
15.	7 and 14

1 **Embase search terms**

1.	((occupation* or work* or job* or employ*) adj2 asthma*).ti,ab.
2.	*occupational asthma/
3.	or/1-2
4.	*occupational disease/
5.	exp *asthma/
6.	4 and 5
7.	3 or 6
8.	exp *anamnesis/
9.	(histories or history).ti,ab.
10.	exp *questionnaire/
11.	question*.ti,ab.
12.	(holiday* or weekend* or vacation*).ti,ab.
13.	((away or absent* or leave*) adj3 (work* or job* or employ* or occupation*)).ti,ab.
14.	or/8-13
15.	7 and 14

2 **Cochrane search terms**

#1.	((occupation* or work* or job* or employ*) near/2 asthma*):ti,ab,kw
#2.	(histories or history or question* or holiday* or weekend* or vacation*):ti,ab,kw
#3.	((away or absent* or leave*) near/3 (work* or job* or employ* or occupation*):ti,ab,kw
#4.	#2 or #3
#5.	#1 and #4

3 **F.3.6 Spirometry/flow volume loop measures**

4 11. In people under investigation for asthma, what is the diagnostic test accuracy and cost-
5 effectiveness of spirometry / flow volume loop measures?

6 Search constructed by combining the columns in the following table using the AND Boolean operator.
7 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Spirometry / flow volume loop measures	n/a	The following filter was used in all databases: DIAG1	See Table 24 English only Exclusion filter applied in Medline and Embase

8 **Medline search terms**

1.	vital capacity/
----	-----------------

2.	forced expiratory volume/
3.	(FEV1 or FEV 1 or FVC).ti,ab.
4.	(flow volume adj (loop* or curve* or graph*)).ti,ab.
5.	(forced expiratory volume* adj6 ("1" or one)).ti,ab.
6.	((force* or time*) adj vital capacit*).ti,ab.
7.	spirometry.ti.
8.	or/1-7

1 **Embase search terms**

1.	vital capacity/
2.	forced expiratory volume/
3.	lung flow volume curve/
4.	(FEV1 or FEV 1 or FVC).ti,ab.
5.	(flow volume adj (loop* or curve* or graph*)).ti,ab.
6.	(forced expiratory volume* adj6 ("1" or one)).ti,ab.
7.	((force* or time*) adj vital capacit*).ti,ab.
8.	spirometry.ti.
9.	or/1-8

2 **Cochrane search terms**

#1.	MeSH descriptor: [Vital Capacity] this term only
#2.	MeSH descriptor: [Forced Expiratory Volume] this term only
#3.	(FEV1 or "FEV 1" or FVC):ti,ab
#4.	(flow volume near/2 (loop* or curve* or graph*)):ti,ab
#5.	(forced expiratory volume* near/6 ("1" or one)):ti,ab
#6.	((force* or time*) near/2 vital capacit*):ti,ab
#7.	spirometry:ti
#8.	{or #1-#7}

3 **F.3.7 Bronchodilator response**

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

6 Search constructed by combining the columns in the following table using the AND Boolean operator.
7 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Bronchodilator response	n/a	The following filter was used in Medline and Cochrane: DIAG1 The following filter was used in Medline only: DIAG2	See Table 24 English only Exclusion filter applied in Medline and Embase

8 **Medline search terms**

1.	exp bronchodilator agents/du
2.	bronchoreversibility.ti,ab.
3.	((bronchodilator* or bronchial dilat* or broncholytic*) adj3 (test* or revers* or respons* or

	respond*)).ti,ab.
4.	(BDR or BDT).ti,ab.
5.	or/1-4

1 **Embase search terms**

1.	bronchoreversibility.ti,ab.
2.	((bronchodilator* or bronchial dilat* or broncholytic*) adj3 (test* or revers* or respons* or respond*)).ti,ab.
3.	(BDR or BDT).ti,ab.
4.	bronchoreversibility.ti,ab.
5.	or/1-4
6.	exp "sensitivity and specificity"/
7.	(sensitivity or specificity).ti,ab.
8.	((pre test or pretest or post test) adj probability).ti,ab.
9.	(predictive value* or PPV or NPV).ti,ab.
10.	likelihood ratio*.ti,ab.
11.	(ROC curve* or AUC).ti,ab.
12.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
13.	diagnostic accuracy/
14.	diagnostic test accuracy study/
15.	gold standard.ab.
16.	sensitiv*.mp.
17.	diagnos*.mp.
18.	di.fs.
19.	or/6-18
20.	5 and 19
21.	exp *bronchodilating agent/
22.	or/6-15
23.	21 and 22
24.	20 or 23

2 **Cochrane search terms**

#1.	((bronchodilator* or bronchial dilat* or broncholytic*) near/3 (test* or revers* or respons* or respond*)):ti,ab,kw
#2.	bronchoreversibility:ti,ab,kw
#3.	(BDR or BDT):ti,ab,kw
#4.	MeSH descriptor: [Bronchodilator Agents] explode all trees and with qualifiers: [Diagnostic use - DU]
#5.	{or #1-#4}

3 **F.3.8 Peak expiratory flow**

4 13.In people under investigation for asthma, what is the diagnostic test accuracy and cost-
5 effectiveness of peak expiratory flow (PEF) variability?

6 Search constructed by combining the columns in the following table using the AND Boolean operator.
7 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Peak expiratory flow (PEF) variability	n/a	The following filter was used in all databases: DIAG1 The following filter was used in Medline and Embase only: DIAG2	See Table 24 English only Exclusion filter applied in Medline and Embase

1 **Medline search terms**

1.	PEFV.ti,ab.
2.	((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 (PEF or PEFR or PFR or peak expiratory flow* or peak flow*)).ti,ab.
3.	peak expiratory flow rate/
4.	exp circadian rhythm/
5.	3 and 4
6.	1 or 2 or 5

2 **Embase search terms**

1.	PEFV.ti,ab.
2.	((diurnal* or circadian or variation* or variability or fluctuat* or alter* or increas* or decreas* or chang*) adj3 (PEF or PEFR or PFR or peak expiratory flow* or peak flow*)).ti,ab.
3.	peak expiratory flow/
4.	circadian rhythm/
5.	3 and 4
6.	1 or 2 or 5

3 **Cochrane search terms**

#1.	pefv:ti,ab,kw
#2.	((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
#3.	{or #1-#2}

4 **F.3.9 Skin prick test**

5 14. In people under investigation for asthma, what is the diagnostic test accuracy and cost-
6 effectiveness of skin prick tests?

7 Search constructed by combining the columns in the following table using the AND Boolean operator.
8 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Skin prick test	n/a	The following filter was used in Medline and Embase only: DIAG1	See Table 24 English only Exclusion filter applied in Medline and Embase

9 **Medline search terms**

1.	((dust or housedust) adj mite*).ti,ab.
----	--

2.	(dermatophagoides or euroglyphus).ti,ab.
3.	pyroglyphidae/
4.	(cat or cats or feline*).ti,ab.
5.	cats/
6.	(dog or dogs or canine*).ti,ab.
7.	dogs/
8.	pollen*.ti,ab.
9.	pollen/
10.	exp aspergillus/
11.	aspergillus.ti,ab.
12.	alternaria/
13.	alternaria.ti,ab.
14.	cladosporium/
15.	cladosporium.ti,ab.
16.	((air* or aero*) adj allergen*).ti,ab.
17.	aeroallergen*.ti,ab.
18.	or/1-17
19.	exp skin tests/
20.	skin prick*.ti,ab.
21.	skin scratch*.ti,ab.
22.	prick* test*.ti,ab.
23.	scratch* test*.ti,ab.
24.	skin test*.ti,ab.
25.	or/19-24
26.	18 and 25

1

Embase search terms

1.	((dust or housedust) adj mite*).ti,ab.
2.	(dermatophagoides or euroglyphus).ti,ab.
3.	(cat or cats or feline*).ti,ab.
4.	(dog or dogs or canine*).ti,ab.
5.	pollen*.ti,ab.
6.	aspergillus.ti,ab.
7.	alternaria.ti,ab.
8.	cladosporium.ti,ab.
9.	exp *dermatophagoides/
10.	*cat/
11.	*dog/
12.	*grass pollen/
13.	*pollen/
14.	exp *aspergillus/
15.	exp *alternaria/
16.	exp *cladosporium/
17.	((air* or aero*) adj allergen*).ti,ab.
18.	aeroallergen*.ti,ab.

19.	or/1-18
20.	exp *skin test/
21.	skin prick*.ti,ab.
22.	skin scratch*.ti,ab.
23.	prick* test*.ti,ab.
24.	scratch* test*.ti,ab.
25.	skin test*.ti,ab.
26.	or/20-25
27.	19 and 26

1 **Cochrane search terms**

#1.	(skin prick* or skin scratch* or prick* test* or scratch* test* or skin test*):ti,ab,kw
#2.	((dust or housedust) near/1 mite*):ti,ab,kw
#3.	(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
#4.	((air* or aero*) near/1 allergen*):ti,ab
#5.	aeroallergen*:ti,ab
#6.	{or #2-#5}
#7.	#1 and #6

2F.3.10 IgE

3 15. In people under investigation for asthma, what is the diagnostic test accuracy and cost-
4 effectiveness of total and specific serum IgE measures?

5 Search constructed by combining the columns in the following table using the AND Boolean operator.
6 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Serum IgE	n/a	The following filters were used in Medline and Embase only: DIAG1, OBS, RCT, SR	See Table 24 English only Exclusion filter applied in Medline and Embase

7 **Medline and Embase search terms**

1.	*radioallergosorbent test/
2.	(RAST or radioallergosorbent).ti.
3.	*immunoglobulin E/
4.	(immunoglobulin E or IgE).ti.
5.	or/1-4

8 **Cochrane search terms**

#1.	(immunoglobulin E or IgE or RAST or radioallergosorbent):ti,kw
-----	--

9F.3.11 FeNO

10 16. In people under investigation for asthma, what is the diagnostic test accuracy and cost-
11 effectiveness of fractional exhaled nitric oxide (FeNO) measures?

- 1 Search constructed by combining the columns in the following table using the AND Boolean operator.
2 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Fractional exhaled nitric oxide (FeNO)	n/a	The following filter was used in Medline and Embase only: DIAG1	See Table 24 English only Exclusion filter applied in Medline and Embase

3 **Medline search terms**

1.	FeNO.ti,ab.
2.	((Fe or exhal* or fraction*) adj2 (NO or nitric or nitrogen)).ti,ab.
3.	or/1-2
4.	nitric oxide/
5.	biological markers/
6.	breath tests/
7.	exhalation/
8.	or/5-7
9.	4 and 8
10.	3 or 9

4 **Embase search terms**

1.	FeNO.ti,ab.
2.	((Fe or exhal* or fraction*) adj2 (NO or nitric or nitrogen)).ti,ab.
3.	or/1-2
4.	*nitric oxide/
5.	*breath analysis/
6.	*expired air/
7.	*biological marker/
8.	*exhalation/
9.	or/5-8
10.	4 and 9
11.	3 or 10

5 **Cochrane search terms**

#1.	FeNO:ti,ab,kw
#2.	((Fe or exhal* or fraction*) near/2 (NO or nitric or nitrogen)):ti,ab,kw
#3.	((NO or nitric or nitrogen) near/2 (marker* or biomarker* or breath* or
#4.	{or #1-#3}
#5.	test* or exhal* or expir*)):ti,ab,kw
#6.	MeSH descriptor: [Nitric Oxide] explode all trees
#7.	MeSH descriptor: [Biological Markers] explode all trees
#8.	MeSH descriptor: [Breath Tests] explode all trees
#9.	MeSH descriptor: [Exhalation] explode all trees
#10.	{or #6-#9}
#11.	#5 and #10

#12.	#4 or #11
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1F.3.12 Peripheral blood eosinophil count

2 17. In people under investigation for asthma, what is the diagnostic test accuracy and cost-
3 effectiveness of eosinophil blood count measures?

4 Search constructed by combining the columns in the following table using the AND Boolean operator.
5 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Eosinophil blood count measures	n/a	The following filter was used in Medline and Embase only: DIAG1	See Table 24 English only Exclusion filter applied in Medline and Embase

6 Medline search terms

1.	*eosinophils/
2.	*eosinophilia/
3.	(blood* adj2 (eosinophil* or acidophil*)).ti,ab.
4.	or/1-3

7 Embase search terms

1.	*eosinophil/
2.	*eosinophil count/
3.	*eosinophilia/
4.	(blood* adj2 (eosinophil* or acidophil*)).ti,ab.
5.	or/1-4

8 Cochrane search terms

#1.	eosinophil*:kw
#2.	(blood* near/2 (eosinophil* or acidophil*)).ti,ab
#3.	{or #1-#2}

9F.3.13 Bronchial challenge test: histamine, methacholine, mannitol

10 Searches for the following two questions were run as one search:

11 18. In people under investigation for asthma, what is the diagnostic test accuracy and cost-
12 effectiveness of airway hyper-reactivity (non-specific bronchial challenge) with histamine and
13 methacholine?

14 19. In people under investigation for asthma, what is the diagnostic test accuracy and cost-
15 effectiveness of airway hyper-reactivity (non-specific bronchial challenge) with mannitol?

16 Search constructed by combining the columns in the following table using the AND Boolean operator.
17 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or	Bronchial challenge tests using histamine and	n/a	The following filter was used in all databases: DIAG1	See Table 24 English only Exclusion filter

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
suspected asthma	methacholine or mannitol			applied in Medline and Embase

1 **Medline search terms**

1.	exp mannitol/
2.	exp histamine/
3.	methacholine chloride/
4.	(mannitol* or histamine* or methacholine*).ti,ab.
5.	or/1-4
6.	bronchial provocation tests/
7.	(inhalation or provocation or provoke* or challenge*).ti,ab.
8.	(hyperresponsiv* or hyperreactiv*).ti,ab.
9.	bronchial hyperreactivity/
10.	or/6-9
11.	5 and 10

2 **Embase search terms**

1.	mannitol/
2.	histamine/
3.	methacholine/
4.	(mannitol* or histamine* or methcholine*).ti,ab.
5.	or/1-4
6.	inhalation test/
7.	provocation test/
8.	bronchus hyperreactivity/
9.	(inhalation or provocation or provoke* or challenge*).ti,ab.
10.	(hyperresponsiv* or hyperreactiv*).ti,ab.
11.	or/6-10
12.	5 and 11

3 **Cochrane search terms**

#1.	MeSH descriptor: [Mannitol] explode all trees
#2.	MeSH descriptor: [Histamine] explode all trees
#3.	MeSH descriptor: [Methacholine Chloride] explode all trees
#4.	(mannitol or histamine or methacholine):ti,ab
#5.	{or #1-#4}
#6.	MeSH descriptor: [Bronchial Provocation Tests] explode all trees
#7.	MeSH descriptor: [Bronchial Hyperreactivity] explode all trees
#8.	(inhalation or provocation or provoke* or challenge*).ti,ab
#9.	(hyperresponsiv* or hyperreactiv*).ti,ab
#10.	{or #6-#9}
#11.	5 and 10

1F.3.14 Bronchial challenge test: exercise

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

4 Search constructed by combining the columns in the following table using the AND Boolean operator.
5 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Clinical history of symptoms in response to exercise	n/a	The following filter was used in all databases: DIAG1	See Table 24 English only Exclusion filter applied in Medline and Embase

6 Medline search terms

1.	exp exercise/
2.	exp sports/
3.	(exercise* or sport*).ti,ab.
4.	(physical* adj (train* or exert* or activit*)).ti,ab.
5.	or/1-4
6.	medical history taking/
7.	(histories or history).ti,ab.
8.	exp questionnaires/
9.	question*.ti,ab.
10.	exp "signs and symptoms, respiratory"/
11.	(symptom or symptoms).ti,ab.
12.	or/6-11
13.	5 and 12

7 Embase search terms

1.	exp *exercise/
2.	exp *sport/
3.	(exercise* or sport*).ti,ab.
4.	(physical* adj (train* or exert* or activit*)).ti,ab.
5.	or/1-4
6.	exp *anamnesis/
7.	(histories or history).ti,ab.
8.	exp *questionnaire/
9.	question*.ti,ab.
10.	(symptom or symptoms).ti,ab.
11.	exp *breathing disorder/
12.	exp *coughing/
13.	or/6-12
14.	5 and 13

8 Cochrane search terms

#1.	(exercise* or sport*):ti,ab,kw
-----	--------------------------------

#2.	(physical* near/1 (train* or exert* or activit*)):ti,ab,kw
#3.	{or #1-#2}
#4.	(histories or history or question*):ti,ab,kw
#5.	(symptom or symptoms):ti,ab,kw
#6.	#4 or #5
#7.	#3 and #6

1F.3.15 Questionnaires

2 21. In people with asthma, what is the clinical and cost-effectiveness of using symptom scores/diaries
3 or validated questionnaires measuring symptom control (e.g. ACT, ACQ, cACT, RCP 3 questions)
4 and/or health related quality of life (e.g. AQLQ, pAQLQ) to monitor asthma?

5 Search constructed by combining the columns in the following table using the AND Boolean operator.
6 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Validated questionnaires	n/a	The following filters were used in Medline and Embase only: OBS, RCT, VAL	See Table 24 English only Exclusion filter applied in Medline and Embase

7 Medline search terms

1.	(diary or diaries).ti,ab.
2.	(symptom* adj2 scor*).ti,ab.
3.	or/1-2
4.	(measur* or assess* or monitor* or evaluat*).ti,ab.
5.	3 and 4
6.	(CACT or ACQ 6 or ACQ 7 or ACQ6 or ACQ7 or PACQ or RCP-3 or RCP3 or PAQLQ or AQLQ or PACQLQ).ti,ab.
7.	asthma control test*.ti,ab.
8.	asthma control questionnaire*.ti,ab.
9.	(rcp3 question* or rcp 3 question* or rcp three question* or royal college of physician*3 question* or royal college of physician* three question*).ti,ab.
10.	asthma quality of life questionnaire*.ti,ab.
11.	((p?ediatric or caregiver* or care giver* or carer*) adj3 quality of life questionnaire*).ti,ab.
12.	or/6-11
13.	5 or 12

8 Embase search terms

1.	(diary or diaries).ti,ab.
2.	(symptom* adj2 scor*).ti,ab.
3.	or/1-2
4.	(measur* or assess* or monitor* or evaluat*).ti,ab.
5.	3 and 4
6.	(CACT or ACQ 6 or ACQ 7 or ACQ6 or ACQ7 or PACQ or RCP-3 or RCP3 or PAQLQ or AQLQ or PACQLQ).ti,ab.
7.	asthma control test*.ti,ab.

8.	asthma control questionnaire*.ti,ab.
9.	(rcp3 question* or rcp 3 question* or rcp three question* or royal college of physician*3 question* or royal college of physician* three question*).ti,ab.
10.	asthma quality of life questionnaire*.ti,ab.
11.	((p?ediatric or caregiver* or care giver* or carer*) adj3 quality of life questionnaire*).ti,ab.
12.	or/6-11
13.	5 or 12

1 **Cochrane search terms**

#1.	(diary or diaries):ti,ab
#2.	(symptom* near/2 scor*):ti,ab
#3.	{or #1-#2}
#4.	(measur* or assess* or monitor* or evaluat*):ti,ab
#5.	#3 and #4
#6.	(CACT or ACQ 6 or ACQ 7 or ACQ6 or ACQ7 or PACQ or RCP-3 or RCP3 or PAQLQ or AQLQ or PACQLQ):ti,ab
#7.	asthma control test*:ti,ab
#8.	asthma control questionnaire*:ti,ab
#9.	(rcp3 question* or rcp 3 question* or rcp three question* or royal college of physician*3 question* or royal college of physician* three question*):ti,ab
#10.	asthma quality of life questionnaire*:ti,ab
#11.	((p?ediatric or caregiver* or care giver* or carer*) near/3 "quality of life questionnaire*"):ti,ab
#12.	{or #6-#11}
#13.	#5 or #12

2F.3.16 Lung functions tests

3 22.In people with asthma, what is the clinical and cost-effectiveness of using measures of pulmonary
4 function assessing asthma control (for example, spirometry and peak expiratory flow) to monitor
5 asthma?

6 Search constructed by combining the columns in the following table using the AND Boolean operator.
7 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Lung function tests	n/a	The following filter was used in Medline and Embase only: RCT	See Table 24 English only Exclusion filter applied in Medline and Embase

8 **Medline search terms**

1.	vital capacity/
2.	forced expiratory volume/
3.	(FEV1 or FEV 1 or FVC).ti,ab.
4.	(flow volume adj (loop* or curve* or graph*)):ti,ab.
5.	(forced expiratory volume* adj6 ("1" or one)).ti,ab.
6.	((force* or time*) adj vital capacit*).ti,ab.
7.	spirometry.ti.

8.	or/1-7
9.	PEFV.ti,ab.
10.	(PEF or PEFR or PFR or peak expiratory flow* or peak flow*).ti,ab.
11.	peak expiratory flow rate/
12.	or/9-11
13.	8 or 12
14.	monitoring, physiologic/
15.	monitor*.ti,ab.
16.	self care/
17.	plan*.ti,ab.
18.	or/14-17
19.	13 and 18

1

Embase search terms

1.	vital capacity/
2.	forced expiratory volume/
3.	lung flow volume curve/
4.	(FEV1 or FEV 1 or FVC).ti,ab.
5.	(flow volume adj (loop* or curve* or graph*)).ti,ab.
6.	(forced expiratory volume* adj6 ("1" or one)).ti,ab.
7.	((force* or time*) adj vital capacit*).ti,ab.
8.	spirometry.ti.
9.	or/1-8
10.	PEFV.ti,ab.
11.	(PEF or PEFR or PFR or peak expiratory flow* or peak flow*).ti,ab.
12.	peak expiratory flow/
13.	or/10-12
14.	(monitor* or plan*).ti,ab.
15.	exp monitoring/
16.	self care/
17.	or/14-16
18.	9 or 13
19.	17 and 18

2

Cochrane search terms

#1.	MeSH descriptor: [Vital Capacity] this term only
#2.	MeSH descriptor: [Forced Expiratory Volume] this term only
#3.	(FEV1 or "FEV 1" or FVC):ti,ab
#4.	(flow volume near/2 (loop* or curve* or graph*)):ti,ab
#5.	(forced expiratory volume* near/6 ("1" or one)):ti,ab
#6.	((force* or time*) near/2 vital capacit*):ti,ab
#7.	spirometry:ti
#8.	{or #1-#7}
#9.	PEFV:ti,ab
#10.	(PEF or PEFR or PFR or peak expiratory flow* or peak flow*):ti,ab,kw
#11.	#9 or #10

#12.	#8 or #11
#13.	(monitor* or plan*):ti,ab,kw
#14.	MeSH descriptor: [Self Care] explode all trees
#15.	#13 or #14
#16.	#12 and #15

1F.3.17 FeNO (monitoring)

2 For search terms see F.3.11

3 23.In people with asthma, what is the clinical and cost-effectiveness of using fractional exhaled nitric
4 oxide (FeNO) measures for monitoring asthma control?

5 Search constructed by combining the columns in the following table using the AND Boolean operator.
6 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Fractional exhaled nitric oxide (FeNO)	n/a	The following filters were used in Medline and Embase only: OBS, RCT, SR	See Table 24 English only Exclusion filter applied in Medline and Embase

7F.3.18 Peripheral blood eosinophil count (monitoring)

8 For search terms see F.3.12

9 24.In people with asthma, what is the clinical and cost-effectiveness of using the peripheral blood
10 eosinophil count for monitoring asthma control?

11 Search constructed by combining the columns in the following table using the AND Boolean operator.
12 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Eosinophil blood count measures	n/a	The following filters were used in Medline and Embase only: OBS, RCT	See Table 24 English only Exclusion filter applied in Medline and Embase

13F.3.19 Airway hyper-reactivity measures

14 For search terms see F.3.13

15 25.In people with asthma, what is the clinical and cost-effectiveness of using indirect challenge tests
16 with mannitol or direct challenge tests with histamine or methacholine for monitoring asthma
17 control?

18 Search constructed by combining the columns in the following table using the AND Boolean operator.
19 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all	Bronchial challenge	n/a	The following filter was	See Table 24

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
ages with asthma or suspected asthma	tests using histamine and methacholine or mannitol		used in Medline and Embase only: RCT	English only Exclusion filter applied in Medline and Embase

1F.3.20 Adherence to treatment

2 26.In people with asthma, what is the clinical and cost-effectiveness of monitoring adherence to
3 treatment?

4 Search constructed by combining the columns in the following table using the AND Boolean operator.
5 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Strategies to monitor or interventions to increase adherence	n/a	The following filters were used in Medline and Embase only: OBS, RCT	See Table 24 English only Exclusion filter applied in Medline and Embase

6 Medline search terms

1.	(adheren* or complian* or concordan* or nonadheren* or noncomplian*).ti,ab.
2.	exp patient compliance/
3.	or/1-2
4.	FeNO.ti,ab.
5.	nitric oxide/
6.	biological markers/
7.	breath tests/
8.	exhalation/
9.	or/6-8
10.	5 and 9
11.	((Fe or exhal* or fraction*) adj2 (NO or nitric or nitrogen)).ti,ab.
12.	4 or 10 or 11
13.	prescription*.ti,ab.
14.	exp pharmaceutical services/
15.	or/13-14
16.	((electronic adj2 inhaler*) or smartinhaler* or smart inhaler*).ti,ab.
17.	prednisolone.ti,ab.
18.	theophylline.ti,ab.
19.	(MARS or (medication adherence adj2 scale*)).ti,ab.
20.	exp adrenal cortex hormones/
21.	administration, inhalation/
22.	20 and 21
23.	(inhal* and (corticosteroid* or steroid* or corticoid* or glucocorticoid* or glucocortico*)).ti,ab.

24.	22 or 23
25.	or/12,15-19,24
26.	exp monitoring, physiologic/
27.	monitor*.ti,ab.
28.	or/26-27
29.	25 or 28
30.	3 and 29

1

Embase search terms

1.	(adheren* or complian* or concordan* or nonadheren* or noncomplian*).ti,ab.
2.	exp *patient compliance/
3.	or/1-2
4.	FeNO.ti,ab.
5.	((Fe or exhal* or fraction*) adj2 (NO or nitric or nitrogen)).ti,ab.
6.	*nitric oxide/
7.	*breath analysis/
8.	*expired air/
9.	*biological marker/
10.	*exhalation/
11.	or/7-10
12.	6 and 11
13.	4 or 5 or 12
14.	prescription*.ti,ab.
15.	*pharmacy/
16.	*prescription/
17.	((electronic adj2 inhaler*) or smartinhaler* or smart inhaler*).ti,ab.
18.	prednisolone.ti,ab.
19.	theophylline.ti,ab.
20.	*prednisolone/
21.	*theophylline blood level/
22.	(MARS or (medication adherence adj2 scale*)).ti,ab.
23.	exp *corticosteroid/ih
24.	(inhal* and (corticosteroid* or steroid* or corticoid* or glucocorticoid* or glucocortico*)).ti,ab.
25.	or/13-24
26.	exp *monitoring/
27.	monitor*.ti,ab.
28.	or/26-27
29.	3 and (25 or 28)

2

Cochrane search terms

#1.	(adheren* or complian* or concordan* or nonadheren* or noncomplian*).ti,ab
#2.	[mh ^"patient compliance"]
#3.	{or #1-#2}
#4.	FeNO:ti,ab
#5.	((Fe or exhal* or fraction*) near/2 (NO or nitric or nitrogen)):ti,ab

#6.	((NO or nitric or nitrogen) near/2 (marker* or biomarker* or breath* or test* or exhal* or expir*)):ti,ab
#7.	[mh ^"Nitric Oxide"]
#8.	[mh ^"Biological Markers"]
#9.	[mh ^"Breath Tests"]
#10.	[mh ^Exhalation]
#11.	{or #8-#10}
#12.	#7 and #11
#13.	{or #4-#6, #12}
#14.	prescription*:ti,ab
#15.	[mh ^"pharmaceutical services"]
#16.	((electronic near/2 inhaler*) or smartinhaler* or smart inhaler*):ti,ab
#17.	prednisolone:ti,ab
#18.	theophylline:ti,ab
#19.	(MARS or medication adherence):ti,ab
#20.	[mh ^"adrenal cortex hormones"]
#21.	[mh "administration, inhalation"]
#22.	(inhal* and (corticosteroid* or steroid* or corticoid* or glucocorticoid* or glucocortico*)):ti,ab
#23.	#20 and #21
#24.	{or #13-#19, #22-#23}
#25.	[mh ^"Monitoring, Physiologic"]
#26.	monitor*:ti,ab
#27.	{or #25-#36}
#28.	#3 and (#24 or #27)

1F.3.21 Inhaler technique

2 27.In people with asthma, what is the optimal frequency and method for monitoring inhaler
3 technique?

4 Search constructed by combining the columns in the following table using the AND Boolean operator.
5 Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
People of all ages with asthma or suspected asthma	Monitoring inhaler technique	n/a	The following filters were used in Medline and Embase only: OBS, RCT	See Table 24 English only Exclusion filter applied in Medline and Embase

6 Medline search terms

1.	((nebuliser* or nebulizer* or vaporiser* or vaporizer* or atomiser* or atomizer* or inhal* or aerosol* or device*) adj5 (technique* or competen* or efficien* or inefficien* or misuse* or check* or correct* or incorrect* or evaluat* or adher*)):ti,ab.
----	--

7 Embase search terms

1.	((nebuliser* or nebulizer* or vaporiser* or vaporizer* or atomiser* or atomizer* or inhal* or aerosol* or device*) adj5 (technique* or competen* or efficien* or inefficien* or misuse* or
----	--

	check* or correct* or incorrect* or evaluat* or adher*)):ti,ab.
--	---

1 **Cochrane search terms**

#1.	((nebuliser* or nebulizer* or vaporiser* or vaporizer* or atomiser* or atomizer* or inhal* or aerosol* or device*) near/5 (technique* or competen* or efficien* or inefficien* or misuse* or check* or correct* or incorrect* or evaluat* or adher*)):ti,ab
-----	---

2 **F.3.22 Tele-healthcare**

3 Searches for the following question were undertaken by the Cochrane Airways Group using the
4 Cochrane Airways Group Specialised Register of trials. Full search methodology is provided in the
5 published Cochrane review.^{1123,1123}
6 28.In people with asthma, what is the clinical and cost-effectiveness of tele-healthcare to monitor
7 asthma control?

8 **F.4 Health economics search**

9 **F.4.1 Health economic reviews**

10 Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
People of all ages with asthma or suspected asthma	n/a	n/a	The following filters were used in Medline and Embase only: HE	Medline and Embase 2012–1 October 2014 CRD EED and HTA All dates to 1 October 2014 English only

11 **Medline and Embase search terms**

4.	exp asthma/
5.	asthma*.ti,ab.
6.	or/1-2

12 **Cochrane search terms**

#4.	MeSH descriptor: [Asthma] explode all trees
#5.	asthma*:ti,ab.
#6.	{or #1-#2}

13 **CRD search terms**

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

14 **HEED search terms**

1.	AX=asthma*
----	------------

15 **F.4.2 Quality of life reviews**

16 Quality of life searches were conducted in Medline and Embase only

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
People of all ages with asthma or suspected asthma	n/a	n/a	The following filters were used in Medline and Embase only: QOL	Medline 1948-02/10/2014 Embase 1980-02/10/2014 English only

1

Appendix G: Clinical evidence tables

G.1 Signs and symptoms for diagnosis

Table 25: CHOI 2007³¹⁸

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments		
Choi et al., 2007. Easy diagnosis of asthma: computer-assisted, symptom-based diagnosis. Journal of Korean Medical Science: 22: 832-838. REF ID: CHOI2007	<u>Study type:</u> Diagnostic cross sectional study	N = 302 Adults <u>Inclusion criteria:</u> • Respiratory symptoms such as dyspnoea, cough or wheezing	<u>Male:Female</u> 127:175 <u>Mean age:</u> Asthma: 46.8 (16.8) Non-asthma: 47.8 (15.6) Medications: Not reported	<u>Index test</u> Questionnaire consisting of 11 questions regarding symptoms within 1 year: Q1 = Have you had wheezing associated with dyspnoea? (score 2) Provoking factors: • Nocturnal aggravation (score 1) • Cold air (score 1) • Exercise (score 1) • Upper respiratory infection (score 1) • Smoke or air pollution (score 1) • Concurrently with coughing (score 1) Q2 = Have you had paroxysmal coughing? (score 1) Q3 = Have you had dyspnoea without wheezing? (score 1) Q4 = Have you had wheezing without dyspnoea? (score 1) Q5 = Have you had fluctuation of	a) only sn/sp values reported, not number of TN, FN, TP and FP. Cut-off ≥3: Sn = 92.4%; Sp = 3.3% Cut-off ≥4: Sn = 85.2%; Sp = 25.0% Cut-off ≥5: Sn = 74.3%; Sp = 47.8% Cut-off ≥6: Sn = 59.5%; Sp = 66.3% Cut-off ≥7: Sn = 40.0%; Sp = 83.7% Cut-off ≥8: Sn = 21.4%; Sp = 89.1% Cut-off ≥9: Sn = 14.3%; Sp = 95.7% Cut-off ≥10: Sn = 8.6%; Sp = 96.7% Cut-off ≥11: Sn = 4.3%; Sp = 98.9% AUC total symptom score: 0.647 (0.033)	<u>Source of funding:</u> Korea Asthma Allergy Foundation Research Grant and Korea Health 21 R&D Project, Ministry of Health <u>Limitations:</u> • No drop-outs • Consecutive or random patient selection not mentioned • time between IT and RS unclear but same time		
	<u>Setting:</u> Hospital outpatient dept.	<u>Country:</u> Korea	<u>Exclusion criteria:</u>	Smokers: Asthma: 36.7% Non-asthma: 21.4%	b)	Ref std +	Ref std -	Total
	<u>Recruitment:</u> Consecutive or random patient selection				Index test +	86	71	157
					Index test -	124	21	145
				Total	210	92	302	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
	not reported			<p>exacerbation and improvement? (score 2)</p> <p>a) Total symptom score b) Responded yes to Q1 (all provoking factors) c) Responded yes to Q2 d) Responded yes to Q3 e) Responded yes to Q4 f) Responded yes to Q5</p> <p>Cut-off: various total symptom score cut-off scores reported. ROC analysis of total symptom scores. With an increase in cut-off, sensitivity decreased and specificity increased. Cut-off value of ≥ 4 associated with highest combination of sn and sp. Even within a total symptom score of ≥ 4, the sn/sp varied with the combination of symptoms (reported in paper Table 6)</p> <p><u>Reference standard</u> Physician Dx with objective test (patients with an FEV1 >70% had MCT, all other patients had BDR to short-acting beta2-agonist). Definite Dx of asthma made using test (MCh PC20 <16mg/ml or BDR FEV1 increase >12% and 200ml)</p>	Sensitivity Specificity PPV / NPV		41.0% 22.8% 54.8% / 14.5%		<p>suggested <u>Additional data:</u> Symptoms and provoking factors with high prevalence in those Dx with asthma: wheezing with dyspnoea (86%); nocturnal aggravation (64%); fluctuation (64%); upper respiratory infection (50%); cold air (44%); exercise (40%).</p>
c)		Ref std +	Ref std -	Total					
Index test +		34	53	87					
Index test -		176	39	215					
Total		210	92	302					
Sensitivity Specificity PPV / NPV		16.2% 42.4% 39.1% / 18.1%							
d)		Ref std +	Ref std -	Total					
Index test +		24	27	51					
Index test -		186	65	251					
Total		210	92	302					
Sensitivity Specificity PPV / NPV		11.4% 70.7% 47.1% / 25.9%							
e)		Ref std +	Ref std -	Total					
Index		18	19	37					

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
				Time between index test and reference standard: unclear <u>Target condition</u> Asthma	test +				
					Index test -	192	73	265	
					Total	210	92	302	
					Sensitivity	9.0%			
					Specificity	79.3%			
					f)	Ref std +	Ref std -	Total	
					Index test +	64	59	123	
					Index test -	146	33	179	
					Total	210	92	302	
				Sensitivity	30.5%				
				Specificity	35.9%				
				PPV / NPV	52.0% / 18.4%				

1

Table 26: SCHLEICH 2012¹⁵³⁰

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Schleich FN, Asandei R, Manise M, Sele J, Seidel L, Louis R. Is FENO50	<u>Study type:</u> Prospective study <u>Data source:</u> Collected for study	N = 174 <u>Inclusion criteria:</u> Patients referred to chest physicians for methacholine challenge for asthma diagnosis;	<u>Male: Female</u> 72: 102 <u>Mean (SD) age:</u> 41 (16) yrs	<u>Index test</u> Questionnaire concerning symptoms: a) diurnal cough b) nocturnal cough c) diurnal wheezing d) nocturnal wheezing e) dyspnoea	a)	Ref std +	Ref std -	Total	<u>Source of funding:</u> Interuniversity Attraction Poles Project <u>Limitations:</u>
					Index test +	54	68	122	
					Index test -	28	24	52	
					Total	82	92	174	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
useful diagnostic tool in suspected asthma? International Journal of Clinical Practice. 2012; 66(2):158-165. (Guideline Ref ID SCHLEICH 2012)	<u>Setting:</u> Department of Pulmonary Medicine <u>Country:</u> Belgium <u>Recruitment:</u> March 13, 2009 to December 30, 2009	bronchodilator test failed to show reversible airway obstruction or baseline spirometry normal <u>Exclusion criteria:</u> Patients already receiving inhaled corticosteroids		<u>Reference standard</u> Methacholine challenge Cut off PC20 <16mg/mL Time between index test and reference standard: same time <u>Target condition</u> Asthma (methacholine challenge positive) vs. methacholine negative FeNO levels: methacholine challenge positive vs. methacholine negative	Sensitivity		65.9		<u>Additional data:</u> None
					Specificity		26.1		
					PPV / NPV		44.3 / 46.2		
					b)	Ref std +	Ref std -	Total	
					Index test +	30	32	62	
					Index test -	52	60	112	
					Total	82	92	174	
					Sensitivity		36.6		
					Specificity		65.2		
					PPV / NPV		48.4 / 53.4		
					c)	Ref std +	Ref std -	Total	
					Index test +	47	35	82	
					Index test -	35	57	92	
					Total	82	92	174	
Sensitivity		57.3							
Specificity		62.0							
PPV / NPV		57.3 / 62.0							
d)	Ref std +	Ref std -	Total						
Index test +	46	19	65						
Index test -	36	73	109						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					Total	82	92	174	
					Sensitivity	56.1			
					Specificity	79.3			
					PPV / NPV	70.8 / 67.0			
					e)	Ref std +	Ref std -	Total	
					Index test +	60	41	101	
					Index test -	22	51	73	
					Total	82	92	174	
					Sensitivity	73.2			
					Specificity	55.4			
					PPV / NPV	59.4 / 69.9			

Table 27: SCHNEIDER 2009A¹⁵³⁵

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Schneider A et al. 2009. Diagnostic accuracy of spirometry in primary	<u>Study type:</u> Cross-sectional study <u>Setting:</u> Index test in primary care, 14 GPs in 10 practices	N = 219 Adults <u>Inclusion criteria:</u> • Visiting GP for the first time with complaints of suggested obstructive airway disease (OAD).	<u>Male: Female</u> 92:127 <u>Mean (SD) age:</u> 43.8 (15.6) <u>% of symptomatic</u>	<u>Index test:</u> Medical history taken with a structured questionnaire: a) 'Do you sometimes suffer from shortness of breath?' b) 'Have you suffered from wheezing in your chest?' c) 'Do you often suffer from cough?'	a)	Ref st +	Ref st -	Total	<u>Source of funding:</u> Federal ministry of education and research (BMBF), Germany. <u>Limitations:</u>
					Index test +	55	80	135	
					Index test -	35	49	84	
					Total	90	129	219	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
care. BMC Pulmonary Medicine: 9: 31. REF ID: SCHNEIDER2009A	<u>Country:</u> Germany <u>Recruitment:</u> Consecutive recruitment	<ul style="list-style-type: none"> Symptoms such as dyspnoea, coughing, or expectoration <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Previous Dx for OAD Previous anti-obstructive medicine Contraindications for BDR of challenge testing (untreated hyperthyreosis, unstable coronary artery disease, cardiac arrhythmia) Pregnancy 	<u>patients with positive/abnormal spirometry:</u> 35.6% <u>Medications:</u> None prior to spirometry at GP. If necessary, therapy initiated by GP for asthma or COPD but stopped 12 hours prior to lung function lab.	d) 'Do you often suffer from expectoration?' e) 'Have you been woken up with a feeling of tightness in your chest?' f) 'Have you been woken up by an attack of shortness of breath?' <u>Reference standard</u> LUNG FUNCTION LAB: Dx by pneumologist based on whole-body plethysmography (FEV1/VC ≤70% or FEV1 <80%) followed by either BDR if obstruction is present (FEV1 ≥12% and ≥200ml) or methacholine if obstruction is not present (PC20 ≤16mg/ml or extreme increase in airway resistance accompanied by clinical symptoms in two patients) Time between index test and reference standard: unclear <u>Target condition</u> OAD: Asthma or COPD	Sensitivity		61.1		<u>Additional data:</u> 3 lost to follow-up
					Specificity		38.0		
					PPV/NPV		40.7/58.3		
					b)	Ref st +	Ref st -	Total	
					Index test +	47	60	107	
					Index test -	43	69	112	
					Total	90	129	219	
					Sensitivity		52.2		
					Specificity		53.5		
					PPV/NPV		43.9 / 61.6		
c)	Ref st +	Ref st -	Total						
Index test +	39	87	126						
Index test -	51	42	93						
Total	90	129	219						
Sensitivity		43.3							
Specificity		32.6							
PPV / NPV		31.0 / 45.2							
d)	Ref st +	Ref st -	Total						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					Index test +	22	52	74	
					Index test -	68	77	145	
					Total	90	129		
					Sensitivity	24.4			
					Specificity	59.7			
					PPV/NPV	29.7 / 53.1			
					e)	Ref st +	Ref st -	Total	
					Index test +	27	22	49	
					Index test -	63	107	170	
					Total	90	129		
					Sensitivity	30.0			
					Specificity	82.9			
					PPV/NPV	55.1 / 62.9			
					f)	Ref st +	Ref st -	Total	
					Index test +	27	24	51	
					Index test -	63	105	168	
					Total	90	129		
					Sensitivity	30.0			
					Specificity	81.4			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
					PPV / NPV	52.9 / 62.5	

Table 28: SCHNEIDER 2012¹⁵³³

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
Antonius Schneider, Mehtap Ay, Bernhard Faderl, Klaus Linde, and Stefan Wagenpfeil. Diagnostic accuracy of clinical symptoms in obstructive airway diseases varied within different health care sectors.	<p><u>Study type:</u> Cross-sectional study</p> <p><u>Setting:</u> 3 parts /settings: 1. GPs 2. Referral practice (pneumologists) • Hospital (Pts in rehab after long-term respiration, or after weaning from artificial respiration, or pts with severe COPD)</p>	<p>N = 778 adults (GP: n=219; pneumologists: n=259; hospital: n=300).</p> <p><u>Inclusion criteria:</u> 1. GPs: • first time visit with complaints of suggested OAD or RAD • symptoms for >2 months 2. Pneumologists: • 1st visit for Dx work-up to include or exclude OAD or RAD • Other criteria as for GPs 3. Hospital • Pts with suspected OAD who were hospitalised for the</p>	<p><u>Female</u> GP: 58% Referral: 60% Hospital: 36%</p> <p><u>Mean age:</u> GP: 43.8 Referral: 46.3 Hospital: 65.3</p> <p><u>% of symptomatic patients Dx with asthma:</u> GP: 90 (41%) Referral: 84 (32%) Hospital: 25 (8.3%)</p> <p><u>Medications:</u> Not mentioned.</p>	<p><u>Index test:</u> Medical history taken with a structured questionnaire: a) Self-reported wheezing b) Coughing c) Dyspnoea attacks d) Dyspnoea going upstairs e) Dyspnoea when walking f) Dyspnoea on minimal exercise g) Expectoration h) Tightness of chest</p> <p><u>Reference standard</u> Symptoms + LUNG FUNCTION LAB: Dx by pneumologist based on whole-body plethysmography (FEV1/VC ≤70% or FEV1 <80%) followed by either BDR if obstruction is</p>	<p>GP (sens/spec) NOTE: some outcome data was previously reported in Schneider 2009A. a) Self-reported wheezing (52.2 / 53.1) b) Coughing (43.8 / 31.5) c) Dyspnoea attacks (40.0 / 78.4) d) Dyspnoea going upstairs (47.1 / 49.6) e) Dyspnoea when walking (4.8 / 93.2) f) Dyspnoea on minimal exercise (2.5 / 94.1) g) Expectoration (25.3 / 58.7) h) Tightness of chest (31.4 / 82.7)</p> <p>Pneumologists (sens/spec) a) Self-reported wheezing (52.4 / 65.6) b) Coughing (52.5 / 63.9) c) Dyspnoea attacks (8.9 / 88.2) d) Dyspnoea going upstairs (54.6 / 40.6) e) Dyspnoea when walking (25.0 / 78.4) f) Dyspnoea on minimal exercise (14.5 / 84.9) g) Expectoration (40.0 / 74.1) h) Tightness of chest (31.7 / 74.7)</p>	<p><u>Source of funding:</u> Federal ministry of education and research (BMBF), Germany.</p> <p><u>Limitations:</u></p> <p><u>Additional data:</u> None.</p>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
<p><i>J.Clin.Epidemiol.</i> 65 (8):846-854, 2012.</p> <p>REF ID: SCHNEIDER2012</p>	<p>needing respiration at home or severe asthma)</p> <p><u>Country:</u> Germany (multicentre)</p> <p><u>Recruitment:</u> Consecutive recruitment</p>	<p>first time.</p> <p><u>Exclusion criteria:</u></p> <p>1. GPs:</p> <ul style="list-style-type: none"> Respiratory infections in prior 6 wks Previous Dx of OAD. <p>2. Pneumologists:</p> <ul style="list-style-type: none"> As above. <p>3. Hospital</p> <ul style="list-style-type: none"> None reported. 		<p>present (FEV1 \geq12% and \geq200ml) or methacholine if obstruction is not present (PC20 \leq16mg/ml). Most asthma pts were identified by the BPT.</p> <p><u>Time between index test and reference standard:</u> unclear</p> <p><u>Target condition</u> OAD: Asthma or COPD</p>	<p>Hospital (sens/spec)</p> <p>a) Self-reported wheezing (76.0 / 33.6)</p> <p>b) Coughing (48.0 / 51.8)</p> <p>c) Dyspnoea attacks (32.0 / 81.6)</p> <p>d) Dyspnoea going upstairs (88.0 / 6.7)</p> <p>e) Dyspnoea when walking (36.0 / 32.3)</p> <p>f) Dyspnoea on minimal exercise (32.0 / 42.9)</p> <p>g) Expectoration (41.7 / 51.1)</p> <p>h) Tightness of chest (44.0 / 53.5)</p>	

Table 29: TOMITA 2013¹⁷⁷³

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
<p>Tomita et al., 2013. A scoring algorithm for predicting the presence of adult asthma: a prospective</p>	<p><u>Study type:</u> Cross-sectional study</p> <p><u>Setting:</u> Outpatient clinic, University Hospital</p> <p><u>Country:</u> Japan</p>	<p>N = 566</p> <p>Adults</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Adult outpatients with non-specific respiratory symptoms including wheeze, shortness of breath, and cough. <p><u>Exclusion criteria:</u></p>	<p><u>Male: Female</u> 221:345</p> <p>Median (range) age: 52 years (18-88)</p> <p>Medications: Could be</p>	<p><u>Index test</u></p> <p>Five additional questions at routine interview, including:</p> <p>a) 'Have you ever had any experiences of wheezing?'</p> <p>b) 'Did your symptoms occur in the early morning or at night (diurnal variation)?'</p> <p>c) 'Have you had similar episodes of respiratory symptoms (recurrent episodes)?'</p>	a)	Ref st +	Ref st -	Total	<p><u>Source of funding:</u> None. None of the authors had a financial relationship with a commercial entity</p> <p><u>Limitations:</u></p> <ul style="list-style-type: none"> Time
					Index test +	110	26	136	
					Index test -	257	173	430	
					Total	367	199	566	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
derivation study. Primary care respiratory journal: 22: 51-58 REF ID: TOMITA2013	<u>Recruitment:</u> All eligible patients between Jan 2008 and Sept 2011 (unclear)	<ul style="list-style-type: none"> Abnormal x-ray findings and other causes Pregnant/breastfeeding Current Dx of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis, other lower respiratory abnormality. Systemic or inhaled CS, beta-blockers or angiotensin converting enzyme inhibitors Symptoms of chest pain or haemosputum. 	started on ICS at first visit before MCT	<u>Reference standard</u> Relevant symptom history (all patients) and BDR (FEV1 <200ml and 12%) and/or BHR (methacholine PC20 <8mg/ml) NB. 64/367 patients Dx had clinically Dx asthma (responsive to ICS with neither BDR or BHR) Time between index test and reference standard: within 8 weeks <u>Target condition</u> Asthma	Sensitivity		30.0%		between tests 8 weeks, but could be started on ICS at first visit • 813 consented but only 566 performed MCT (others declined participation or no AHR) <u>Additional data:</u>
					Specificity		86.9%		
					PPV / NPV		80.9% / 40.2%		
					b)	Ref std +	Ref std -	Total	
					Index test +	198	62	260	
					Index test -	169	137	306	
					Total	367	199	566	
					Sensitivity		54.0%		
					Specificity		68.8%		
					PPV / NPV		76.2% / 44.8%		
c)	Ref std +	Ref std -	Total						
Index test +	107	18	125						
Index test -	260	181	441						
Total	367	199	566						
Sensitivity		29.2%							
Specificity		91.0%							

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
					PPV / NPV	85.6% / 41.0%	

Table 30: WEVERHESS 1999¹⁹⁰⁸

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					a)	Ref st +	Ref st -	Total	
Weverhess et al., 1999. Prognostic characteristics of asthma diagnosis in early childhood in clinical practice. Acta Paediatrica: 88: 827-834. REF ID: WEVERHESS1999	<u>Study type:</u> Longitudinal prognostic study <u>Setting:</u> Outpatient department, Children's Hospital <u>Country:</u> Netherlands <u>Recruitment:</u> All children from Jan 1991 to Jan 1993	N = 188 (including aged 2-4yr subgroup only) <u>Inclusion criteria:</u> Aged 0-4 years with symptoms that were suggestive of asthma <u>Exclusion criteria:</u> Symptoms that could be explained by other respiratory disorders, such as respiratory syncytial virus bronchiolitis, cystic fibrosis, gastro-oesophageal reflux	<u>Male: Female</u> 108:80 <u>Mean (SD) age:</u> 37 (8.4) months Medications at initial visit: Beta-agonists 42%, depropine 10%, anticholinergics 3%, antihistamines 20%, anti-inflammatory 5%, antibiotics 49%.	<u>Index test</u> Symptoms (visit and questionnaire): a) cough b) wheeze c) cough and wheeze d) shortness of breath <u>Reference standard</u> Dx taken from medical notes at follow-up (2 years later). Dx made by a paediatrician on clinical grounds, based on recurrence of symptoms and need for and response to therapy according to the guidelines for diagnosis of asthma in young children (follow up statement from the International Paediatric Asthma Consensus Group).	Index test +	127	41	168	<u>Source of funding:</u> Supported financially by Stichting Astmabestrijding, Amsterdam <u>Limitations:</u> Follow up at 2 years, prognostic design <u>Additional data:</u> Data provided from children aged 0-1 year separately but does not match protocol.
					Index test -	17	3	20	
					Total	144	44	188	
					Sens / Spec PPV / NPV		88.2% / 6.8% 75.6% / 15.0%		
					b)	Ref std +	Ref std -	Total	
					Index test +	78	19	97	
					Index test -	66	25	91	
					Total	144	44	188	
					Sens / Spec PPV / NPV		54.2% / 56.8% 80.4% / 27.5%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments																																																
				<p><u>Time between index test and reference standard:</u> 2 years</p> <p><u>Target condition</u></p>	<table border="1"> <tr> <td>c)</td> <td>Ref std +</td> <td>Ref std -</td> <td>Total</td> </tr> <tr> <td>Index test +</td> <td>70</td> <td>18</td> <td>88</td> </tr> <tr> <td>Index test -</td> <td>74</td> <td>26</td> <td>100</td> </tr> <tr> <td>Total</td> <td>144</td> <td>44</td> <td>188</td> </tr> <tr> <td colspan="2">Sens / Spec</td> <td colspan="2">48.6% / 59.1%</td> </tr> <tr> <td colspan="2">PPV / NPV</td> <td colspan="2">79.5% / 26.0%</td> </tr> </table> <table border="1"> <tr> <td>d)</td> <td>Ref std +</td> <td>Ref std -</td> <td>Total</td> </tr> <tr> <td>Index test +</td> <td>109</td> <td>21</td> <td>130</td> </tr> <tr> <td>Index test -</td> <td>35</td> <td>23</td> <td>58</td> </tr> <tr> <td>Total</td> <td>144</td> <td>44</td> <td>188</td> </tr> <tr> <td colspan="2">Sens / Spec</td> <td colspan="2">75.7% / 52.3%</td> </tr> <tr> <td colspan="2">PPV / NPV</td> <td colspan="2">83.8% / 39.7%</td> </tr> </table> <p>PROGNOSTIC DATA (multivariate): Predictors of Asthma Dx 2 years later (n=188)</p> <ul style="list-style-type: none"> • Shortness of breath was a prognostic factor (OR 3.10, 95% CI 1.49-6.47) • Wheeze was not a prognostic factor 	c)	Ref std +	Ref std -	Total	Index test +	70	18	88	Index test -	74	26	100	Total	144	44	188	Sens / Spec		48.6% / 59.1%		PPV / NPV		79.5% / 26.0%		d)	Ref std +	Ref std -	Total	Index test +	109	21	130	Index test -	35	23	58	Total	144	44	188	Sens / Spec		75.7% / 52.3%		PPV / NPV		83.8% / 39.7%		
c)	Ref std +	Ref std -	Total																																																			
Index test +	70	18	88																																																			
Index test -	74	26	100																																																			
Total	144	44	188																																																			
Sens / Spec		48.6% / 59.1%																																																				
PPV / NPV		79.5% / 26.0%																																																				
d)	Ref std +	Ref std -	Total																																																			
Index test +	109	21	130																																																			
Index test -	35	23	58																																																			
Total	144	44	188																																																			
Sens / Spec		75.7% / 52.3%																																																				
PPV / NPV		83.8% / 39.7%																																																				

G.2 History of atopic disorders

Table 31: CORDIERO 2011³⁶⁵

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					Ref st +	Ref st -	Total		
Cordiero et al., 2011. Utility of nitric oxide for the diagnosis of asthma in an allergy clinic population. Allergy and Asthma Proceedings: 32: 119-126. REF ID: CORDIERO 2011	<u>Study type:</u> Cross-sectional observational study <u>Setting:</u> General outpatient allergy clinic <u>Country:</u> The Netherlands <u>Recruitment:</u> All from January 2007 to September 2007	N = 114 Adults and children/young people <u>Inclusion criteria:</u> <ul style="list-style-type: none"> New referrals to outpatient allergy clinic Symptoms of nasal or ocular complaints; pulmonary complaints; skin complaints and general complaints. <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Patients using inhaled corticosteroids or oral corticosteroids within 6 weeks 	<u>Male: Female</u> 43:71 <u>Median (range) age:</u> 38.5 (7-87) Medications: Treatment with short acting bronchodilators allowed up to 8 hours before and long acting bronchodilators and antihistamines up to 48 hours before.	<u>Index test</u> Family history (unclear if first degree relatives and if history of asthma or atopy) <u>Reference standard</u> History of typical respiratory symptoms and FEV1 improvement >12% and >200mL with salbutamol 400µg or PC20 histamine ≤8mg/mL according to GINA. Time between index test and reference standard: 6 weeks <u>Target condition</u> Asthma diagnosis vs. non-asthma (Allergic rhinitis, non-allergic rhinitis, eczema, urticarial, other analysed all together)					<u>Source of funding:</u> Not stated <u>Limitations:</u> <ul style="list-style-type: none"> Family history (unclear if first degree relatives and if history of asthma or atopy). <u>Additional data:</u>
					Index test +	25	32	57	
					Index test -	17	40	57	
					Total	42	72	114	
					Sensitivity		59.5%		
					Specificity		55.6%		
					PPV		43.9%		
					NPV		70.2%		

Table 32: DEILAMI 2009⁴¹³

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments	
					Ref st +	Ref st -	Total			
Deilami et al., 2009. Evaluation of methacholine challenge test results in chronic cough patients referring to clinic of pulmonary disease. Acta Medica Iranica: 47: 175-179. REF ID: DEILAMI2009	<u>Study type:</u> Cross sectional study <u>Setting:</u> Hospital pulmonary disease clinic <u>Country:</u> Iran <u>Recruitment:</u> All patients who were not excluded (unclear)	N = 81 <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Suffering from cough for at least 8 weeks and went to the pulmonary disease clinic. Normal spirometry <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Patients with PND Patients of GERD who were untreated Respiratory infection within the last 3 weeks or contraindication to methacholine. 	<u>Male: Female</u> 45:36 <u>Mean age:</u> 32.5 (13.1) Medications: n=7 smokers	<u>Index test</u> Personal history of allergy NB Family history of asthma sens/spec data was not extracted as was not first class relatives only <u>Reference standard</u> Methacholine challenge test: concentrations of 0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16mg/ml, until FEV1 drop of 20% or more. Cut-off: PC20 ≤4mg/ml Time between index test and reference standard: <u>Target condition</u> Asthma					<u>Source of funding:</u> Not reported <u>Limitations:</u> <ul style="list-style-type: none"> <u>Additional data:</u>	
					Index test +	13	15	28		
					Index test -	11	42	53		
					Total	24	57	80		
					Sensitivity		54.2%			
					Specificity		73.7%			
					PPV		46.4%			
					NPV		20.8%			

Table 33: TOMITA 2013¹⁷⁷³

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
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Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
<p>Tomita et al., 2013. A scoring algorithm for predicting the presence of adult asthma: a prospective derivation study. Primary care respiratory journal: 22: 51-58</p> <p>REF ID: TOMITA2013</p>	<p><u>Study type:</u> Cross-sectional study</p> <p><u>Setting:</u> Outpatient clinic, University Hospital</p> <p><u>Country:</u> Japan</p> <p><u>Recruitment:</u> All eligible patients between Jan 2008 and Sept 2011 (unclear)</p>	<p>N = 566 Adults</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Adult outpatients with non-specific respiratory symptoms including wheeze, shortness of breath, and cough. <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Abnormal x-ray findings and other causes Pregnant/breastfeeding Current Dx of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, chronic bronchitis, other lower respiratory abnormality. Systemic or inhaled CS, beta-blockers or angiotensin converting enzyme inhibitors Symptoms of chest pain or 	<p><u>Male: Female</u> 221:345</p> <p>Median (range) age: 52 years (18-88)</p> <p>Medications: Could be started on ICS at first visit before MCT</p>	<p><u>Index test</u></p> <p>Routine interview including following questions:</p> <p>a) Personal history: 'Have you had any medical history of allergic diseases such as asthma, atopic dermatitis, and allergic rhinitis?'</p> <p>b) Family history: 'Do you have any close relatives with allergic disease?'</p> <p><u>Reference standard</u></p> <p>Relevant symptom history (all patients) and BDR (FEV1 <200ml and 12%) and/or BHR (methacholine PC20 <8mg/ml)</p> <p>NB. 64/367 patients Dx had clinically Dx asthma (responsive to ICS with neither BDR or BHR)</p> <p>Time between index test and reference standard: within 8 weeks</p> <p><u>Target condition</u> Asthma</p>	a)	Ref st +	Ref st -	Total	<p><u>Source of funding:</u> None. None of the authors had a financial relationship with a commercial entity</p> <p><u>Limitations:</u></p> <ul style="list-style-type: none"> Time between tests 8 weeks, but could be started on ICS at first visit 813 consented but only 566 performed MCT (others declined participation or no AHR) <p><u>Additional data:</u></p>
					Index test +	202	64	266	
					Index test -	165	135	300	
					Total	367	199	566	
					Sensitivity		55.0%		
					Specificity		67.8%		
					PPV		75.9%		
					NPV		45.0%		
					b)	Ref std +	Ref std -	Total	
					Index test +	95	34	129	
Index test -	272	165	437						
Total	367	199	566						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
		haemosputum.			Sensitivity	25.9%	
					Specificity	82.9%	
					PPV	73.6%	
					NPV	37.8%	

1

Table 34: WEVERHESS 1999¹⁹⁰⁸

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Weverhess et al., 1999. Prognostic characteristics of asthma diagnosis in early childhood in clinical practice.	<u>Study type:</u> Longitudinal prognostic study <u>Setting:</u> Outpatient department, Children's Hospital <u>Country:</u> Netherlands	N = 188 (including aged 2-4yr subgroup only) <u>Inclusion criteria:</u> • Aged 0-4 years with symptoms that were suggestive of asthma <u>Exclusion criteria:</u>	<u>Male: Female</u> 108:80 <u>Mean (SD) age:</u> 37 (8.4) months Medications at initial visit: Beta-agonists 42%,	<u>Index test</u> History taken at initial visit: a) Past or present rhinitis b) past or present eczema c) family history <u>Reference standard</u> Dx taken from medical notes at follow-up (2 years later). Dx made by a paediatrician on clinical	a)	Ref st +	Ref st -	Total	<u>Source of funding:</u> Supported financially by Stichting Astmabestrijding, Amsterdam <u>Limitations:</u>
					Index test +	89	35	124	
					Index test -	55	9	64	
					Total	144	44	188	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Acta Paediatrica: 88: 827-834. REF ID: WEVERHESS1999	<u>Recruitment:</u> All children from Jan 1991 to Jan 1993	<ul style="list-style-type: none"> Symptoms that could be explained by other respiratory disorders, such as respiratory syncytial virus bronchiolitis, cystic fibrosis, gastro-oesophageal reflux 	depropine 10%, anticholinergics 3%, antihistamines 20%, anti-inflammatory 5%, antibiotics 49%.	<p>grounds, based on recurrence of symptoms and need for and response to therapy according to the guidelines for diagnosis of asthma in young children (follow up statement from the International Paediatric Asthma Consensus Group).</p> <p>Time between index test and reference standard: 2 years</p> <p><u>Target condition</u></p>	Sensitivity		61.8%		<p><u>Additional data:</u> Data provided from children aged 0-1 year separately but does not match protocol.</p>
					Specificity		20.5%		
					PPV		71.8%		
					NPV		14.1%		
					b)	Ref std +	Ref std -	Total	
					Index test +	67	11	78	
					Index test -	77	33	110	
					Total	144	44	188	
					Sensitivity		46.5%		
Specificity		75.0%							
PPV		85.9%							
NPV		30.0%							
c)	Ref std +	Ref std -	Total						
Index test +	63	19	82						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					Index test -	81	25	106	
					Total	144	44	188	
					Sensitivity		43.8%		
					Specificity		56.8%		
					PPV		76.8%		
					NPV		23.6%		

Table 35: VANDERMARK 2014¹⁸²³

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Predicting asthma in preschool children at high risk presenting in primary care: development of a clinical asthma prediction score.	<u>Study type:</u> Longitudinal prognostic study (demographic data and clinical history obtained from questionnaire. Sensitivity and specificity calculated from for Dx	N = 771 (438 had information for diagnosis at age 6 years) <u>Inclusion criteria:</u> Aged 1-5 years. Presented in primary care in the previous 12 months with current coughing (≥2 visits), wheezing (≥1 visits), and/or shortness of breath (≥1 visits) (only those	<u>Male: Female</u> 249:189 <u>Mean (SD) age:</u> At baseline for study: 3.0 (1.3). Note: diagnosis made at aged 6 years Medications: unclear	<u>Index test</u> Questionnaire administered at baseline and at 6 years: a) Family history of asthma (parents and/or siblings) <u>Reference standard</u> At age 6 years, spirometry and BHR obtained in children with wheezing, shortness of breath, recurrent coughing or use of asthma medication during the previous 12	a)	Ref st +	Ref st -	Total	<u>Source of funding:</u> Not reported <u>Limitations:</u> <u>Additional data:</u>
					Index test +	80	76	156	
					Index test -	107	175	282	
					Total	187	251	438	
					Sens	43.8%			
					Spec	69.7%			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
<p>Primary Care Respiratory Journal. 2014; 68(1):52-59.</p> <p>REF ID: VANDERMARK2014</p>	<p>at 6 years of age)</p> <p><u>Setting:</u> Primary care</p> <p><u>Country:</u> Netherlands</p> <p><u>Recruitment:</u> Children participating in the ARCADE prospective cohort study</p>	<p>with symptoms in the past year included in asthma Dx at age 6 years).</p> <p><u>Exclusion criteria:</u></p>		<p>months.</p> <p>Dx defined as having persistent symptoms and/or using asthma medication in the last year in combination with BHR (methacholine <8mg.ml) or BDR (>10% increase in FEV1).</p> <p><u>Time between index test and reference standard:</u> Unclear if index test (clinical history) was taken at baseline or at 6 years.</p> <p><u>Target condition</u> Asthma</p>		

G.3 Symptoms after exercise

Table 36: Choi 2007^{318,319}

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					Ref std +	Ref std -	Total		
Choi et al., 2007. Easy diagnosis of asthma: computer-assisted, symptom-based diagnosis. Journal of Korean Medical Science: 22: 832-838. REF ID: CHOI2007	<u>Study type:</u> Diagnostic cross sectional study <u>Setting:</u> Hospital outpatient dept. <u>Country:</u> Korea <u>Recruitment:</u> Consecutive or random patient selection not reported	N = 302 Adults <u>Inclusion criteria:</u> • Respiratory symptoms such as dyspnoea, cough or wheezing <u>Exclusion criteria:</u>	<u>Male:Female</u> 127:175 <u>Mean age:</u> Asthma: 46.8 (16.8) Non-asthma: 47.8 (15.6) Medications: Not reported Smokers: Asthma: 36.7% Non-asthma: 21.4%	<u>Index test</u> Questionnaire consisting of 11 questions regarding symptoms. Q3 = Have you had wheezing associated with dyspnoea (provoking factor – exercise)? Cut-off: affirmative answer to Q3 <u>Comparator test</u> n/a <u>Reference standard</u> Physician Dx with objective test (patients with an FEV1 >70% had MCT, all other patients had BDR to short-acting beta2-agonist). Definite Dx of asthma made using test (MCh PC20 <16mg/ml or BDR FEV1 increase >12% and 200ml) Time between index test and reference standard: unclear					<u>Source of funding:</u> Korea Asthma Allergy Foundation Research Grant and Korea Health 21 R&D Project, Ministry of Health <u>Limitations:</u> • No drop-outs • Consecutive or random patient selection not mentioned • time between IT and RS unclear but same time suggested <u>Additional data:</u>
					Index test +	84	20	104	
					Index test -	126	72	198	
					Total	210	92	302	
					Sensitivity		40.0%		
					Specificity		78.3%		
					PPV		80.8%		
					NPV		36.4%		
						Ref std +	Ref std -	Total	
					Index test +				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
				<u>Target condition</u> Asthma	Index test -				
					Total				
					Sensitivity				
					Specificity				
					PPV				
					NPV				

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2 G.4 Occupational asthma

3 **Table 37: BAUR 1998¹²⁹**

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Baur X et al. Relation between occupatio	<u>Study type:</u> Diagnostic Cross-sectional study	N = 62 healthcare workers (airborne latex; 12 asthma)	<u>Male: Female</u> <u>Not stated</u> <u>Mean age:</u>	<u>Index test</u> Asking whether their symptoms are better away from work	Occupational asthma: health care workers (latex)	Ref std +	Ref std -	Total	<u>Source of funding:</u> None stated

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
nal asthma case history, bronchial methacholine challenge, and specific challenge test in patients with suspected occupational asthma. Am J Industr Med 1998; 33: 114-122. BAUR1998	<u>Data source:</u> Industrial medicine institute <u>Setting:</u> Symptomatic <u>Country:</u> Germany <u>Recruitment:</u> 1992 to 1997	28 bakers (flour, baking enzymes; 7 asthma) 114 isocyanate workers (isocyanates; 21 asthma) <u>Inclusion criteria:</u> Healthcare workers with contact with latex gloves, bakers or isocyanate workers presenting with suspected occupational asthma <u>Exclusion criteria:</u> Challenge tests contraindicated or declined	Healthcare workers 31 (8.1); bakers 32 (11.9); isocyanate workers 39 (11.1) years	CUT-OFF: positive = Reversible airways narrowing (SOB, wheeze) causally related to exposure in the working environment occurred repeatedly <u>Reference standard</u> Clinical Dx including objective test: Specific conductance (sG _{aw}) dropped ≥40% from baseline and absolute value ≤0.5(kPa*s) ⁻¹ Time between index test and reference standard: same time <u>Target condition</u> Occupational asthma	Question +	11	34	45	<u>Limitations:</u> <u>Additional data:</u> Sensitivity etc calculated
					Question -	1	16	17	
					Total	12	50	62	
					Sensitivity		92%		
					Specificity		32%		
					PPV		24%		
					NPV		94%		
					Occupational asthma: bakers (flour/enzyme)	Ref std +	Ref std -	Total	
					Question +	7	8	15	
					Question -	0	13	13	
					Total	7	21	28	
					Sensitivity		100%		
					Specificity		62%		
					PPV		47%		
					NPV		100%		
Occupational asthma: isocyanate workers	Ref std +	Ref std -	Total						
Question	14	32	46						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments	
					+			
					Question	7	61	68
					-			
					Total	21	93	114
					Sensitivity		67%	
					Specificity		66%	
					PPV		30%	
					NPV		90%	

Table 38: Malo 1991¹⁰⁷⁹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments	
Malo J-L et al. Is the clinical history a satisfactory means of diagnosing occupational asthma? Am Rev Respir Dis 1991; 143: 528-532.	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Chest clinic <u>Setting:</u> Symptomatic <u>Country:</u> Canada	N = 162 <u>Inclusion criteria:</u> Consecutive cases referred for possible occupational asthma <u>Exclusion criteria:</u> None given	<u>Male:</u> <u>Female</u> 125:37 <u>Mean age:</u> 39.6 (11.8) years	<u>Index test</u> Asking whether their symptoms are better away from work CUT-OFF: positive = Whether symptoms worse during or after work and improved during weekends and holidays – history “very likely” or “likely” <u>Reference standard</u> Clinical Dx including objective test: Final diagnosis including specific inhalation challenges, serial monitoring of peak flow at work and away from work or both. Fall in FEV1 > 20% (or ≥15% in late component of dual reactions) on specific challenge	Occupational asthma Ref std + Question + Question - Total Sensitivity Specificity PPV NPV	Ref std – 65 10 75 87% 55% 63% 83%	Total 104 58 162 87% 55% 63% 83%	<u>Source of funding:</u> Not stated <u>Limitations:</u> <u>Additional data:</u> PPV and NPV reported; sensitivity and specificity calculated

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
MALO 1991	<u>Recruitment:</u> 1987 to 1989			<p>or patterns suggestive of work-related asthma using graphs of individual, mean, maximum and minimum daily values using Burge criteria</p> <p>Time between index test and reference standard: same time</p> <p><u>Target condition</u> Occupational asthma (isocyanates, flour, grain dust, red and white cedar, pharmaceutical products, sawmills, laboratory animals)</p>			

Table 39: Vandenplas 2001¹⁸⁴²

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes		Comments	
Vandenplas O et al. Occupational asthma in symptomatic workers exposed to natural rubber latex:	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Chest clinic <u>Setting:</u> Symptomatic	N = 45 <u>Inclusion criteria:</u> Consecutive patients referred for investigation of possible OA caused by latex; exposed at work to airborne natural rubber latex (NRL) allergens from NRL gloves.	<u>Male: Female</u> 2:43 <u>Mean age:</u> 33.6 years	<u>Index test:</u> Asking whether their symptoms are better away from work CUT-OFF: positive = Symptoms present only on work days <u>Reference standard:</u> Clinical Dx including objective test: SICs with NRL gloves; FEV1 fell by more than 20%	Occupational asthma (latex)	Ref std +	Ref std -	<u>Source of funding:</u> Programme d'appui scientifique à la protection des travailleurs, Services fédéraux des affaires scientifiques, techniques et	
					Question +	15	4		19
					Question -	16	10		26
					Total	31	14		45
					Sensitivity	48%			
Specificity	71%								

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Evaluation of diagnostic procedures. J Allergy Clin Immunol 2001; 107(3): 542-547. VANDENPLAS 2001	<u>Country:</u> Belgium <u>Recruitment:</u> 1993 to 1998	<u>Exclusion criteria:</u> None given		Time between index test and reference standard: same time <u>Target condition</u> Occupational asthma (latex)	PPV NPV	79% 38%	culturelles <u>Limitations:</u> <u>Additional data:</u> Sensitivity and specificity etc calculated

Table 40: Vandenplas 2005¹⁸⁴²

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
What are the questionnaire items most useful in identifying subjects with occupational asthma? European Respirator	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Chest clinic <u>Setting:</u> Symptomatic	N = 212 <u>Inclusion criteria:</u> Prospectively assessed in outpatient clinics of four hospital centres and who underwent objective testing with specific inhalation challenges.	<u>Male: Female</u> 125:87 <u>Mean age:</u> 38.8 (10.7) years	<u>Index test:</u> Asking whether their symptoms are better away from work • CUT-OFF: positive = a) Improvement or disappearance of symptoms at weekends • b) Improvement or disappearance of symptoms during vacations <u>Reference standard</u> Clinical Dx	Occupational asthma – Question a	Ref std +	Ref std	Total	<u>Source of funding:</u> <u>Actions de Recherche Concertées, Communauté Française de Belgique, Belgium.</u>
					Question +	55	64	119	
					Question -	17	76	93	
					Total	72	140	212	
					Sensitivity	76%		<u>Limitations:</u>	
Specificity	54%								

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments	
y Journal. 2005; 26(6):105 6-1063 VANDENP LAS 2005	<u>Country:</u> Belgium, Canada, Italy, Spain <u>Recruitment:</u> not stated	<u>Exclusion criteria:</u> None given		including objective test: specific inhalation challenge; a sustained fall in forced expiratory volume in one second of 20% Time between index test and reference standard: same time <u>Target condition</u> Occupational asthma (flour and cereals, latex, isocyanates, other chemicals, wood dust, laboratory animals, persulfate, resins and glues, various proteins, metals)	PPV NPV Occupational asthma – question b Question + Question - Total Sensitivity Specificity PPV question NPV	41% 80% Ref std + - Ref std - 60 80 140 74% 57% 57% 74%	Total 113 99 212	<u>Additional data:</u> Sensitivity and specificity etc reported; raw data calculated

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2 G.5 Spirometry/flow volume loop measures

3 **Table 41: FORTUNA 2007**⁵¹¹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
Fortuna et al., 2007. Diagnostic utility of inflammatory	<u>Study type:</u> Cross sectional study <u>Setting:</u> Referred to	N = 50 Adults <u>Inclusion criteria:</u> • Referred with a clinical history suggestive of	<u>Male: Female</u> 21:29 <u>Age range:</u> 18-68	<u>Index test</u> Spirometry was performed following international guidelines with a Datospir 120 (Sibelmed, Barcelona, Spain). A FEV1 ≥80% of predicted and/or a ratio of	Ref st + Ref st - Total Index test + Index test -	<u>Source of funding:</u> Not reported <u>Limitations:</u> • RS objective MCT is

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					Total	22	22	44	
biomarkers in asthma: exhaled nitric oxide and induced sputum eosinophil count. Respiratory Medicine: 101: 2416-2421 REF ID: FORTUNA	hospital based outpatient clinic <u>Country:</u> Spain <u>Recruitment:</u> Consecutive	asthma (dry cough, wheezing, and shortness of breath) <u>Exclusion criteria:</u> <ul style="list-style-type: none"> • Conditions that could affect FENO or Eos% measurement for reasons other than asthma: subjects with symptoms of respiratory tract infection in the previous 6 weeks or with systemic manifestations of atopy (rash, digestive 	<u>% of symptomatic patients with positive/abnormal spirometry (FEV1/FVC<75% or FEV1 <80%):</u> 10% <u>Medications:</u> no CS within the last 4 weeks	FEV1/FVC ≥75% were considered to lie within normal limits. Cut-off: Obstruction: FEV1 <80% <u>Comparator test</u> n/a <u>Reference standard</u> Methacholine challenge test (PD20 ≤16mg/ml) following guidelines of the GINA Time between index test and reference standard: 1 day					16mg/ml <ul style="list-style-type: none"> • Unclear why 6 patients not included in analysis of sn/sp • Suggests IT is FEV1<80% and unclear if also includes FEV1/FVC <u>Additional data:</u> 7 of original 57 patients excluded as on CS treatment 6 out of the 50
					Sensitivity	22.7%			
Specificity	100%								
PPV	100%								
NPV	56.4%								
AUC FEV1/FVC	0.64 (95% CI, 0.49–0.77; p<0.008)								
	0.63 (95% CI, 0.48–0.76; p<0.006)								

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
2007		symptoms, etc.) <ul style="list-style-type: none"> Received treatment with inhaled or oral corticosteroids in the last 4 weeks 		<u>Target condition</u> Asthma		patients not included in analysis of sn/sp for spirometry and not mentioned

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Table 42: PINO 1996¹³⁶⁵

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments
Pino et al., 1996.	<u>Study type:</u> Cross-	N = 84 Adults	<u>Male: Female</u> 53:31	<u>Index test</u> Spirometry: Pneumoscreen II	Ref st +	Ref st -	Total	<u>Source of funding:</u>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Value of the peak expiratory flow in bronchodynamic tests. Allergologia et Immunopathologia: 24: 54-57 REF ID: PINO1996	sectional study <u>Setting:</u> University hospital <u>Country:</u> Spain <u>Recruitment:</u> Not stated	<u>Inclusion criteria:</u> <ul style="list-style-type: none"> Clinically suspected of bronchial asthma <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Worsening of symptoms in the preceding 2 months A respiratory infection in the lower or upper tract in the preceding 6 weeks Vaccination with live attenuated virus 6 weeks prior to the test The existence of a recurrent pathology Cases of whistling in observed in pulmonary auscultation were excluded from the bronchial provocation test. 	<u>Mean age:</u> 46.5 (13.7) Medications: Smoking prohibited 2 hours before the study; discontinuation 48 hours in advance of beta-agonists; theophyllines; anticholinergics; antihistamines; nedochromil; chromoglicate.	(Jagger) according to ATS criteria Cut-off: FEV1/FVC<70% and FEV1<80% <u>Comparator test</u> n/a <u>Reference standard</u> If obstructive spirometry: performed BDR (400µg salbutamol; FEV1 >15% initial) If normal spirometry: methacholine challenge test five breaths of 5mg/ml and five breaths of 25mg/ml, test positive if a 20% drop in FEV1 Time between index test and reference standard: <u>Target condition</u>	Index test +	20	24	44	Not reported <u>Limitations:</u> <ul style="list-style-type: none"> Unclear of the directness of the population as few details reported Unclear time between RS and IT Random or consecutive recruitment not reported Patients have different RS objective tests depending on if they were negative or positive to IT Unclear if suitable cut-off used for MCT <u>Additional data:</u>
					Index test -	23	17	40	
					Total	43	41	84	
					Sensitivity		46.5%		
					Specificity		41.5%		
					PPV		45.5%		
					NPV		42.5%		
						Ref std +	Ref std -	Total	
					Index test +				
					Index test -				
Total									

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
					Sensitivity Specificity		
					PPV NPV		

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Table 43: POPOVIC 2012¹³⁸¹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Popovic-Grle et al., 2002. Clinical validation of bronchial hyperresponsiveness, allergy tests and lung	<u>Study type:</u> Cross-sectional study <u>Setting:</u> Outpatient department, University Hospital <u>Country:</u> Croatia	N = 195 Adults <u>Inclusion criteria:</u> • Referred by GP with suspected asthma and symptoms of breathlessness / dyspnoea. <u>Exclusion criteria:</u> • Serious diseases of	<u>Male, %</u> 51% of those given an asthma Dx <u>Mean age:</u> 36.5 (6.2) in those given an asthma Dx (n=141)	<u>Index test</u> Spirometry: measured at least 3 times by forced expiration on Vitalograph apparatus with a pneumotachograph. Best attempt recorded. Cut-off: FEV1 <80% predicted <u>Comparator test</u> n/a		Ref st +	Ref st -	Total	<u>Source of funding:</u> Not reported <u>Limitations:</u> • Details of reference standard objective test not given • Unclear if RS results
					Index test +	63	37	100	
					Index test -	78	17	95	
					Total	141	54	195	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
function in the diagnosis of asthma in persons with dyspnoea. Collegium Antropologicum: 26 Suppl: 119-127 REF ID: POPOVIC 2002	<u>Recruitment:</u> Random	other organ systems or the lungs (apart from those of an obstructive and/or allergic nature)	Medications: Not reported	<u>Reference standard</u> Dx made on the basis of questionnaire, with typical medical history data of occasional asthma attacks with wheezing and nocturnal awakening because of dyspnoea, and reversible bronchial obstruction after salbutamol test (no further details stated) Time between index test and reference standard: same time <u>Target condition</u> Asthma	Sensitivity Specificity PPV NPV	44.7% 31.5%	interpreted without knowledge of the IT results • Unclear if IT results interpreted without knowledge of the RS results (but objective) <u>Additional data:</u>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments

Table 44: SCHNEIDER 2009A¹⁵³⁵

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments	
Schneider A et al. 2009. Diagnostic accuracy of spirometry in primary care. BMC Pulmonary Medicine: 9: 31. REF ID: SCHNEIDER2009A	<u>Study type:</u> Cross-sectional study <u>Setting:</u> Index test in primary care, 14 GPs in 10 practices <u>Country:</u> Germany <u>Recruitment:</u> Consecutive recruitment	N = 219 Adults <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Visiting GP for the first time with complaints of obstructive airway disease (OAD). Symptoms such as dyspnoea, coughing, or expectoration <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Previous Dx for OAD Previous anti-obstructive medicine Contraindications 	<u>Male: Female</u> 92:127 <u>Mean (SD) age:</u> 43.8 (15.6) <u>% of symptomatic patients with positive/abnormal spirometry:</u> 35.6% <u>Medications:</u> None prior to spirometry at GP. If necessary, therapy initiated by GP for asthma or	<u>Index test: Spirometry at GP</u> Electronic spirometer (Medikro Spirostar USB). Best of 3 consecutive spirometric values used in accordance with European Respiratory Society (ERS). Max inspiratory and expiratory flow volume curves generated by forced deep inspiration and expiration with intervening periods of tidal breathing. Cut-off: OAD if FEV1/VC ≤70% and/or FEV1 <80% <u>Comparator test</u> None <u>Reference standard</u> LUNG FUNCTION LAB: Dx by		Ref st +	Ref st -	Total	<u>Source of funding:</u> Federal ministry of education and research (BMBF), Germany. <u>Limitations:</u> <ul style="list-style-type: none"> Spirometry performed with full adherence to ERS guidelines in 39.8% of cases and moderate adherence in 38% of cases. ERS criteria
					Index test +	26	52	78	
					Index test -	63	75	138	
					Total	89	127	216	
					Sensitivity	29.2%			
					Specificity	59.1%			
PPV	33.3%								
NPV	54.3%								

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
		for BDR of challenge testing (untreated hyperthyreosis, unstable coronary artery disease, cardiac arrhythmia) <ul style="list-style-type: none"> • Pregnancy 	COPD but stopped 12 hours prior to lung function lab.	pneumologist based on whole-body plethysmography (FEV1/VC $\leq 70\%$ or FEV1 $< 80\%$) followed by either BDR if obstruction is present (FEV1 $\geq 12\%$ and $\geq 200\text{ml}$) or methacholine if obstruction is not present (PC20 $\leq 16\text{mg/ml}$ or extreme increase in airway resistance accompanied by clinical symptoms in two patients)		not fulfilled in 22.2% of cases. <ul style="list-style-type: none"> • Unclear time between IT and RS; 74 patients from original 293 only wanted the IT and did not have RS • RS objective MCT is 16mg/ml Additional data: 3 lost to follow-up
				Time between index test and reference standard: unclear		
				<u>Target condition</u> OAD: Asthma or COPD		Gives sn/sp of spirometry for asthma and COPD separately (data combined here to include all patients presenting with respiratory symptoms regardless of their final Dx)

Table 45: SIVAN 2009¹⁶¹⁹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments	
					Ref st +	Ref st -	Total			
Sivan et al., 2009. The use of exhaled nitric oxide in the diagnosis of asthma in school children. Journal of Pediatric s: 155: 211-216 REF ID: SIVAN2009	<u>Study type:</u> Cross-sectional study <u>Setting:</u> Outpatient paediatric pulmonary clinic, Children’s Hospital <u>Country:</u> Israel <u>Recruitment:</u> Consecutive	N = 150 (113 excluding those on ICS from analysis) Children <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Non-specific respiratory symptoms suggestive of asthma for at least 3 months, including cough, wheezing and shortness of breath with or without trials of treatment with bronchodilators and ICS. Follow-up for at least 1 year <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Symptoms of unresolved respiratory tract infection Systemic clinical manifestations of atopy such as anaphylaxis, angioedema, food allergy, urticarial, systemic or inflammatory disease 	<u>Male: Female</u> ~56% male <u>Age range:</u> 5-18yrs (mean 12) Medications: Withheld bronchodilators for 24 hours. Unclear if on medications for 18 months between IT and RS.	<u>Index test</u> Spirometry: hand-held spirometer (Micro-lab ML3500/S, Micro-Medical, UK). Cut-off: FEV1 <80% <u>Reference standard</u> Made by paediatric pulmonologist after 18 months follow-up. Based on history of 2 or more clinical exacerbations of wheezing documented by a physician; dyspnoea or cough relived by bronchodilators; documented variability in FEV1 ≥15% in response to bronchodilators at any time during the follow-up period; OR documented variability in FEV1 ≥15% over time with or without controller medications (ICS or montelukast). Results of provocation tests included when available. Time between index test and reference standard: 18 months		Ref st +	Ref st -	Total	<u>Source of funding:</u> Not reported <u>Limitations:</u> <ul style="list-style-type: none"> Recruited 150 patients but excluded 37 on ICS from analysis Time between IT and RS = 18 months Unclear if all had objective test with RS Interpretation of RS not done blinded to results of spirometry IT <u>Additional data:</u>	
					Index test +	36	12	48		
					Index test -	33	32	65		
					Total	69	44	113		
					Sensitivity		52%			
					Specificity		72%			
					PPV		75%			
					NPV		48%			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
				<u>Target condition</u> Asthma		

Table 46: SMITH 2004¹⁶³⁰

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments			
Smith et al., 2004. Clinical usefulness of fractional exhaled nitric	<u>Study type:</u> Cross-sectional study <u>Setting:</u> Referred to hospital pulmonary	N = 47 Adults and children (8-75 years) <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Referred to hospital pulmonary function lab by GP for possible asthma 	<u>Male: Female</u> <u>Mean age:</u> Medications:	<u>Index test</u> Spirometry Cut-off: FEV1 <90% predicted FEV1 <80% predicted FEV1/FVC <80%	FEV1/FVC <70%	Ref st + Ref st - Total	<u>Source of funding:</u> Supported by Otago Medical Research Foundation and the Otago respiratory		
					Index test +	6		0	6
					Index test -	11		30	41
					Total	17		30	47

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
oxide for diagnosis of prolonged cough. Respiratory Medicine: 102: 1452-1459. REF ID: SMITH2004	function lab <u>Country:</u> New Zealand <u>Recruitment:</u> Consecutive	<ul style="list-style-type: none"> Respiratory symptoms for a minimum of 6 weeks <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Used ICS in the preceding 4 weeks Typical respiratory tract infection in the preceding 6 weeks 	Short-acting beta-agonists and anticholinergic inhalers permitted during the study period but withheld for a minimum of 6 hours before the study visit.	FEV1/FVC <70% <u>Comparator test</u> n/a <u>Reference standard</u> Relevant symptom history (all patients) and a positive hypertonic saline challenge test (PD15<20ml) or BDR increase in FEV1 ≥12%	Sensitivity 35.3% Specificity 100% PPV 100% NPV 73.2% AUC FEV1/FVC 0.678				research trust. GSK personal education grant to one author. <u>Limitations:</u> <ul style="list-style-type: none"> <u>Additional data:</u> 4 of the original 51 patients withdrew after first study visit due to time commitments.
				Time between index test and reference standard: 2 weeks	Sensitivity 47.1% Specificity 80.0% PPV 57.1% NPV 72.7%				
				<u>Target condition</u> Asthma					

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					AUC FEV1%pred		0.804		
					FEV1 <90% pred	Ref st +	Ref st -	Total	
					Index test +	6	2	8	
					Index test -	11	28	39	
					Total	17	30	47	
					Sensitivity		35.3%		
					Specificity		93.3%		
					PPV		75%%		
					NPV		71.8%		

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2 G.6 Bronchodilator reversibility

3 Table 47: BRAND 1992²¹¹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
Brand PLP et al. Interpretation of bronchodilator response	<u>Study type:</u> Diagnostic cross-sectional study	N = 150 <u>Inclusion criteria:</u> • Adults with chronic respiratory symptoms (asthma)	<u>Male: Female</u> Not stated <u>Mean age:</u> 18-60 years; mean not stated	<u>Index test</u> Bronchodilator reversibility: Response to inhaled terbutaline 1000µg a) change [Δ]FEV1 % init; b) ΔFEV1[l] i.e. absolute value in litres; c) ΔFEV1 % init and ΔFEV1[l]; d) ΔFEV1 %pred; e) standardised residual [SR]-FEV1;	Asthma	Ref std +	Ref std -	Total	<u>Source of funding:</u> Not stated <u>Limitations:</u> Some
					Bronchodilator reversibility	68	24	92	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
in patients with obstructive airways disease. Thorax 1992; 47: 429-436. BRAND19 92	<p><u>Data source:</u> University hospital outpatients departments</p> <p><u>Setting:</u> Secondary care</p> <p><u>Country:</u> The Netherlands</p> <p><u>Recruitment:</u> Not stated.</p>	or COPD) in university hospital outpatients departments; baseline FEV1 >1.2 litres and 1.64-4.5 residual standard deviations below predicted value, or FEV1/inspiratory vital capacity ratio >1.64 RSD below predicted; hyperresponsive to inhaled histamine	Tx was withdrawn for 14days and BD Tx for 12 days.	<p>f) FEV1 post-bronchodilator [pb] %pred</p> <p>CUT-OFF: positive = a) ΔFEV1 % init >15%; b) ΔFEV1[I] > 0.200; c) ΔFEV1 % init >15% and ΔFEV1[I] > 0.200; d) ΔFEV1 %pred >9%; e) SR-FEV1 > 0.5; f) FEV1 pb %pred >80%</p> <p><u>Reference standard</u>Clinical Dx Standardised history using criteria of American Thoracic Society: asthma = attacks of breathlessness and wheeze (asthma attacks) without chronic (>3 months/year) cough or sputum production; COPD = Current or former smokers without a history of asthma attacks reporting either chronic cough +/- sputum production, or dyspnoea when walking quietly on level ground, or both</p> <p>Plus hyper-responsiveness to inhaled histamine</p> <p>Time between index test and reference standard: same time</p> <p><u>Target condition</u> Asthma</p>	(a) +			<p>exclusions may limit generalisability</p> <p><u>Additional data:</u> Raw data not stated; calculated from sensitivity and specificity</p>	
					Bronchodilator reversibility (a) -	31	27		58
					Total	99	51		150
					Sensitivity (a)		68.7%		
					Specificity (a)		52.9%		
					Likelihood ratio (a)		1.459		
					Asthma	Ref std +	Ref std -		Total
					Br. rev. (b) +	87	33		120
					Br. rev. (b) -	12	18		30
					Total	99	51		150
					Sensitivity (b)		87.9%		
					Specificity (b)		35.3%		
					Likelihood ratio (b)		1.359		
					Asthma	Ref std +	Ref std -		Total
Br. rev. (c) +	68	23	91						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
					Br. rev. (c) -	31	28	59	
					Total	99	51	150	
					Sensitivity (c)		68.7%		
					Specificity (c)		54.9%		
					Likelihood ratio (c)		1.523		
					Asthm a	Ref std +	Ref std -	Total	
					Br. rev. (d) +	73	22	95	
					Br. rev. (d) -	26	29	55	
					Total	99	51	150	
					Sensitivity (d)		73.7%		
					Specificity (d)		56.9%		
					Likelihood ratio (d)		1.710		
					Asthm a	Ref std +	Ref std -	Total	
					Br. rev. (e) +	80	28	108	
					Br. rev. (e) -	19	23	42	
					Total	99	51	150	
					Sensitivity(e)		80.8%		
					Specificity (e)		45.1%		
					Likelihood ratio (e)		1.472		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Asthm a	Ref std +	Ref std -	Total	
					Br. rev. (f) +	45	16	61	
					Br. rev. (f) -	54	35	89	
					Total	99	51	150	
					Sensitivity (f)	45.5%			
					Specificity (f)	68.6%			
					Likelihood ratio (f)	1.449			

Table 48: CHHABRA 2005³¹³

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Asthm a	Ref std +	Ref std -	Total	
Chhabra SK. Acute bronchodilator response has limited value in differentiating bronchial asthma from COPD. J Asthma 2005; 42:	<u>Study type:</u> Diagnostic cross-sectional study <u>Data source:</u> Outpatient clinic <u>Setting:</u> Secondary care <u>Country:</u>	N = 354 <u>Inclusion criteria:</u> • Clinical diagnosis of asthma (non-smokers) or COPD; stable clinical state with no history of acute exacerbation in previous 4 weeks; acceptable performance of spirometry; FEV1/FVC ratio 70% or less	<u>Male: Female</u> Asthma: 122:78; COPD: 149:5 <u>Mean age:</u> Asthma mean 35.60 (12.47); COPD mean 56.28 (9.57) years Participants were already on (and remained on)	<u>Index test:</u> Bronchodilator reversibility: Response to inhaled salbutamol 200µg: a) absolute change in FEV1 (ΔFEV1); b) ΔFEV1%init; c) ΔFEV1%pred; d) ΔFEV1≥0.2l and ΔFEV1%init ≥12% <u>CUT-OFF:</u> positive = a) absolute change in FEV1 (ΔFEV1) a1: 0.2l; a2: 0.3l; a3: 0.4l; b) ΔFEV1%init b1: 12%; b2: 15%; b3: 20%; c) ΔFEV1%pred c1: 9%; c2: 15%; d) ΔFEV1≥0.2l and ΔFEV1%init ≥12% <u>Reference standard:</u> Clinical Dx	Asthm a Bronchodilator reversibility (a1) + Bronchodilator reversibility (a1) - Total	Ref std + 146 54 200	Ref std - 31 123 154	Total 177 177 354	<u>Source of funding:</u> Not stated <u>Limitations:</u> Time between index test and reference standard: unclear. Some exclusions may limit generalisability <u>Additional data:</u>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments																																
367-372. CHHABRA 2005	India <u>Recruitment:</u> Not stated.	<u>Exclusion criteria:</u> Smokers with asthma; any other concurrent pulmonary or systemic disease	corticosteroid treatment. BD Tx was withdrawn for 12 hrs.	Physician diagnosis based on clinical criteria suggested by the National Institute of Health Global Strategy for Asthma Management and Prevention (asthma = recurrent episodes of breathlessness and wheezing, with or without cough and phlegm, with seasonal and diurnal variations and any identifiable trigger factors) and the Global Initiative for Chronic Obstructive Lung Disease (COPD = history of smoking >10 pack-years, cough with expectoration for at least 3 consecutive months in a year for 2 years or more and progressive dyspnoea on exertion). Time between index test and reference standard: unclear <u>Target condition</u> Asthma	Sensitivity (a1) Specificity (a1) PPV (a1) NPV (a1) Likelihood ratio (a1) <table border="1"> <tr> <td>Asthm a</td> <td>Ref std +</td> <td>Ref std -</td> <td>Total</td> </tr> <tr> <td>Br. rev. (a2) +</td> <td>106</td> <td>20</td> <td>126</td> </tr> <tr> <td>Br. rev. (a2) -</td> <td>94</td> <td>134</td> <td>228</td> </tr> <tr> <td>Total</td> <td>200</td> <td>154</td> <td>354</td> </tr> </table> Sensitivity(a2) Specificity (a2) PPV (a2) NPV (a2) Likelihood ratio (a2) <table border="1"> <tr> <td>Asthm a</td> <td>Ref std +</td> <td>Ref std -</td> <td>Total</td> </tr> <tr> <td>Br. rev. (a3) +</td> <td>68</td> <td>8</td> <td>76</td> </tr> <tr> <td>Br. rev. (a3) -</td> <td>132</td> <td>146</td> <td>278</td> </tr> <tr> <td>Total</td> <td>200</td> <td>154</td> <td>354</td> </tr> </table> Sensitivity (a3) Specificity (a3)	Asthm a	Ref std +	Ref std -	Total	Br. rev. (a2) +	106	20	126	Br. rev. (a2) -	94	134	228	Total	200	154	354	Asthm a	Ref std +	Ref std -	Total	Br. rev. (a3) +	68	8	76	Br. rev. (a3) -	132	146	278	Total	200	154	354	73% 80% 82% 69% 3.60	Raw data not stated; calculated from sensitivity and specificity
Asthm a	Ref std +	Ref std -	Total																																				
Br. rev. (a2) +	106	20	126																																				
Br. rev. (a2) -	94	134	228																																				
Total	200	154	354																																				
Asthm a	Ref std +	Ref std -	Total																																				
Br. rev. (a3) +	68	8	76																																				
Br. rev. (a3) -	132	146	278																																				
Total	200	154	354																																				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
					PPV (a3) NPV (a3) Likelihood ratio (a3)	91% 53% 7.37	
					Asthm a	Ref std + Ref std - Total	
					Br. rev. (b1) +	150 62 212	
					Br. rev. (b1) -	50 92 142	
					Total	200 154 354	
					Sensitivity (b1) Specificity (b1)	75% 60%	
					PPV (b1) NPV (b1) Likelihood ratio (b1)	71% 65% 1.88	
					Asthm a	Ref std + Ref std - Total	
					Br. rev. (b2) +	132 48 170	
					Br. rev. (b2) -	68 106 174	
					Total	200 154 354	
					Sensitivity (b2) Specificity (b2)	66% 69%	
					PPV (b2) NPV (b2) Likelihood ratio	73% 61% 2.12	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
					(b2)		
					Asthm a	Ref std + Ref std -	Total
					Br. rev. (b3) +	106 34	140
					Br. rev. (b3) -	94 120	214
					Total	200 154	354
					Sensitivity (b3)	53%	
					Specificity (b3)	78%	
					PPV (b3)	76%	
					NPV (b3)	56%	
					Likelihood ratio (b3)	2.42	
					Asthm a	Ref std + Ref std -	Total
					Br. rev. (c1) +	126 25	151
					Br. rev. (c1) -	74 129	203
					Total	200 154	354
					Sensitivity (c1)	63%	
					Specificity (c1)	84%	
					PPV (c1)	84%	
					NPV (c1)	64%	
					Likelihood ratio (c1)	4.03	
					Asthm a	Ref std + Ref std -	Total

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
					Br. rev. (c2) +	76	8	84	
					Br. rev. (c2) -	124	146	270	
					Total	200	154	354	
					Sensitivity (c2)	38%			
					Specificity (c2)	95%			
					PPV (c2)	92%			
					NPV (c2)	54%			
					Likelihood ratio (c2)	8.36			
					Asthma	Ref std +	Ref std -	Total	
					Br. rev. (d) +	130	29	159	
					Br. rev. (d) -	70	125	195	
					Total	200	154	354	
					Sensitivity (d)	65%			
					Specificity (d)	81%			
					PPV (d)	81%			
					NPV (d)	64%			
					Likelihood ratio (d)	3.34			

1 **Table 49: KIM 2012⁸⁷⁰**

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
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Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Asthma	Ref std +	Ref std -	Total	
Kim T-B et al. The reality of an intermediate type between asthma and COPD in practice. Respir Care 2012; 57: 1248-1253. KIM2012	<u>Study type:</u> Diagnostic cross-sectional study <u>Data source:</u> Disease cohorts <u>Setting:</u> Secondary care <u>Country:</u> Republic of Korea <u>Recruitment:</u> Not stated	N = 514 <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Adults with chronic obstructive airways disorders included in an asthma cohort or a COPD cohort; all had at least one chronic persistent respiratory symptom (dyspnoea, cough, sputum production or wheeze) for >3 months or repetition of the symptom for >3 months <u>Exclusion criteria:</u> Patients with tuberculous destroyed lungs, bronchiectasis or lung resection	<u>Male: Female</u> 49% male in asthma group and 91.7% in COPD group <u>Mean age:</u> 48 (16) years for asthma and 65 (8) years for COPD	<u>Index test:</u> Bronchodilator reversibility: Bronchodilator response to albuterol 400µg CUT-OFF: positive = Increase in FEV1 >200mL and >12% above baseline <u>Reference standard:</u> Clinical Dx Clinical decision (no definite diagnostic criteria) by specialists in allergy or pulmonary departments Time between index test and reference standard: same time <u>Target condition:</u> Asthma	Asthma	Ref std +	Ref std -	Total	<u>Source of funding:</u> Korea Healthcare Technology Research and Development Project, Ministry of Health and Welfare, Republic of Korea <u>Limitations:</u> No definite diagnostic criteria used; unclear if index test could be part of diagnostic criteria. Some exclusions may limit generalisability <u>Additional data:</u> None
					Bronchodilator reversibility +	62	56	118	
					Bronchodilator reversibility -	307	89	396	
					Total	369	145	514	
					Sensitivity	16.8%			
					Specificity	61.4%			
PPV	52%								
NPV	22%								

Table 50: QUADRELLI 1999¹⁴¹⁷

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Asthm a	Ref std +	Ref std -	Total	
Quadrelli SA et al. Evaluation of bronchodilator response in patients with airway obstruction. Respir Med 1999; 93: 630-636. QUADRELLI 1999	<u>Study type:</u> Diagnostic cross-sectional study <u>Data source:</u> University hospital <u>Setting:</u> Secondary care <u>Country:</u> Argentina <u>Recruitment:</u> Not stated	N = 119 (subset of 61 patients with asthma with FEV1<55% from overall sample 142 asthma patients, plus all 58 patients with COPD) <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Patients with previously diagnosed airways obstruction; present baseline spirometry: FEV1/FVC relationship 1.64 SEE below predicted value or lower; people with asthma had FEV1 <55% predicted (to match with COPD patients' baseline lung function) <u>Exclusion criteria:</u>	<u>Male: Female</u> Overall: asthma 74:68; COPD 46:12 <u>Mean age:</u> Overall asthma: 55.4 (19.0) years; COPD 67.3 (7.0) years	<ul style="list-style-type: none"> <u>Index test</u> Bronchodilator reversibility: Response to inhaled salbutamol 200µg a) ΔFEV1[L]; b) ΔFEV1%init; c) ΔFEV1[L] plus ΔFEV1%init; d) ΔFEV1%pred; e) ΔFEV1%max (% of maximal possible response) CUT-OFF: positive = a) ΔFEV1[L]: 200mL; b) ΔFEV1%init: 15%; c) ΔFEV1[L] >200mL plus ΔFEV1%init >15% ; d) ΔFEV1%pred: 9%; e) ΔFEV1%max (% of maximal possible response): 50% Positive and negative predictive values calculated for two arbitrary prevalences of asthma A] prevalence of asthma 30% and B] prevalence of asthma 70% <u>Reference standard</u> Clinical Dx Clinical diagnosis: asthma = attacks of breathlessness or wheeze according to ATS criteria (smokers excluded) and at least 2 of: 1;	Asthm a	Ref std +	Ref std -	Total	<u>Source of funding:</u> Not stated <u>Limitations:</u> Time between index test and reference standard: unclear. Some exclusions may limit generalisability <u>Additional data:</u> Raw data not stated; calculated from sensitivity and specificity
					Br. rev. (a) +	43	17	60	
					Br. rev. (a) -	18	41	59	
					Total	61	58	119	
					Sensitivity (a)		70.4%		
					Specificity(a)		70.6%		
					PPV(a) [A]		50.5%		
					[B]		84.8%		
					NPV (a) [A]		84.7%		
					[B]		50.6%		
					Asthm a	Ref std +	Ref std -	Total	
					Br. rev. (b) +	52	29	81	
Br. rev. (b) -	9	29	38						
Total	61	58	119						
Sensitivity (b)		85.2%							
Specificity(b)		50.0%							
PPV(b) [A]		39.4%							

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments																																
		Those mentioned in inclusion and reference standard sections, plus patients not clearly classified as either asthma or COPD, or those under current treatment with systemic steroids		<p>history of symptoms since childhood or adolescence; 2. symptomatic-free periods of >3 months; 3. spontaneous variations in FEV1 during the year of >20% of baseline value; 4. histamine challenge test <8mg/mL. COPD = heavy current or ex-smokers with no history of asthma reporting chronic cough or sputum (non-smokers excluded)</p> <p>Time between index test and reference standard: unclear</p> <p><u>Target condition</u> Asthma</p>	<p>[B] NPV (b) [A] [B]</p> <table border="1"> <thead> <tr> <th>Asthm a</th> <th>Ref std +</th> <th>Ref std -</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>Br. rev. (c) +</td> <td>42</td> <td>17</td> <td>59</td> </tr> <tr> <td>Br. rev. (c) -</td> <td>19</td> <td>41</td> <td>60</td> </tr> <tr> <td>Total</td> <td>61</td> <td>58</td> <td>119</td> </tr> </tbody> </table> <p>Sensitivity (c) Specificity(c)</p> <p>PPV(c) [A] [B] NPV(c) [A] [B]</p> <table border="1"> <thead> <tr> <th>Asthm a</th> <th>Ref std +</th> <th>Ref std -</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>Br. rev. (d) +</td> <td>41</td> <td>17</td> <td>58</td> </tr> <tr> <td>Br. rev. (d) -</td> <td>20</td> <td>41</td> <td>61</td> </tr> <tr> <td>Total</td> <td>61</td> <td>58</td> <td>119</td> </tr> </tbody> </table> <p>Sensitivity (d) Specificity(d)</p> <p>PPV(d) [A] [B] NPV (d) [A]</p>	Asthm a	Ref std +	Ref std -	Total	Br. rev. (c) +	42	17	59	Br. rev. (c) -	19	41	60	Total	61	58	119	Asthm a	Ref std +	Ref std -	Total	Br. rev. (d) +	41	17	58	Br. rev. (d) -	20	41	61	Total	61	58	119	<p>78.0% 82.9% 47.3%</p> <p>68.8% 70.6%</p> <p>48.1% 83.5% 81.9% 45.5%</p> <p>67.2% 70.6%</p> <p>49.2% 84.1% 83.1%</p>	
Asthm a	Ref std +	Ref std -	Total																																				
Br. rev. (c) +	42	17	59																																				
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Asthm a	Ref std +	Ref std -	Total																																				
Br. rev. (d) +	41	17	58																																				
Br. rev. (d) -	20	41	61																																				
Total	61	58	119																																				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments	
					[B]	47.5%		
					Asthma	Ref std +	Ref std -	Total
					Br. rev. (e) +	4	1	5
					Br. rev. (e) -	57	57	114
					Total	61	58	119
					Sensitivity (e)	6.5%		
					Specificity(e)	98.2%		
					PPV(e) [A]	75.5%		
					[B]	94.5%		
					NPV (e) [A]	72.3%		
					[B]	32.4%		

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2

3 G.7 PEF variability

4 **Table 51: BROUWER 2010^{232,233}**

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
Brouwer AFJ, Visser CAN, Duiverman EJ,	<u>Study type</u> :DiagnosticCross-sectional study	N = 61 <u>Inclusion criteria</u> : Children with non-specific respiratory	<u>Male: Female</u> 27:34 <u>Mean age</u> : 6 to 16 years;	<u>Index test</u> PEF variation amp%mean CUT-OFF : positive = >95 th centile for healthy children i.e. ≥12.3%	Asthma	Ref std +	Ref std -	Total	<u>Source of funding</u> : AstraZeneca NL <u>Limitations</u> :
					PEF +	10	11	21	
					PEF -	10	28	38	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments																								
Roorda RJ, and Brand PLP. Is home spirometry useful in diagnosing asthma in children with nonspecific respiratory symptoms? Pediatric Pulmonology 2010; 45: 326-332 REF ID: BROUWER2010.	<p><u>Data source:</u> Paediatric asthma clinic</p> <p><u>Setting:</u> Secondary care</p> <p><u>Country:</u> The Netherlands</p> <p><u>Recruitment:</u> Not stated.</p>	<p>symptoms such as cough and breathlessness in whom GP uncertain of diagnosis referred to hospital-based paediatric asthma clinic</p> <p><u>Exclusion criteria:</u> Straightforward diagnosis of asthma based on classical respiratory symptoms; referred for poorly controlled asthma; systemic corticosteroids or long-acting beta-2 agonists in last 4 weeks</p>	<p>mean 10.4 years</p>	<p><u>Reference standard</u> Clinical Dx including objective test: Asthma diagnosed by paediatric pulmonologist including history, physical examination and lung function tests including methacholine challenge</p> <p>Time between index test and reference standard: same time</p> <p><u>Target condition</u> Asthma</p>	<table border="1"> <tr> <td>Total</td> <td>20</td> <td>39</td> <td>59</td> </tr> <tr> <td>Sensitivity</td> <td></td> <td>50%</td> <td></td> </tr> <tr> <td>Specificity</td> <td></td> <td>72%</td> <td></td> </tr> <tr> <td>PPV</td> <td></td> <td>48%</td> <td></td> </tr> <tr> <td>NPV</td> <td></td> <td>74%</td> <td></td> </tr> <tr> <td>Likelihood ratio</td> <td></td> <td>1.77</td> <td></td> </tr> </table>	Total	20	39	59	Sensitivity		50%		Specificity		72%		PPV		48%		NPV		74%		Likelihood ratio		1.77			<p>Home spirometry data lost for 2 patients due to battery failure of the device</p> <p><u>Additional data:</u> <u>None</u></p>
Total	20	39	59																												
Sensitivity		50%																													
Specificity		72%																													
PPV		48%																													
NPV		74%																													
Likelihood ratio		1.77																													

1

Table 52: DEN OTTER 1997⁴²²

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments								
den Otter JJ, Reijnen GM, van den Bosch	<p><u>Study type:</u> Diagnostic Cross-sectional</p>	<p>N = 323</p> <p><u>Inclusion criteria:</u> adults between 25</p>	<p><u>Male: Female</u> 135:188</p> <p><u>Mean age:</u></p>	<p><u>Index test</u> PEF variability = $(PEF_{highest} - PEF_{lowest}) / PEF_{mean} \times 100\%$ (mean over 21 days' readings)</p>	<table border="1"> <tr> <td>Asthma</td> <td>Ref std +</td> <td>Ref std -</td> <td>Total</td> </tr> <tr> <td>PEF var >15%</td> <td>6</td> <td>4</td> <td>10</td> </tr> </table>	Asthma	Ref std +	Ref std -	Total	PEF var >15%	6	4	10		<p><u>Source of funding:</u> Not stated.</p>
Asthma	Ref std +	Ref std -	Total												
PEF var >15%	6	4	10												

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes		Comments	
WJ, van Schayck CP, Molema J, Van Weel C. Testing bronchial hyper-responsiveness: provocation or peak expiratory flow variability? British Journal of General Practice. 1997; 47(421):487-492 DENOTTE R1997	study <u>Data source:</u> Population screening <u>Setting:</u> General population <u>Country:</u> The Netherlands <u>Recruitment:</u> Not stated.	and 70 years old with signs or symptoms indicating asthma (persistent or recurrent respiratory symptoms or signs of reversible bronchial obstruction) <u>Exclusion criteria:</u> None given	43 (12) years	CUT-OFF: positive = >5% or 10% or 15% <u>Reference standard</u> Clinical Dx including objective test: Reference standard = BHR, defined as a PC20 histamine of ≤8 mg/ml Time between index test and reference standard: unclear <u>Target condition</u> Asthma	PEF var ≤15%	124	184	308	<u>Limitations:</u> None <u>Additional data:</u> None
					Total	130	188	318	
					Sensitivity		5%		
					Specificity		97%		
					PPV		60%		
					NPV		60%		
					PLR and NLR				
						Ref std +	Ref std -	Total	
					PEF var >10%	18	8	26	
					PEF var ≤10%	112	180	292	
					Total	130	188	318	
					Sensitivity		14%		
					Specificity		96%		
					PPV		69%		
					NPV		62%		
PLR and NL									
	Ref std +	Ref std -	Total						
PEF var >5%	73	58	131						
PEF var ≤5%	57	130	187						
Total	130	188	318						
Sensitivity		56%							

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
					Specificity	69%	
					PPV	56%	
					NPV	66%	
					PLR and NL		

Table 53: THIADENS 1998^{1746,1746}

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
Thiadens HA, De Bock GH, Dekker FW, Huysman JA, Van Houwelingen JC, Springer MP et al. Value of measuring diurnal peak flow variability in the recognition of asthma: a study in general practice.	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Community <u>Setting:</u> Primary care <u>Country:</u> The Netherlands <u>Recruitment:</u> January 1994 – March 1995	N = 170 <u>Inclusion criteria:</u> 18–75 yrs of age, who consulted their GP with coughing that had lasted for at least 2 weeks <u>Exclusion criteria:</u> Already had a diagnosis of asthma or COPD, pregnant, or had a cardiovascular or concomitant pulmonary disease	<u>Male:</u> Female 61: 109 <u>Mean age:</u> 44 (16) years	<u>Index test:</u> PEF variability (DPV) = $(PEF_{highest} - PEF_{lowest}) / PEF_{highest} \times 100\%$ = amplitude % highest (a) MDPV = mean over 2 week period (b) DPV more than threshold on 4 days or more (c) DPV more than threshold on 3 days or more <u>CUT-OFF:</u> (a) MDPV > 10% and MDPV >15% (b) DPV >15% on 4 days or more (c) DPV >20% on 3 days or more <u>Reference standard</u> Clinical Dx including objective test: A patient was considered to have asthma if there had been a		Ref std +	Ref std –	Total	<u>Source of funding:</u> GlaxoWellcome BV, Medical Division, The Netherlands. <u>Limitations:</u> Sensitivity etc calculated <u>Additional data:</u> None
					MDPV (a) >10% +	10	3	13	
					MDPV -	59	98	157	
					Total	69	101	170	
					Sensitivity		14.5%		
					Specificity		97.0%		
					PPV		76.9%		
					NPV		62.4%		
					PLR and NL				
						Ref std +	Ref std –	Total	
MDPV (a) 15% +	2	1	3						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
European Respiratory Journal. 1998; 12(4):842-847 THIADENS 1998				previous period of respiratory symptoms for >3 weeks in the last year, accompanied by a provocative dose causing a 20% fall in FEV1 (PD20) ≤15.6 μmol methacholine and/or reversibility ≥9% of predicted Time between index test and reference standard: same time <u>Target condition</u> Asthma	MDPV -	67	100	167	
					Total	69	101	170	
					Sensitivity		2.9%		
					Specificity		99.0%		
					PPV		66.7%		
					NPV		59.9%		
					PLR and NL				
						Ref std +	Ref std -	Total	
					DPV(b) >15% ≥4 days +	14	3	17	
					PEF -	55	98	153	
					Total	69	101	170	
					Sensitivity		20.3%		
					Specificity		97.0%		
PPV		82.4%							
NPV		64.1%							
PLR and NL									
	Ref std +	Ref std -	Total						
DPV (c)	8	1	9						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments	
					>20% on ≥3 days +			
					PEF -	61	100	161
					Total	69	101	170
					Sensitivity	11.6%		
					Specificity	99.0%		
					PPV	88.9%		
					NPV	62.1%		
					PLR and NL			

Table 54: ULRİK 2005^{1809,1810}

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
Ulrik CS, Postma DS, Backer V. Recognition of asthma in adolescents and young adults: which objective measure is best? Journal of	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Community survey <u>Setting:</u> Community <u>Country:</u>	N = 74 people with asthma out of sample of 609 adolescents and young adults in survey <u>Inclusion criteria:</u> Children and adolescents born between 1969 and 1979 in central Copenhagen <u>Exclusion criteria:</u> None given	<u>Male: Female</u> 37:37 <u>Mean age:</u> 18.5 (2.8) years	<u>Index test</u> PEF variability (amp%mean) CUT-OFF: positive = PEF amp%mean ≥20% <u>Reference standard</u> Clinical Dx including objective test: 1) Histamine challenge test; cut off PC20 <16.0mg/mL histamine (airways hyper-responsiveness) 2) Bronchodilator reversibility: change in FEV1 (ΔFEV1%post) >10%	Asthma	Ref std (1) +	Ref std (1) –	Total	<u>Source of funding:</u> Danish Lung Association <u>Limitations:</u> Asthma patients only <u>Additional data:</u> <u>None</u>
					PEF +	32	1	33	
					PEF -	37	4	41	
					Total	69	5	74	
					Sensitivity	46.4%			
					Specificity	80.0%			
					PPV	97.0%			
					NPV	9.8%			
					PLR and NLR				
AUC									

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
Asthma. 2005; 42(7):549-554 ULRIK2005	Denmark <u>Recruitment:</u> 1992.			Time between index test and reference standard: same time <u>Target condition</u> Asthma	Diagnostic yield				
						Ref std (2) +	Ref std (2) –		Total
					PEF +	5	28		33
					PEF -	2	39		41
					Total	7	67		74
					Sensitivity		71.4%		
					Specificity		58.2%		
					PPV		15.2%		
					NPV		95.1%		
					PLR and NL				
AUC									
Diagnostic yield									

1 G.8 Skin prick tests

2 **Table 55: DRKULEC 2013**⁴⁵⁵

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
Sensitization profile in differential diagnosis: allergic	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u>	N = 131 (N=71 asthma) <u>Inclusion criteria:</u> • 1-15 year olds in Zagreb	<u>Male: Female</u> 89:32 <u>Mean age:</u> 7.5 years	<u>Index test SPT</u> • Allergopharma (Croatia) • Allergens: • SPT for <i>Dermatophagoides pteronyssinus</i> (house dust)	Der P	Asthma	Chronic cough	Total	<u>Source of funding:</u> Departmental sources
					SPT +	59	17	76	
					SPT -	12	43	55	
					Total	71	60	131	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
asthma vs. chronic (nonspecific) cough syndrome. Medical science monitor: 19: 409-415 Drkulec V, Nogalo B, Perica M, Plavec D, Pezer M, and Turkalj M 2013. REF ID: DRKULEC2013.	Clinic <u>Setting:</u> Patients attending Department of Allergology <u>Country:</u> Croatia <u>Recruitment:</u> 6 month period (date not stated)	<ul style="list-style-type: none"> Respiratory symptoms Sent to department for diagnosis <u>Exclusion criteria:</u> None given		mite) <ul style="list-style-type: none"> <i>Ambrosia artemisifoliae</i> (common ragweed) <i>Phleum pratense</i> (timothy grass) CUT-OFF: not stated. <u>Reference standard Clinical Dx</u> At least 3 episodes of wheezing and/or positive bronchodilatation test Time between index test and reference standard: same time <u>Target condition</u> Allergic asthma (vs. chronic cough, i.e. <3 episodes of wheezing, with persistent cough >6 weeks)	Der P Sensitivity Specificity	83.6% (72.4, 90.8) 71.4% (59.9, 80.7)	<u>Limitations:</u> none <u>Additional data:</u> Raw data calculated not presented		
					PPV NPV Likelihood + test Likelihood - test	71.8% (60.5, 80.9) 83.3% (71.9, 90.7) 2.9 (2.6, 3.3) 0.23 (0.19, 0.28)			
					Diagnostic accuracy	77.1% (69.2, 83.5)			
					Diagnostic odds	12.8 (5.4, 29.9)			
					Amb A	Asthma	Chronic cough	Total	
					SPT +	47	31	78	
					SPT -	24	29	53	
					Total	71	60	131	
					Amb A Sensitivity Specificity	66.7% (46.7, 82.0) 48.6% (39.3, 57.9)			
					PPV NPV Likelihood + test Likelihood - test	22.5% (14.4, 33.5) 86.7% (75.8, 93.1) 1.30 (1.18, 1.4) 0.69 (0.52, 0.91)			
					Diagnostic accuracy	51.9% (43.4, 60.3)			
					Diagnostic odds	1.89 (0.75, 4.8)			
					Phl P	Asthma	Chronic cough	Total	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes		Comments	
					SPT +	47	30	77	
					SPT -	24	30	54	
					Total	71	60	131	
					Phl P		66.7% (48.8, 80.8)		
					Sensitivity		49.5% (39.9, 59.1)		
					Specificity				
					PPV		28.2% (19.0, 39.5)		
					NPV		83.3% (71.9, 90.7)		
					Likelihood + test		1.3 (1.2, 1.4)		
					Likelihood - test		0.67 (0.53, 0.85)		
					Diagnostic accuracy		53.4% (44.9, 61.8)		
					Diagnostic odds		1.96 (0.84, 4.60)		
					≥1 allergens	Asthma	Chronic cough	Total	
					SPT +	56	5	61	
					SPT -	15	55	70	
					Total	71	60	131	
					SPT to ≥1 allergen		78.8% (68.9, 86.2)		
					Sensitivity		91.3% (79.7, 96.6)		
					Specificity				
					PPV		94.4% (86.4, 97.8)		
					NPV		70% (57.5, 80.1)		
					Likelihood + test		9.1 (5.5, 14.9)		
					Likelihood - test		0.23 (0.21, 0.26)		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
					Diagnostic accuracy	83.21% (75.88, 88.64)	
					Diagnostic odds	39.1 (12.4, 123.4)	

Table 56: Gaig 1999⁵³⁹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Der P/ Der F	Asthma	Rhinitis	Total	
Asthma, mite sensitization, and sleeping in bunks. Annals of allergy, asthma and immunology: 82: 531-533 Gaig P, Enrique E, Garcia-Ortega P, Olona M, del Mar San Miguel M, and Richart C 1999.	<u>Study type:</u> Cross-sectional study <u>Data source:</u> Clinic <u>Setting:</u> Outpatient allergy clinic <u>Country:</u> Spain <u>Recruitment:</u> Consecutive patients, date not stated	N = 94 (47 sibling pairs); (N=41 asthma) <u>Inclusion criteria:</u> Patients attending outpatient allergy clinic who had been sharing a bunk with a sibling for >6 months, occupying always the same position (top or bottom bunk) <u>Exclusion criteria:</u> not stated	<u>Male: Female</u> 43:51 <u>Mean age:</u> 16 years	<u>Index test SPT</u> • ALK Abelló (Madrid, Spain) • Allergens: • <i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides farinae</i> CUT-OFF: skin wheal diameter to at least one of the two mites 3mm larger than control <u>Reference standard Clinical Dx</u> Clinical history and current symptoms (asthma or rhinitis) Time between index test and reference standard: not stated <u>Target condition</u> Allergic asthma (vs. rhinitis)	Der P/ Der F	Asthma	Rhinitis	Total	<u>Source of funding:</u> ALK Abelló (Madrid, Spain) supported antibody testing <u>Limitations:</u> No mention of objective test for asthma; study not designed to assess diagnostic test <u>Additional data:</u> Sensitivity etc calculated from 2 x 2 table
					SPT +	35	17	52	
					SPT -	6	9	15	
					Total	41	26	67	
					Mite Sensitivity		85.4%		
Specificity		34.6%							
PPV		67.3%							
NPV		60%							

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
REF ID: GAIG1999							

Table 57: May 1990¹¹⁰⁸

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments			
Allergy to <i>Artemisia vulgaris</i> in the region of Warsaw. Allergologia et Immunopathologia: 18: 57-60 May KL 1990. REF ID: MAY1990.	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Clinic <u>Setting:</u> Allergology clinic <u>Country:</u> Poland <u>Recruitment:</u> consecutive patients, date not stated	N = 446 (N=190 asthma) <u>Inclusion criteria:</u> Consecutive unselected patients for allergological consultation for conjunctivitis, rhinitis and/or asthma which appeared or deteriorated in late spring and summer <u>Exclusion criteria:</u> None stated	<u>Male: Female</u> 256:190 <u>Mean age:</u> Range 6 to 56 years, mean not stated	<u>Index test SPT</u> <ul style="list-style-type: none"> • Haarlem-Holland • Allergens: <ul style="list-style-type: none"> • <i>Gramineae</i> (grasses both wild and cultivated) • <i>Artemisia vulgaris</i> (weed: mugwort) CUT-OFF: 3+ or 4+ <u>Reference standard Clinical Dx</u> Clinically evident bronchial symptoms Time between index test and reference standard: not stated <u>Target condition</u> Asthma with or without	Gramineae Asthma with or without rhinitis and with or without conjunctivitis	Rhinitis with or without conjunctivitis Total	<u>Source of funding:</u> Not stated <u>Limitations:</u> No mention of objective test for asthma <u>Additional data:</u> Sensitivity etc calculated from 2 x 2 table			
					SPT +	170		228	398	
					SPT -	20		28	48	
					Total	190		256	446	
					Gramineae Sensitivity Specificity			89.5% 10.9%		
					PPV NPV			42.7% 58.3%		
					Artemisia vulgaris Asthma	Rhinitis Total				
					SPT +	92			95	187
					SPT -	98			161	259

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
				rhinitis and with or without conjunctivitis (vs. rhinitis with or without conjunctivitis.)	Total 190	256 446	
					Artemisia vulgaris Sensitivity Specificity	48.4% 62.9%	
					PPV NPV	49.2% 62.2%	

Table 58: Miraglia del Giudice 2002¹¹⁵⁶

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
Atopy and house dust mite sensitization as risk factors for asthma in children. Allergy: 57: 169-172 Miraglia Del Giudice M, Pedulla M, Piacentini GL,	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Clinic <u>Setting:</u> Paediatric Asthma and Allergy clinic <u>Country:</u> Italy	N = 1426 (N=925 asthma) <u>Inclusion criteria:</u> Children referred to our Paediatric Asthma and Allergy Centre because of allergic symptoms (see reference standard) <u>Exclusion criteria:</u> Children without a confirmed	<u>Male: Female</u> 814:612 <u>Mean age:</u> Range 0 to 12 years, mean not stated	<u>Index test SPT</u> <ul style="list-style-type: none">Bayer DHS Diagnostics, Epernon Cedex-FranceAllergens:house dust mites (HDM) (<i>Dermatophagoides pteronyssinus</i>, <i>D. farinae</i>), <i>Parietaria officinalis</i> (lichwort, in the nettle family), grasses (<i>Dactylis glomerata</i>, <i>Lolium perenne</i>, <i>Phaleum pratense</i>), moulds (<i>Alternaria</i>, <i>Aspergillus</i>, <i>Cladosporium</i>), dog fur, cat fur, egg albumin, and cow's milk CUT-OFF: wheal was at least 3 mm in diameter <u>Reference standard Clinical Dx</u> Clinical diagnosis: asthma, allergic	≥1 test +ve	Asthma	Chronic cough	Total	<u>Source of funding:</u> None stated
					SPT +	411	218	629	
					SPT -	514	283	797	
					Total	925	501	1426	
					≥1 test +ve	Sensitivity		44%	<u>Limitations:</u> No mention of objective test for asthma <u>Additional data:</u> Sensitivity,
						Specificity		56%	
	PPV	65%							
		NPV	36%						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
<p>Capristo C, Brunese FP, Decimo F, Maiello N, and Capristo AF 2002. REF ID: MIRAGLIA DELGIUDI CE2002.</p>	<p><u>Recruitment:</u> January–December 1998</p>	<p>diagnosis</p>		<p>rhinoconjunctivitis, atopic dermatitis and food allergy was confirmed by a paediatric allergologist.</p> <p>Bronchial asthma defined as ≥ 3 episodes of wheezing < 2 years of age, or 1 episode from 2 years of age, or any episode of wheezing independent of age, if combined with atopic symptoms in the family or other atopic symptoms in the child.</p> <p>Allergic rhino-conjunctivitis: sneezing, nasal obstruction, watery rhinorrhea, nasal itching, conjunctival hyperemia and photophobia at least twice after exposure to a particular allergen and unrelated to infection.</p> <p>Food allergy: acute onset of symptoms e.g. skin reactions, wheezing, oral allergic symptoms, vomiting or diarrhoea on >1 occasion after ingestion of, or oral contact with, a particular type of food.</p> <p>Atopic dermatitis: defined according to Hanifin and assessed with the Scrad index</p> <p>Time between index test and reference standard: not stated</p> <p><u>Target condition</u> Allergic asthma (vs. allergic rhinoconjunctivitis, atopic dermatitis or</p>			<p>specificity calculated</p>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
				food allergy)			

Table 59: Popovic 2002¹³⁸¹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
S. Popovic-Grle, M. Mehulic, F. Pavicic, I. Babic, and Z. Beg-Zec. Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. <i>Coll. Antro</i>	<u>Study type:</u> Cross-sectional study <u>Data source:</u> Random sample <u>Setting:</u> Outpatient allergy department <u>Country:</u> Croatia <u>Recruitment:</u> Just says 'sample' of patients, date not stated	N = 195 (N=141 asthma, n=17 COPD, n=29 rhinitis/sinusitis, n=8 unsolved) <u>Inclusion criteria:</u> <ul style="list-style-type: none"> • Pts with dyspnoea • Treated for breathlessness in the Outpt dept of Allergology • Referred by GPs due to suspected asthma <u>Exclusion criteria:</u> <ul style="list-style-type: none"> • All serious diseases of other organ systems or the lungs (apart from those of an obstructive and/or 	ASTHMA PTS: <u>Male: Female</u> 51%:49% <u>Mean age:</u> 36.5 years	<u>Index test SPT</u> <ul style="list-style-type: none"> • House dust • <i>D. pteronyssinus</i> • Grass pollen • Weed pollen • Tree pollen • Animal dander • Cat fur • Dog fur • Feathers • Fungi mixture • Insect antigens CUT-OFF: skin wheal diameter ≥3mm. <u>Reference standard Clinical Dx (with obj test)</u> Questionnaire of clinical history of occasional asthma attacks with wheezing and nocturnal awakening because of dyspnoea, and BDR test with salbutamol.	≥1 aeroallergen	Asthma	Non-asthma	Total	<u>Source of funding:</u> None reported <u>Limitations:</u> No major ones identified
					SPT +	87	20	1074	
					SPT -	54	34	88	
					Total	141	54	195	
					Sensitivity		62%		
					Specificity		63%		
					PPV		81%		
NPV		61%							
							<u>Additional data:</u> n/a		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
pol. 26 Suppl:119-127, 2002. REF ID: POPOVIC 2002.		allergic nature)		Time between index test and reference standard: not stated <u>Target condition</u> Allergic asthma (vs. rhinitis/sinusitis, COPD or unsolved)			

Table 60: Soriano 1999A¹⁶⁴⁵

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
JB Soriano, JM. Anto, J. Sunyer, A. Tobias, M. Kogevinas, E. Almar, N. Muniozgueren, JL. Sanchez, L. Palenciano, P. Burney, J. Martinez-Moratalla et al. Risk of asthma in the general Spanish	<u>Study type:</u> Cross-sectional study <u>Data source:</u> Sub sample of general population reporting respiratory symptoms <u>Setting:</u> General population	N = 1816 (N=136 asthma) <u>Inclusion criteria:</u> • Subsample of pts from a general population, who reported respiratory symptoms in a screening questionnaire. <u>Exclusion criteria:</u> • Already selected in	<u>Male: Female</u> 48%:52% <u>Mean age:</u> 32 years	<u>Index test SPT</u> • <i>D. pteronyssinus</i> • <i>Cladosporium</i> • <i>Alternaria</i> • Timothy grass • Olive • Birch • Parieta or ragweed CUT-OFF: skin wheal diameter ≥3mm. <u>Reference standard Clinical Dx with objective test</u> Clinical history and current symptoms (woken up by attack of	≥1 allergen +ve	Asthma	Non-asthma	Total	<u>Source of funding:</u> Fondo de Investigaciones Sanitarias, Madrid and Generalitat de Catalunya.
					SPT +	60.7% (n=83)	31.4% (n=528)	611	
					SPT -	39.3% (n=53)	68.6% (n=1152)	1205	
					Total	136	1680	1816	
					Sensitivity	60.7%			
					Specificity	68.6%			
					PPV	-			
					NPV	-			
Alternaria	Asthma	Non-asthma	Total						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes		Comments	
population attributable to specific immunoresponse. <i>Int.J.Epidemiol.</i> 28 (4):728-734, 1999. REF ID: SORIANO 1999A.	<u>Country:</u> Spain <u>Recruitment:</u> date not stated	an earlier random sample		shortness of breath during last 12 months, or having an attack of asthma during last 12 months, or currently taking medication for asthma) – using questionnaire, plus methacholine challenge for bronchoresponsiveness (BR). Asthma defined as symptomatic BR. Time between index test and reference standard: not stated <u>Target condition</u> Allergic asthma	SPT +	6.7% (n=9)	1.4% (n=24)	33	
					SPT -	93.3% (n=127)	98.6% (n=1656)	1783	
					Total	136	1680	1816	
					Sensitivity		6.7%		
					Specificity		98.6%		
					Birch	Asthma	Non-asthma	Total	
					SPT +	5.9% (n=8)	1.6% (n=27)	35	
					SPT -	94.1% (n=128)	98.4% (n=1653)	1781	
					Total	136	1680	1816	
					Sensitivity		5.9%		
					Specificity		98.4%		
					Cat	Asthma	Non-asthma	Total	
					SPT +	20.7% (n=28)	6.3% (n=106)	134	
					SPT -	79.3% (n=108)	93.7% (n=1574)	1682	
					Total	136	1680	1816	
Sensitivity		20.7%							
Specificity		93.7%							
Cladosporium	Asthma	Non-asthma	Total						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes		Comments	
					SPT +	7.4% (n=10)	2.8% (n=47)	57	
					SPT -	92.6% (n=126)	97.2% (n=1633)	1759	
					Total	136	1680	1816	
					Sensitivity	7.4%			
					Specificity	97.2%			
					Dust mite	Asthma	Non-asthma	Total	
					SPT +	39.3% (n=53)	20.0% (n=336)	389	
					SPT -	60.7% (n=83)	80.0% (n=1344)	1427	
					Total	136	1680	1816	
					Sensitivity	39.3%			
					Specificity	80.0%			
					Timothy grass	Asthma	Non-asthma	Total	
					SPT +	31.9% (n=43)	13.3% (n=223)	266	
					SPT -	68.1% (n=93)	86.7% (n=1457)	1550	
					Total	136	1680	1816	
					Sensitivity	31.9%			
					Specificity	86.7%			

G.9 IgE

Table 61: ABRAHAM 2007⁸

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
CM. Abraham, DR Ownby, EL Peterson, G Wegienka, EM Zoratti, LK Williams, CLM Joseph, and C Cole Johnson. The relationship between seroatopy and symptoms of either allergic rhinitis or asthma. <i>J.Allergy Clin.Immunol.</i> 119 (5):1099-1104, 2007.	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Information from a regional survey of pregnant women in a primary care practice, and subsequent interview and blood test. <u>Setting:</u> Primary care <u>Country:</u> USA <u>Recruitment:</u> Dates not	N = 702 <u>Inclusion criteria:</u> • Pregnant women in second trimester or later • Age 21-49 years <u>Exclusion criteria:</u> None given	<u>Male: Female</u> 0 : 100% <u>Mean age:</u> 29 years <u>Dx of asthma:</u> N=140 self-reported, N=138 physician provided Dx.	<u>Index test</u> Specific IgE • Pharmacia UniCAP system • Allergens: ○ Dust mite (American) <i>D. farinae</i> ○ Dust mite (European) <i>D. pteronyssinus</i> ○ Cat ○ Dog ○ Cockroach ○ Ragweed ○ Grass (timothy) ○ Egg ○ <i>Alternaria</i> CUT-OFF: positive = ≥ 0.35 kU/l. <u>Reference standard</u> Clinical Dx Physician Dx of asthma (by answer to questionnaire). <u>Time between index test</u>	Dust mite (Ameri) asthma	Ref std +	Ref std –	Total	<u>Source of funding:</u> National Institute of Allergy and Infectious Diseases and by the Fund for Henry Ford Health System, Detroit. <u>Limitations:</u> High IgE cut off, pregnant women only, consecutive recruitment; Unclear time between Ref standard and Index test
					IgE +				
					IgE -				
					Total				
					Sensitivity				
					Specificity				
					Dust mite (Euro) asthma	Ref std +	Ref std –	Total	
					IgE +	37.9% (~n=47)	21.8% (~n=90)		
					IgE -	62.1% (~n=77)	78.2% (~n=403)		
					Total	N=124	N=493	N=617	
Sensitivity		37.9 (47/124)							
Specificity		78.2 (97/493)							
Grass (tim)	Ref std +	Ref std –	Total						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments			
ABRAHAM 2007	given			<p><u>and reference standard</u>: Index done much later (because physican Dx was determined by people answering a questionnaire, so the Dx could have been made any previous time)</p> <p><u>Target condition</u> Allergic asthma</p>	asthma			<u>Additional data:</u>		
					IgE +	33.3% (~n=41)	19.5% (~n=96)			
					IgE -	66.7% (~n=83)	80.5% (~n=397)			
					Total	N=124	N=493		N=617	
					Sensitivity		33.3 (41/124)			
					Specificity		80.5 (397/493)			
					Alternariaasthma	Ref std +	Ref std -		Total	
					IgE +	33.9% (~n=42)	14.4% (~n=71)			
					IgE -	66.1% (~n=82)	85.6% (~n=422)			
					Total	N=124	N=493		N=617	
					Sensitivity		33.9 (167/124)			
					Specificity		85.6 (106/493)			
					Cat asthma		Ref std +		Ref std -	Total
					IgE +	39.8% (~n=49)	12.2% (~n=60)			
IgE -	(~n=75)	87.8% (~n=433)								
Total	N=124	N=493	N=617							
Sensitivity		39.8%								
Specificity		87.87%								
Dog asthma		Ref std +	Ref std -	Total						
IgE +	33.9%	12.3%								

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
						(~n=42) (n=61)	
					IgE -	66.1% (n=82) (n=432)	
					Total	N=124 N=493	
					Sensitivity	33.9%	
					Specificity	88%	

Table 62: LINNEBERG 2006¹⁰²⁷

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
A. Linneberg, L. Husemoen, N. Nielsen, F. Madsen, L. Frolund, and N. Johansen. Screening for allergic respiratory disease in the general population with the ADVIA Centaur Allergy Screen Assay. <i>Allergy</i> 61 (3):344-348, 2006.	<u>Study type</u> : Diagnostic Cross-sectional study <u>Data source</u> : Random sample from a prospective cohort study (Copenhagen Allergy Study). <u>Setting</u> : General population <u>Country</u> : Denmark	N = 709 <u>Inclusion criteria</u> : <ul style="list-style-type: none"> 15-69 year olds in Copenhagen Participants in the study who responded at follow-up Random group and a respiratory symptom group were used for analysis 	<u>Male</u> : Female Not reported <u>Mean age</u> : Not reported	<u>Index test</u> Specific IgE <ul style="list-style-type: none"> ADIVA Centaur immunoassay Allergens: <ul style="list-style-type: none"> Birch Grass (timothy) Mugwort Mammals (includes dog, cat, horse, hamster and others) Dust mite CUT-OFF : positive = >0.35 kU/l. <u>Reference standard</u> Clinical Dx Allergic asthma clinical Dx by presence of positive symptoms (via questionnaire) and positive SPT. Time between index test and	Pollen asthma	Ref std +	Ref std -	Total	<u>Source of funding</u> : Not stated <u>Limitations</u> : Unclear time between Ref standard and Index test
					IgE +	49	238	287	
					IgE -	2	420	422	
					Total	51	658	709	
					Sensitivity	96.1 (49/51)			
					Specificity	63.8 (420/658)			
					PPV	17.1 (49/287)			
					NPV	99.5 (420/658)			
					PLR and NLR	-			
					Dust mite asthma	Ref std +	Ref std -	Total	
IgE +	27	260	287						
IgE -	5	417	422						
Total	32	677	709						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
LINNEBERG 2006	<u>Recruitment:</u> Oct 1997-Nov 1998	<u>Exclusion criteria:</u> None given		reference standard: unclear <u>Target condition</u> Allergic asthma	Sensitivity		84.4 (27/32)		<u>Additional data:</u>
					Specificity		62.0 (417/677)		
					PPV		9.4 (27/287)		
					NPV		61.5 (417/677)		
					ALL allergic asthma	Ref std +	Ref std -	Total	
					IgE +	79	208	287	
					IgE -	6	416	422	
					Total	85	624	709	
Sensitivity		92.9 (79/85)							
Specificity		66.7 (416/624)							
PPV		27.5 (79/287)							
NPV		98.6 (416/422)							
PLR and NLR		-							

Table 63: PLASCHKE 1999A¹³⁶⁸

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
P. Plaschke, C. Janson, E. Norrman, E. Björnsson, S. Ellbjär, and B. Järholm. Association between atopic sensitization	<u>Study type:</u> Diagnostic cross-sectional study <u>Data source:</u> Random sample (1800 men, 1800 women) from population registers.	N = 1572 in final analysis. <u>Inclusion criteria:</u> • Aged 20-44 years • Responded to questionnaire and agreed to	<u>Male:</u> Female 46: 54% <u>Mean age:</u> 33 years <u>Current smokers:</u> 30%	<u>Index test</u> Specific IgE • Pharmacia CAP system • Allergens: ○ Cat ○ Dust mite <i>D. pteronyssinus</i> ○ Grass ○ Birch	Dust mite (Euro) asthma	Ref std +	Ref std -	Total	<u>Source of funding:</u> Fondo de Investigaciones Sanitarias, Madrid and Generalitat de Catalunya.
					IgE +	18.8% (~n=16)	5.8% (~n=86)	102	
					IgE -	81.2% (~n=68)	94.2% (~n=1402)	1470	
					Total	N=84	N=1488	N=1572	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
and asthma and bronchial hyperresponsiveness in Swedish adults: pets, and not mites, are the most important allergens. <i>J.Allergy Clin.Immunol</i> . 104 (1):58-65, 1999. PLASCHKE 1999A	Postal questionnaire (modified ECRHS) was sent and had an 86% response rate. 89.2% of those who answered, agreed to participate in clinical examinations. <u>Setting:</u> General population <u>Country:</u> Sweden <u>Recruitment:</u> Feb 1991 – June 1992	have clinical examination and perform SPT, RAST and bronchial methacholine challenge. <u>Exclusion criteria:</u> None given	<u>Dx of asthma:</u> N=84 (according to symptoms and previous Dx ascertained by questionnaire).	<ul style="list-style-type: none"> o <i>Cladosporium</i> CUT-OFF: positive = class ≥ 2 (≥ 0.7 kU/l). <u>Reference standard</u> Clinical Dx Dx of asthma (by answer to questionnaire) <u>Time between index test and reference standard:</u> Not mentioned. <u>Target condition</u> Allergic asthma	Sensitivity	18.8 (16/84)			<u>Limitations:</u> High IgE cut off; Unclear time between Ref standard and Index test <u>Additional data:</u>
					Specificity	94.2 (1402/1488)			
					Grass asthma	Ref std +	Ref std –	Total	
					IgE +	35.3% (~n=30)	12.6% (~n=187)	217	
					IgE -	64.7% (~n=54)	87.3% (~n=1301)	1355	
					Total	N=84	N=1488	N=1572	
					Sensitivity	35.3 (30/84)			
					Specificity	87.3 (1301/1572)			
					Birch asthma	Ref std +	Ref std –	Total	
					IgE +	29.4% (~n=25)	10.4% (~n=155)	180	
					IgE -	70.6% (~n=59)	89.6% (~n=1333)	1392	
					Total	N=84	N=1488	N=1572	
Sensitivity	29.4 (25/84)								
Specificity	89.6 (1333/1488)								
Cladosporium asthma	Ref std +	Ref std –	Total						
IgE +	3.5% (~n=3)	1.0% (~n=15)	18						
IgE -	96.5% (~n=81)	99.0% (~n=1473)	1554						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
					Total	N=84	N=1488	N=1572	
					Sensitivity		3.5 (3/84)		
					Specificity		99.0 (1473/1488)		
					Cat asthma	Ref std +	Ref std –	Total	
					IgE +	40% (~n=34)	9.4% (~n=140)		
					IgE -	60% (~n=50)	90.6% (~n=1348)		
					Total	N=84	N=1488		
					Sensitivity		40%		
					Specificity		90.6%		

Table 64: SORIANO 1999¹⁶⁴⁴

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
J. B. Soriano, J. M. Anto, J. Sunyer, A. Tobias, et al. Risk of asthma in the general Spanish population attributable to	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Info from a 20% random subsample of a questionnaire	N = 1816 <u>Inclusion criteria:</u> • Aged 20-44 years • Responded to questionnaire and provided blood samples, had SPTs and spirometry as	<u>Male:</u> <u>Female</u> 48 : 52% <u>Mean age:</u> 32 years <u>Current smokers:</u> 52%	<u>Index test:</u> Specific IgE or SPT • Pharmacia CAP system • Allergens: ○ Cat ○ <i>Cladosporium</i> ○ Dust mite <i>D. pteronyssinus</i> ○ Grass (timothy) ○ <i>Parietaria</i> ○ <i>Alternaria</i> (SPT only)	<i>Cladosporium</i> asthma IgE + IgE - Total Sensitivity / Specificity Dust mite asthma	Ref std + 7.4% (~n=10) 92.6% (~n=126) N=136 Ref std +	Ref std – 2.8% (~n=47) 97.2% (~n=1633) N=1680 Ref std –	Total 57 1759 N=1816 7.0 and 97.2 Total	<u>Source of funding:</u> Fondo de Investigaciones Sanitarias, Madrid and Generalitat de Catalunya.

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
specific immunoresponse. Spanish Group of the European Community Respiratory Health Survey. <i>Int.J.Epidemiol.</i> 28 (4):728-734, 1999. SORIANO 1999	given to a random sample (N=16844) of general population aged 20-44 yrs in 5 areas of Spain. <u>Setting:</u> General population <u>Country:</u> Spain <u>Recruitment:</u> Dates not given	well as methacholine challenge test. <u>Exclusion criteria:</u> None given	<u>Dx of asthma:</u> N=136 (according to symptoms and BR results) performed by the study and questionnaire. N=1689 (not asthma).	<ul style="list-style-type: none"> o Birch (SPT only) o Olive Ragweed (SPT only) CUT-OFF: positive = >0.35 kU/l. <u>Reference standard</u> Clinical Dx of asthma (by answer to questionnaire and BR results). <u>Time between index test and reference standard:</u> Index done same time as BR tests <u>Target condition</u> Allergic asthma	IgE +	39.3% (~n=53)	20.0% (~n=336)	389	<u>Limitations:</u> Unclear time between Ref standard and Index test; results mix of IgE + SPT. <u>Additional data:</u>
					IgE -	60.7% (~n=83)	80.0% (~n=1344)	1427	
					Total	N=136	N=1680	N=1816	
					Sensitivity		39.3 (53/136)		
					Specificity		80.0 (1344/1680)		
					Grass timothy asthma	Ref std +	Ref std -	Total	
					Index test +	31.9% (~n=93)	13.3% (~n=223)	316	
					Index test -	68.1% (~n=43)	86.7% (~n=1457)	1500	
					Total	N=136	N=1680	N=1816	
					Sensitivity		68.0 (93/136)		
Specificity		86.7 (1457/1680)							
					Cat asthma	Ref std +	Ref std -	Total	
					IgE +	20.7% (~n=27)	6.3% (~n=106)		
					IgE -	79.3% (~n=109)	93.7% (~n=1574)		
					Total	136	1680		
					Sensitivity		20.7%		
					Specificity		94%		

Table 65: TSCHOPP 1998¹⁷⁸⁸

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Current allergic asthma	Ref std +	Ref std -	Total	
J. M. Tschopp, D. Sistek, C. Schindler, P. Leuenberger, A. P. Perruchoud, B. Wuthrich, M. Brutsche, J. P. Zellweger, W. Karrer, and O. Brandli. Current allergic asthma and rhinitis: diagnostic efficiency of three commonly used atopic markers (IgE, skin prick tests, and Phadiatop). Results from 8329 randomized adults from the SAPALDIA Study. Swiss Study on	<p><u>Study type:</u> Diagnostic Cross-sectional study</p> <p><u>Data source:</u> Information from a random sample of residents (part of the SAPALIDA study) from the general population aged 18-60 yrs.</p> <p><u>Setting:</u> General population</p>	<p>N = 8329</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Aged 18-60 Undertaken the 3 atopic tests (total IgE, SPT and Phadiatop) <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Not done the 3 atopic 	<p><u>Male: Female</u></p> <p>Data in another publication – ON ORDER</p> <p><u>Mean age:</u></p> <p>Data in another publication – ON ORDER</p> <p><u>Current smokers:</u></p> <p>Data in another publication – ON ORDER</p> <p><u>Dx of asthma (in N=8329):</u></p> <p>DA (DrDx): N=566, CA (current asthma): N=208, CAA (current allergic asthma): N=153, CAR (current allergic</p>	<p><u>Index test Total IgE</u></p> <ul style="list-style-type: none"> Pharmacia CAP FEIA technology <p>CUT-OFF: positive = ≥ 100 kU/l.</p> <p><u>Index test Specific IgE</u></p> <ul style="list-style-type: none"> Phadiatop fluoroenzyme immunoassay Allergens: <ul style="list-style-type: none"> Pollens House dust mite Moulds Cat – total IgE only <p>NOT USING DATA AS RESULTS ARE COMBINED</p> <p>CUT-OFF: positive = above the reference serum value.</p> <p><u>Reference standard Clinical Dx</u></p> <p>Dx of current allergic asthma (by qu'aire results: CA + respiratory symptoms related to common allergy exposure in the last 12 mths asthma.</p>	Current allergic asthma	Ref std +	Ref std -	Total	<p><u>Source of funding:</u></p> <p>Swiss National Science Foundation and Federal Office of Education and Science.</p> <p><u>Limitations:</u></p> <p>High cut off; Unclear time between Ref standard and Index test</p>
					Total IgE +	87	1807	1894	
					Total IgE -	66	6369	6435	
					Total	153	8176	8329	
					Sensitivity	56.9			
					Specificity	77.9			
					PPV, NPV	4.6, 99.0			
					Current allergic asthma (all allergens)	Ref std +	Ref std -	Total	
					Sp IgE +	NR	NR	NR	
					Sp IgE -	NR	NR	NR	
					Total	NR	NR	8329	
					Sensitivity	72.5			
					Specificity	71.9			
					PPV, NPV PLR and NLR	4.6, 99.3 -			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Air Pollution and Lung Diseases in Adults. <i>Allergy</i> 53 (6):608-613, 1998. TSCHOPP 1998	<u>Country:</u> Switzerland <u>Recruitment:</u> 1 year period	tests.	rhinitis): N=1361, CAA and/or CAR: N=1422, Phadiatop: N=2410, SPT+: N=1912, IgE+: N=1890.	<u>Time between index test and reference standard:</u> not reported (likely to be different time as one was based on questionnaire results). <u>Target condition</u> Current allergic asthma. DATA NOT GIVEN FOR DA (Dr Dx asthma).			<u>Additional data:</u>

G.10 FeNO for diagnosis

Table 66: BERLYNE 2000¹⁶⁰

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
G. S. Berlyne, K. Parameswaran, D. Kamada, A. Efthimiadis, and F. E. Hargreave. A comparison of exhaled nitric oxide and induced sputum as markers of airway inflammation. <i>J. Allergy Clin. Immunol.</i> 106 (4):638-644, 2000.	<p><u>Study type:</u> Case-control study</p> <p><u>Data source:</u> clinic pts</p> <p><u>Setting:</u> Chest allergy clinic pts</p> <p><u>Country:</u> Canada</p> <p><u>Recruitment:</u> Not reported</p>	<p>N = 131 adults</p> <ul style="list-style-type: none"> - n=38 asthma – steroid naive (1) - n=35 asthma – steroid Tx (2) - n=8 eosinophilic bronchitis (3) - n=28 healthy controls - atopic (4) - n=22 healthy controls – nonatopic (5) <p><u>Inclusion criteria:</u></p> <p>(1): Asthma (steroid naive). Symptoms of wheeze, breathlessness or cough in past year plus MCT PC20 <8 mg/ml if the FEV1/VC >70%; or a post-BD FEV1 >15% if the FEV1/VC was <70%. Not received ICS in previous month.</p> <p>(2): Asthma (steroid-Tx). As above but receiving regular ICS Tx.</p> <p>(3): Eosinophilic bronchitis without asthma. Cough in the past yr, FEV1/VC >80%, MCT PC20 >16 mg/ml, and induced sputum eos count >5% of total squamous cell count (above the 90th percentile for sputum eos).</p> <p>(4): Healthy controls - atopic. No symptoms. FEV1/VC >70% and MCT PC20 >16 mg/ml. Positive SPT to at least 1 common allergen.</p> <p>(5): Healthy controls -nonatopic. As</p>	<p><u>Male: Female</u> 43%/57%</p> <p><u>Mean age:</u> 39 years</p>	<p><u>Index test</u></p> <p>FeNO: chemiluminescence analyser; fixed flow rate 45 ml/s. Sievers 240 device.</p> <p><u>Target condition</u></p> <p>FeNO levels asthma vs. healthy vs. eosinophilic bronchitis (separately)</p>	<p>Median (IQR) FeNO levels:</p> <ol style="list-style-type: none"> 1. Asthma – steroid naive: 39 (43) ppb 2. Asthma – steroid Tx: 17 (12) ppb 3. Eosinophilic bronchitis: 65 (92) ppb 4. Healthy - atopic: 11 (6) ppb 5. Healthy - nonatopic: 9 (7) ppb <p>- median of healthy = 10</p> <p>The median FeNO was SS different between the groups.</p> <p>Median FeNO was SS higher in the group with asthma (steroid naive) vs. healthy controls (p<0.001)</p> <p>Median FeNO was SS lower in the group with asthma (steroid Tx) vs. steroid naive (p<0.001)</p> <p>Median FeNO was SS lower in the group with asthma (steroid Tx) vs. Eosinophilic bronchitis.</p>	<p><u>Source of funding:</u> Not reported</p> <p><u>Limitations:</u> -</p> <p><u>Additional data:</u> None</p>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
BERLYNE 2000		above but negative SPT to at least 1 common allergen. <u>Exclusion criteria:</u> <ul style="list-style-type: none"> • Current smokers (as reduces ENO levels) • Ex-smokers <1 year • Symptoms of RTI in 4 wks before study or other complicating respiratory disease 				There was NS difference in median FeNO levels between the control groups (ie. atopic status does not matter).

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Table 67: CARDINALE 2005²⁷⁰

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
F.	<u>Study type:</u>	N = 175 children (mean 10 years)	<u>Male: Female</u>	<u>Index test</u>	Median (IQR) FeNO levels:	<u>Source of</u>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
<p>Cardinale, F. M. De Benedictis, V. Muggeo, P. Giordano, M. S. Loffredo, G. Iacoviello, and L. Armenio. Exhaled nitric oxide, total serum IgE and allergic sensitization in childhood asthma and allergic rhinitis. <i>Pediatr. Allergy Immunol.</i> 16 (3):236-242, 2005.</p>	<p>Case-control study</p> <p><u>Data source:</u> Pts from clinic</p> <p><u>Setting:</u> Paediatric allergy clinic</p> <p><u>Country:</u> Italy</p> <p><u>Recruitment:</u> No detail if consecutive. Nov 2002 - Sept 2003.</p>	<p>- n=109 asthma (83.4% were allergic – SPT+; 51% of all asthma had additional allergic rhinitis (1a and 1b = atopic/nonatopic asthma)</p> <p>- n=41 allergic rhinitis, moderate persistent (2)</p> <p>- n=25 healthy controls (3)</p> <p><u>Inclusion criteria:</u> (1): mild intermittent asthma. History of symptoms, pulmonary function tests and response to inhaled beta-adrenergic agents according to international guidelines. History of at least 1 episode of asthma in past year and stable at time of study. (2): moderate persistent allergic rhinitis. Clinical history and positive SPT to common allergens. None had ever had wheezing or received asthma medication. Steroid Tx or antihistamine had to be withdrawn >3 months before study. (3): Healthy controls. Non-atopic (absence of allergic symptoms in history and negative SPT), no history of airway disease, allergy or significant medical illness and not taking any medication.</p> <p><u>Exclusion criteria:</u></p>	<p>1:2 (overall)</p> <p><u>Mean age:</u> 10 years (overall)</p>	<p>FeNO: chemiluminescence analyser; flow rate 50 ml/s. NOA Tm280 Sievers device</p> <p><u>Target condition</u> FeNO levels asthma vs. allergic rhinitis vs. healthy controls (separately)</p>	<p>1. All asthma: 22.7 (9.1 - 48) ppb 1a. n=91 Asthma atopic: 25.6 (11.4 – 56.2) ppb 1b. n=18 Asthma non-atopic: 11.5 (5.4 - 15.5) ppb 2. Allergic rhinitis: 15.3 (9.4 – 31.0) 3. Healthy: 5.9 (3.4 – 9.3)</p> <p>Asthma pts and allergic rhinitis has SS higher FeNO levels than controls (p=0.0001 and p=0.016)</p> <p>The mean eNO was SS higher in allergic vs. non-allergic asthma (p<0.001)</p> <p>There was NS difference in eNO between the non-allergic asthma pts vs. healthy controls.</p> <p>There was NS difference in eNO between all asthma pts vs. allergic rhinitis.</p> <p>The median FeNO level was SS higher in allergic asthma vs. allergic rhinitis. (p=0.03)</p>	<p><u>funding:</u> Not reported</p> <p><u>Limitations:</u> -</p> <p><u>Additional data:</u> None</p>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
CARDINAL E 2005		History of significant medical illness, previous or current allergen hyposensitisation, history or signs of RTI in 4 wks before study, tobacco smoke exposure in the family.				

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Table 68: CHATKIN 1999³⁰⁶

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments	
Chatkin JM, Ansarin K, Silkoff PE, McClean P, Gutierrez C, Zamel N et al. Exhaled	<u>Study type:</u> Cross-sectional observational study <u>Data source:</u>	N = 38 chronic cough + 23 healthy controls <u>Inclusion criteria:</u> Chronic cough (>3 weeks) of unknown cause referred for	<u>Male:</u> Female 11:27 chronic cough plus 8:15 controls <u>Mean age:</u> Adult: asthma:	<u>Index test</u> FeNO: chemiluminescence analyser (Sievers 280 device); mouth pressure 20mm Hg. Flow rate 45ml/s Optimal cut-off 30ppb		Ref std +	Ref std -	Total	<u>Source of funding:</u> Dr Chatkin recipient of a grant from CAPES
					Index test +	6	4	10	
					Index test -	2	26	28	
					Total	8	30	38	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
nitric oxide as a noninvasive assessment of chronic cough. American Journal of Respiratory and Critical Care Medicine. 1999; 159(6):1810-1813. (Guideline Ref ID CHATKIN1999)	Data collected for this study	diagnosis; normal CXR and FEV1 >80% predicted	41 (12) yr; chronic cough non-asthma: 47 (15) yr; healthy controls: 38 (8)	<u>Reference standard</u> Positive to methacholine challenge (PC20 ≤8mg/mL) Tests done within 24 hours	Sensitivity	75%	<u>Limitations:</u> None <u>Additional data:</u> None
	<u>Setting:</u> Asthma centre (tertiary referral centre) or affiliated community respiratory clinics	<u>Exclusion criteria:</u> Use of codeine or any other medication for chronic cough, upper respiratory infection within 4 weeks; use of corticosteroids within 6 weeks; current smoking; any significant medical conditions; contra-indications to methacholine challenge.	Non-asthma = chronic cough (mean 53.8 weeks) but methacholine negative	<u>Target condition</u> Asthma diagnosis vs. chronic cough non-asthma FeNO levels asthma vs. chronic cough non-asthma or vs. healthy controls	Specificity	87%	
	<u>Country:</u> Canada				PPV	60%	
	<u>Recruitment:</u> Not stated				NPV	93%	
					PLR / NLR	5.8 / 0.3	
					AUC	Not stated	
					Median (25 th to 75 th percentile) FeNO levels: asthma (chronic cough and methacholine positive): 75.0 (34.1 to 104.0) ppb n=8, p=0.0014 vs. non-asthma, p=0.007 vs. controls	Non-asthma (chronic cough and methacholine negative): 16.7 (11.0 to 21.7) ppb n=30 Healthy controls: 28.3 (23 to 30) ppb, n=23	

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Table 69: CIPRANDI 2013³³⁸

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
Giorgio	<u>Study type:</u>	N = 330 children (median 12 years)	<u>Male: Female</u>	<u>Index test</u>	Median (IQR) FeNO levels:	<u>Source of</u>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
<p>Ciprandi, Maria Angela Tosca, and Michele Capasso. High exhaled nitric oxide levels may predict bronchial reversibility in allergic children with asthma or rhinitis. <i>J.Asthma</i> 50 (1):33-38, 2013.</p> <p>CIPRANDI 2013</p>	<p>Case-control study</p> <p><u>Data source:</u> Hospital pts</p> <p><u>Setting:</u> Hospital</p> <p><u>Country:</u> Italy</p> <p><u>Recruitment:</u> Not reported</p>	<p>- n=180 allergic intermittent asthma (1) - n=150 allergic rhinitis (2)</p> <p><u>Inclusion criteria:</u> (1): allergic asthma. Paediatrician using validated criteria (GINA). Consistent symptoms and signs, lung function impairment and BDR. BDR FEV1>12%. Allergy by SPT for common aeroallergens. (2): rhinitis. Paediatrician using validated criteria (GINA).</p> <p><u>Exclusion criteria:</u> Negative SPT Acute or chronic uRTI Anatomical or nasal disorders Previous or current immunotherapy Use of CS, nasal or oral vasoconstrictors, LABA anti-leukotrienes or antihistamines in previous 4 weeks.</p>	<p>56%/44%</p> <p><u>Median age:</u> (1) children 13 yrs (2) children 10 yrs</p>	<p>FeNO: chemiluminescence analyser; flow rate 50 ml/s. Sievers 280 device.</p> <p><u>Target condition</u> FeNO levels allergic asthma vs. rhinitis (separately)</p>	<p>1. Asthma allergic: 34 (29 - 381) ppb 2. Rhinitis: 27 (21 - 35)</p> <p>The median FeNO was SS higher in the allergic asthma vs. rhinitis group (p<0.001)</p>	<p><u>funding:</u> No sponsorship.</p> <p><u>Limitations:</u> -</p> <p><u>Additional data:</u> None</p>

Table 70: CORDEIRO 2011³⁶⁵

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments	
					Ref std +	Ref std -	Total		
<p>Cordeiro D, Rudolphus A, Snoey E, Braunstahl GJ. Utility of nitric oxide for the diagnosis of asthma in an allergy clinic population. Allergy and Asthma Proceedings. 2011; 32(2):119-126. (Guideline Ref ID CORDEIRO2011)</p> <p><u>Setting:</u> General outpatient allergy clinic</p> <p><u>Country:</u> The Netherlands</p> <p><u>Recruitment:</u> January 2007 to September 2007</p>	<p><u>Study type:</u> Cross-sectional observational study</p> <p><u>Data source:</u> Routine prospective database</p>	<p>N = 114</p> <p><u>Inclusion criteria:</u> New referrals to outpatient allergy clinic</p> <p><u>Exclusion criteria:</u> Patients using inhaled corticosteroids or oral corticosteroids within 6 weeks</p>	<p><u>Male:</u> <u>Female:</u> 43: 71</p> <p><u>Median age:</u> Asthma: 39 (range 7-83); non-asthma 38 (7-87)</p>	<p><u>Index test</u> FeNO: measured online at constant flow rate 50mL/s (Niox-Flex device) Optimal cut off 27ppb. Flow rate 50ml/s</p> <p><u>Reference standard</u> History of typical respiratory symptoms and FEV1 improvement >12% and >200mL with salbutamol 400µg or PC20 histamine ≤8mg/mL</p> <p>Time between index test and reference standard: within 6 weeks</p> <p><u>Target condition</u> Asthma diagnosis vs. non-asthma (Allergic rhinitis, non-allergic rhinitis, eczema, urticarial, other analysed all together); raw data calculated from sensitivity/ specificity</p> <p>FeNO levels: Asthma vs. Allergic rhinitis, non-allergic rhinitis, eczema, urticarial, other analysed all together Asthma vs. allergic rhinitis</p>				<p><u>Source of funding:</u> Not stated</p> <p><u>Limitations:</u> Unclear if pts treated with asthma medication apart from corticosteroids (steroid-naïve)</p> <p><u>Additional data:</u> None</p>	
					Index test +	33	6		39
					Index test -	9	66		75
					Total	42	72		114
					Sensitivity Specificity	78% 92%			
					PPV / NPV	86% / 87%			
					AUC	0.88			
					Median (range) FeNO levels: Asthma: 44 (6-290) ppb, n=42	Non-asthma (all diagnoses): 17 (5-45) ppb, n=72 p<0.001 Allergic rhinitis only (sub-group of above): 21 ppb, n=32 p<0.001			

Table 71: DEYKIN 2002⁴³³

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments	
					Ref std +	Ref std -	Total		
Deykin et al., 2002. Exhaled nitric oxide as a diagnostic test for asthma: online versus offline techniques and effect of flow rate. American Journal of Respiratory and Critical Care Medicine: 165: 1597-1601 REF ID: DEYKIN2002	<u>Study type:</u> Prospective case-control study <u>Data source:</u> Collected for study <u>Setting:</u> Pulmonary and Critical Care Division, Department of Medicine <u>Country:</u> US <u>Recruitment:</u> Not stated	N = 62 <u>Inclusion criteria:</u> <ul style="list-style-type: none"> • Adult nonsmokers with and without asthma • Those with asthma had a history of asthma, with either a 12% improvement in FEV1 after inhalation of a beta-agonist or a methacholine PC20 of 8 mg/ml or less • Those without asthma had no history of asthma, normal spirometry, and a methacholine PC20 more than 8 mg/ml. • Free of upper respiratory infection for at least 6 weeks <u>Exclusion criteria:</u> Systemic or inhaled corticosteroids used within 8 weeks	<u>Male: Female</u> 26:36 <u>Mean (SEM)</u> <u>age:</u> People with asthma (n=34) 29.6 (1.6) Healthy (n=28) 27.3 (1.3) Medications: No asthma medications except for short-acting bronchodilators, which were withheld for at least 8 hours before all testing	<u>Index test</u> FeNO: chemiluminescence analyser (NOA 280 Sievers device); triplicate recordings. <u>Target condition</u> FeNO levels asthma vs. healthy controls				<u>Source of funding:</u> Supported by the National Institutes of Health (P50-HL-56383) and an educational grant from Merck USHH <u>Limitations:</u> <u>Additional data:</u> Other flow rates reported but not relevant	
					Index test +	-	-		-
					Index test -	-	-		-
					Total	-	-		-
					Sensitivity		-		
					Specificity		-		
Various flow rates reported: 50ml/s: Asthma: 57.9 (6.5) Healthy: 26.3 (2.2); (p<0.001 for comparison)									

Table 72: FUKUHARA 2011⁵³⁵

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments				
					Ref st +	Ref st -	Total						
Fukuhara et al., 2011. Validation study of asthma screening criteria based on subjective symptoms and fractional exhaled nitric oxide. Annals of Allergy, Asthma and Immunology: 107: 480-486 REF ID: FUKUHAR A2011	<u>Study type:</u> Cross-sectional study <u>Setting:</u> Outpatients, Dept. of Pulmonary Medicine, University Hospital <u>Country:</u> Japan <u>Recruitment:</u> Not reported	N = 61 Adults <u>Inclusion criteria:</u> <ul style="list-style-type: none"> At least 1 of the subjective symptoms: recurrent cough, wheezing or dyspnoea (including chest tightness) <ul style="list-style-type: none"> <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Prior history of asthma Taking oral or inhaled steroids or anti-leukotriene agents 	<u>Male: Female</u> 31:30 <u>Mean age (range):</u> 55.6 (17-81) Medications: 6 current smokers and 13 former smokers	<u>Index test</u> FeNO level: measured using online method in accordance with American Thoracic Society/European Respiratory Society and a chemiluminescence analyser (NA623N, Chest MI, Japan). Information on the compatibility with other NO analysers provided. FeNO level measured 3 times with differences within 10%, mean of 3 measurements used. Flow rate 50ml/s. Cut-off: ≥40ppb <u>Comparator test</u> n/a <u>Reference standard</u> At least 2 of the following: induced sputum eosinophilia, airway hyperresponsiveness, reversible airway obstruction. Airway reversibility defined as a change in FEV1 of 200ml or ≥12% after short-acting β-agonist or after 2-4 weeks treatment with ICS or bronchodilator. Airway					<u>Source of funding:</u> Not reported <u>Limitations:</u> <ul style="list-style-type: none"> Consecutive or random recruitment not reported 97 patients with symptoms gave consent but 36 were unable to undergo testing (reasons not reported) <u>Additional data:</u>				
					Index test +	33	2	35					
					Index test -	9	17	26					
					Total	42	19	61					
					Sensitivity	78.6%							
					Specificity	89.5%							
					PPV	94.3%							
					NPV	65.4%							
					FeNO levels, mean (95% CI), ppb								
					Asthma 90.1 (65.9 -114.3)								
Non-asthma (with symptoms): 40.1 (21.8 – 58.5)													

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
				<p>hyperresponsiveness defined as dose of MCh at which airway resistance began to rise (cut-off <12.5U). And other diseases ruled out using chest radiography, computed tomography and other lab tests.</p> <p>Time between index test and reference standard: FeNO measured before other pulmonary function tests</p> <p><u>Target condition</u> Asthma</p>		

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Table 73: HEFFLER 2006⁶⁵⁷

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments			
Heffler E, Guida G, Marsico P, Bergia R, Bommarito L, Ferrero N et al.	<p><u>Study type:</u> Prospective study</p> <p><u>Data source:</u> Collected for study</p>	<p>N = 48 symptomatic + 30 healthy controls</p> <p><u>Inclusion criteria:</u> Patients referred to allergy department for diagnostic evaluation of</p>	<p><u>Male: Female</u> 21:27</p> <p><u>Mean age:</u> Asthma: 42.33 (range 17-69) yr; non-asthma: 38.73 (11-75) yr</p>	<p><u>Index test</u> FeNO: chemiluminescence analyser (Niox device); mouth pressure 10 cm H₂O; exhalation rate 50mL/s; mean of 3 recordings.</p> <p>Different cut offs used: optimal cut off for highest combination of</p>		<p><u>Source of funding:</u> Regione Piemonte-Ricerca Sanitaria Finalizzata 2003</p>			
							Ref std +	Ref std -	Total
					Index test +		14	12	26
					Index test -		4	18	22
Total	18	30	48						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
Exhaled nitric oxide as a diagnostic test for asthma in rhinitic patients with asthmatic symptoms . Respirator Y Medicine. 2006; 100(11):1981-1987. (Guideline Ref ID HEFFLER2006)	<u>Setting:</u> Allergy outpatients clinic	persistent rhinitis and asthma-like lower airways symptoms (cough, dyspnoea, chest tightness and wheezing) during the last 2 months		sensitivity and specificity was 36ppb <u>Reference standard</u> Typical symptoms and significant response to bronchodilator (≥12% improvement in FEV1 with salbutamol) or airway hyper-responsiveness to methacholine (PD20 FEV1 ≤800µg) Time between index test and reference standard: same time <u>Target condition</u> Asthma vs. no asthma (not meeting criteria for diagnosis of asthma but final diagnoses not reported); raw data calculated from sensitivity/specificity FeNO levels: asthma vs. no asthma (symptomatic) or healthy controls	Sensitivity	77.8%	<u>Limitations:</u> None
	Specificity				60.0%	<u>Additional data:</u> None	
	PPV / NPV				54.0% / 81.8%		Geometric mean (95% CI) FeNO levels: asthma 59.7 (50.2 to 89.0) ppb, n=18 Non-asthma (symptomatic): 30.4 (28.1 to 45.1) ppb, n=30, p=0.001 vs. asthma Healthy controls: 12.2 (11.1 to 15.1) ppb, n=30, p<0.001 vs. asthma
	Accuracy				66.67%		
	<u>Country:</u> Italy				AUC	0.78	
	<u>Recruitment:</u> Not stated	<u>Exclusion criteria:</u> Use of steroids or any other anti-inflammatory medications in last 2 months, current smoking (in previous 12 months), previous diagnosis of asthma, respiratory infection in last 6 weeks					

1 **Table 74: KOSTIKAS 2008⁹¹⁶**

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments	
Kostikas K, Papaioannou AI, Tanou K, Koutsoker	<u>Study type:</u> Prospective study	N = 149 symptomatic + 70 healthy controls	<u>Male: Female</u> 76: 73 symptomatic + 37:33 controls	<u>Index test</u> FeNO: exhalation flow rate 50mL/s (NIOX MINO device) Optimal cut off 19ppb		Ref std	Ref std	Total	<u>Source of funding:</u> Not stated
	+					-			
	<u>Data source:</u>	Subjects with at least						<u>Limitations:</u>	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments			
a A, Papala M, Gourgouli anis Kl. Portable exhaled nitric oxide as a screening tool for asthma in young adults during pollen season. Chest. 2008; 133(4):90 6-913. (Guideline Ref ID KOSTIKAS 2008)	<p>Collected for the study</p> <p><u>Setting:</u> University students</p> <p><u>Country:</u> Greece</p> <p><u>Recruitment:</u> Spring 2006</p>	<p>one asthma symptom on a screening questionnaire among students</p> <p><u>Exclusion criteria:</u> Previous diagnosis of asthma or rhinitis treated with anti-inflammatory medication (inhaled or nasal corticosteroids, long-acting β-agonists, leukotriene modifiers, antihistamines or methylexanthines); respiratory tract infection in past 6 weeks; recent smoking cessation (<2 months prior to study)</p>	<p><u>Mean age:</u> Asthma: 21.6 (2.7) yr; allergic rhinitis: 21.8 (3.0) yr; non-specific symptoms: 22.1 (3.1) yr; healthy controls: 21.4 (2.3) yr</p>	<p><u>Reference standard</u> History + significant bronchodilator reversibility, positive methacholine challenge test, or clinical or spirometric response to a 4-week trial of inhaled corticosteroids</p> <p>Time between index test and reference standard: same time</p> <p><u>Target condition</u> Asthma vs. Allergic rhinitis (raw data calculated from sensitivity/specificity)</p> <p>FeNO levels: Asthma vs. Allergic rhinitis or non-specific respiratory symptoms or healthy controls (separately)</p>	Index test +		Population symptomatic but had not presented to healthcare professionals			
					Index test -					
					Total					
					Sensitivity Specificity		Not used as calculated including healthy control group		<u>Additional data:</u> None	
					PPV NPV PLR NLR					
					AUC	0.544				
					Median (IQR) FeNO levels: Asthma: 20.0 (14.0 to 31.0), n=63	<p>Allergic rhinitis: 17.0 (12.5 to 23.0), n=57, p=0.28 vs. asthma</p> <p>Non-specific symptoms: 11.0 (8.5 to 12.5), n=29, p<0.0001 vs. asthma</p> <p>Healthy controls: 10.5 (7.0 to 13.0), n=70,</p>				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
					p<0.0001 vs. asthma	

Table 75: KOWAL 2009⁹²⁴

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments			
Kowal K, Bodzenta-Lukaszyk A, Zukowski S. Exhaled nitric oxide in evaluation of young adults with chronic cough. Journal of Asthma 2009; 46(7):692-698. (Guideline Ref ID KOWAL2009)	<u>Study type:</u> Prospective study	N = 540 symptomatic + 100 healthy controls	<u>Male:</u> Female Not stated	<u>Index test</u> FeNO: chemiluminescence analyser (NOA 280 Sievers device); fixed expiratory resistance 16cm H ₂ O; exhalation flow rate 50mL/s; mean of 3 recordings	Ref std +	<u>Source of funding:</u> Medical University of Bialystok <u>Limitations:</u> None <u>Additional data:</u> None			
	<u>Data source:</u> Collected for study	<u>Inclusion criteria:</u> Young adult patients with chronic cough (at least 8 weeks) referred to asthma clinic for evaluation	<u>Mean age:</u> Symptomatic: 26.5 (range 18-45) years; healthy controls: 24 (18-39) years	Optimal cut off 40ppb	Index test +		157	63	220
	<u>Setting:</u> Asthma clinic				Index test -		21	299	320
	<u>Country:</u> Poland	<u>Exclusion criteria:</u> Use of any anti-asthma medication, treatment with angiotensin converting enzyme inhibitors, use of codeine or other cough suppressant, upper respiratory tract infection within 4 weeks before study, presence of any systemic disease, contra-indications to			Total		178	362	540
	<u>Recruitment:</u> September 2000 to November 2006			<u>Reference standard</u> Significant diurnal changes in PEF or significant improvement of FEV1 with 200µg salbutamol over next 6 months	Sensitivity		88.3%		
				Time between index test and reference standard: up to 6 months	Specificity		82.6%		
				<u>Target condition</u> Asthma vs. Rhinitis/sinusitis or gastroesophageal reflux; raw data calculated from sensitivity/specificity	PPV		72.6%		
				FeNO levels: Asthma vs.	NPV		94%		
					PLR		5.08		
					NLR		0.14		
				AUC	0.924				
				Median (95% CI) FeNO levels: asthma: 86ppb (95% CI 72 to 94.5), n=178	Rhinitis/sinusitis: 37ppb (95% CI 35.6 to 42.9), n=211, p<0.0001 Gastroesophageal reflux: 14.8ppb (95% CI 13.3 to 16.2),				

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
		bronchial histamine test; people with seasonal allergies if cough appeared in pollen season or up to 4 weeks after the season		Rhinitis/sinusitis; gastroesophageal reflux; healthy controls (separately)		n=108, p<0.0001 vs. asthma Healthy controls: 13ppb (95% CI 11 to 15), n=100, p<0.0001 vs. asthma

Table 76: LOUHELAINEN 2008¹⁰⁴¹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments
Louhelainen N, Ryttilä P, Obase Y, Makela M, Haahtela T, Kinnula VL et al. The value of sputum 8-isoprostan e in detecting oxidative stress in mild asthma. Journal of	<u>Study type:</u> Prospective study	N = 37 asthma + 11 COPD + 28 healthy controls	<u>Male: Female</u> Asthma: 17:20 COPD: 7:4 Healthy controls: 11:17	<u>Index test</u> FeNO: chemiluminescence analyser (Niox device); exhalation flow rate 50mL/s; mean of 3 recordings	Ref std +	Ref std -	Total	<u>Source of funding:</u> Finnish Tuberculosis Association Foundation, funding of the Helsinki University Hospital (EVO), the Sigrid Juselius Foundation, the Ida Montin Foundation, an unrestricted research grant from GSK
	<u>Data source:</u> Collected for study	<u>Inclusion criteria:</u> Patients with newly-diagnosed asthma (wheezing, prolonged cough and shortness of breath plus significant bronchial reversibility i.e. reduction in post-exercise PEF and/or FEV1 ≥15% or improvement in FEV1 ≥12% after bronchodilator or PD15 of histamine	<u>Mean age:</u> Patients with asthma and healthy controls grouped by age (adult asthma mean 38 yr, range 16-72 yrs; adult control mean 40, range 19 to 56 yr; asthma child mean 10, range	<u>Reference standard</u> BDR ≥12%, Exercise challenge test ≥15% or histamine challenge test PD15 <0.4mg	Index test +	-	-	
	<u>Setting:</u> Division of Pulmonary Medicine			<u>Target condition</u> FeNO levels: Asthma vs. healthy controls (COPD not reported)	Index test -	-	-	
	<u>Country:</u> Finland				Total	-	-	
	<u>Recruitment:</u> Not stated				Sensitivity Specificity	-	-	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
Asthma. 2008; 45(2):149-154. (Guideline Ref ID LOUHELAI NEN2008 A)		<p><0.4mg or ≥20% diurnal variation in PEF values and/or ≥15% improvement in PEF after bronchodilator at home)</p> <p>COPD exacerbation</p> <p>Healthy controls</p> <p><u>Exclusion criteria:</u> Not stated</p>	7-14 yr; healthy child mean 11, range 8-14 yrs); COPD all adult (mean 72, range 54 to 85)		PPV	-	<p><u>Limitations:</u> None</p> <p><u>Additional data:</u> None</p>
					NPV		
					PLR		
					NLR		
					AUC	-	
					<p>Median FeNO levels:</p> <p>Asthma children: 35.5ppb, n unclear – between 19 and 23</p> <p>Asthma adults: 81.8ppb, n unclear – between 5 and 14</p>	<p>Healthy children: 11.9ppb, n unclear – between 9 and 13, p<0.001 vs. children with asthma</p> <p>Healthy adults: 16.6ppb, n unclear – between 6 and 15, p=0.025 vs. adults with asthma</p>	

Table 77: SATO 2008¹⁵¹⁵

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments	
					Ref std +	Ref std -	Total		
Sato S, Saito J, Sato Y, Ishii T, Xintao W, Tanino Y et al. Clinical usefulness of fractional exhaled nitric oxide for diagnosing prolonged cough. Respirator Y Medicine. 2008; 102(10):1452-1459. (Guideline Ref ID SATO2008)	<u>Study type:</u> Prospective	N = 71	<u>Male: Female</u> Bronchial asthma: 20:10	<u>Index test</u> FeNO: chemiluminescence analyser (Device from Kimoto, Japan - no further details given); exhalation flow rate 50mL/s; mouth pressure 16 cm H ₂ O; mean of 3 recordings				<u>Source of funding:</u> Not stated	
	<u>Data source:</u> Collected for study	<u>Inclusion criteria:</u> Prolonged cough or wheezing >3 weeks attending	Cough variant asthma: 7:11	Optimal cut off 38.8ppb	Index test +	38	2	40	<u>Limitations:</u> None
	<u>Setting:</u> Department of Pulmonary Medicine	Department of Pulmonary Medicine; age 20-78 years; no abnormalities on CXR or CT scan; no prior history of treatment for pulmonary disease; never used oral or inhaled corticosteroids	Eosinophilic bronchitis without asthma: 4:4		Index test -	10	21	31	
	<u>Country:</u> Japan		Others: 8:7		Total	48 (BA + CVA)	23 (EB + other)	71	<u>Additional data:</u> None
	<u>Recruitment:</u> January 2004 to January 2007	<u>Exclusion criteria:</u> None apart from above		<u>Reference standard</u> Bronchial asthma (BA): cough and wheezing for 3 weeks or longer, sputum eosinophilia and positive airway hyper-responsiveness (methacholine <12.5 units) or reversible airflow limitation (improvement in FEV1 of 200mL and ≥12% from baseline after salbutamol 200µg or long-acting β ₂ -agonist). Cough variant asthma (CVA): As above except without wheezing	Sensitivity	79.2%		Mean (95% CI) FeNO levels: Bronchial asthma: 93.5 (72.5 to 120.7) ppb, n=30, p=0.001 vs. CVA group, p<0.001 vs. EB group, p<0.001 vs. others Cough variant asthma: 46.7 (33.6 to 64.8) ppb, n=18, p<0.001 vs. EB	
			<u>Mean (95% CI) age:</u> Bronchial asthma: 55.5 (48.9 to 62.5)		Specificity	91.3%			
			Cough variant asthma: 48.2 (39.4 to 57.0)	Time between index test and reference standard: same time					
			Eosinophilic bronchitis without asthma: 45.3 (33.3 to 57.2)	<u>Target condition</u> Asthma group = bronchial asthma + cough variant asthma together; compared with non-asthma group = eosinophilic bronchitis without asthma (EB), post-infectious cough, post-nasal drip, COPD, chronic bronchitis, cough					
			Others: 55.5 (47.5 to 63.5)						

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
				<p>with GERD or sino-bronchial syndrome (i.e. one comparator group); raw data calculated from sensitivity/ specificity</p> <p>FeNO levels: Bronchial asthma and cough variant asthma (separately); compared with a) eosinophilic bronchitis without asthma, and b) other = post-infectious cough, post-nasal drip, COPD, chronic bronchitis, cough with GERD or sino-bronchial syndrome (i.e. two comparator groups)</p>	<p>group, p<0.001 vs. others</p>	

Table 78: SHIMODA 2013¹⁵⁸⁰

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments																								
Shimoda T, Obase Y, Kishikawa R, Iwanaga T, Miyatake A, Kasayama S. The fractional exhaled nitric oxide and	<p><u>Study type:</u> Prospective study, case-control</p> <p><u>Data source:</u> Collected for study</p> <p><u>Setting:</u> Department of respiratory</p>	<p>N = 90 cough variant asthma + 92 bronchial asthma + 90 healthy controls</p> <p><u>Inclusion criteria:</u> Both patients with cough variant asthma and bronchial asthma were to be free of attacks and newly diagnosed. The diagnoses of cough variant asthma</p>	<p><u>Male: Female</u> Bronchial asthma: 44:48 Cough variant asthma: 32:58 Controls: 47:43</p> <p><u>Mean age:</u> Bronchial asthma: 38.6 (13.8) yr Cough variant asthma: 44.7</p>	<p><u>Index test</u> FeNO: chemiluminescence analyser (NOA 280 Sievers device); mouth pressure 16 cm H₂O; flow rate 50mL/s; mean of 3 recordings</p> <p>Cut off: n/a (case-control study for levels only)</p> <p><u>Reference standard</u> Newly diagnosed asthma (bronchial or cough variant) using GINA guidelines: Cough variant asthma: chronic cough</p>	<table border="1"> <tr> <td></td> <td>Ref std +</td> <td>Ref std -</td> <td>Total</td> </tr> <tr> <td>Index test +</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Index test -</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Total</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Sensitivity</td> <td colspan="3"></td> </tr> <tr> <td>Specificity</td> <td colspan="3"></td> </tr> </table>		Ref std +	Ref std -	Total	Index test +				Index test -				Total				Sensitivity				Specificity				<p><u>Source of funding:</u> Not stated</p> <p><u>Limitations:</u> Patient groups not comparable at baseline</p> <p><u>Additional data:</u> None</p>
						Ref std +	Ref std -	Total																						
					Index test +																									
					Index test -																									
					Total																									
					Sensitivity																									
Specificity																														

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments
serum high sensitivity C-reactive protein levels in cough variant asthma and typical bronchial asthma. Allergology International. 2013; 62(2):251-257. (Guideline Ref ID SHIMODA 2013)	medicine <u>Country:</u> Japan <u>Recruitment:</u> Not stated	and bronchial asthma were based on the GINA guidelines Healthy subjects had no past history of asthma, atopic diseases, or other respiratory diseases and had no current respiratory symptoms <u>Exclusion criteria:</u> Treated with any type of steroid; concurrent hypertension, diabetes mellitus, hyperlipidaemia; cough too severe to measure bronchial hypersensitivity	(14.7) yr Controls: 37.4 (11.5) yr; p=0.004 between groups Symptom duration: bronchial asthma: 6.0 (8.8) yr; cough variant asthma: 2.5 (4.4) yr, p=0.001	persisting for longer than 8 weeks but without wheezing or dyspnoea; no past history of asthma or other respiratory diseases; wheeze or rhonchi not audible on chest auscultation; BHR to inhaled acetylcholine; bronchodilators effective against their coughs; normal chest radiograph results. Bronchial asthma: history of episodic dyspnoea, wheezing and cough; at least 15% reversibility in FEV1 after inhalation of 200 µg of salbutamol and/or BHR to acetylcholine. Time between index test and reference standard: n/a <u>Target condition</u> Bronchial asthma vs. cough variant asthma FeNO levels: Each type of asthma compared separately with healthy controls.	Mean (SD) FeNO levels: bronchial asthma: 92.6 (85.5) ppb, n=92, p<0.001 vs. controls	Healthy controls: 18.0 (6.4) ppb, n=90 Cough variant asthma: 35.6 (43.3) ppb, n=90, p<0.001 vs. bronchial asthma, p<0.001 vs. controls		

Table 79: SHOME 2006¹⁵⁸⁵

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments	
Shome GP, Starnes III	<u>Study type:</u> Prospective study	N = 19 asthma (11 mild; 8 moderate to severe) + 17 healthy	<u>Male: Female</u> Not stated	<u>Index test</u> FeNO: 10cm H2O resistance; flow rate 50mL/s (CLD 88sp, EcoPhysics)		Ref std	Ref std	Total	<u>Source of funding:</u> Department of
					Index	+	-	-	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments			
JD, Shearer M, Kennedy R, Way A, Arif A et al. Exhaled nitric oxide in asthma: Variability, relation to asthma severity, and peripheral blood lymphocyte cytokine expression. Journal of Asthma. 2006; 43(2):95-99. (Guideline Ref ID SHOME2006)	<u>Data source:</u> Collected for study <u>Setting:</u> Division of Allergy and Immunology <u>Country:</u> USA <u>Recruitment:</u> Not stated	controls <u>Inclusion criteria:</u> Patients with newly-diagnosed asthma (symptoms, signs and spirometry according to National Heart, Lung and Blood Institute) plus increase $\geq 12\%$ after albuterol 2.5mg; untreated at baseline <u>Exclusion criteria:</u> COPD, CF, lupus pneumonitis, sepsis, respiratory infection in previous 6 weeks, congestive heart failure, smoking, other systemic diseases with pulmonary symptoms	<u>Mean (SEM) age:</u> Mild asthma: 52.36 (17.10) yr; moderate to severe asthma: 38.25 (8.52) yr; controls: 38.71 (13.04) yr, mild vs. control: $p < 0.05$	device) <u>Reference standard</u> BDR $\geq 12\%$ <u>Target condition</u> FeNO levels: asthma vs. healthy controls. Patients with asthma grouped by mild versus moderate/severe disease	test +				Internal Medicine, Texas Tech University Health Sciences Center <u>Limitations:</u> Groups not comparable at baseline <u>Additional data:</u> None
					Index test -	-	-	-	
					Total	-	-		
					Sensitivity Specificity		-		
					Mean (SEM) FeNO levels: Moderate to severe asthma: 18.53 (2.00) ppb, $n=8$, $p < 0.001$ vs. controls Mild asthma: 6.27 (3.79) ppb, $n=11$, NS vs. controls MEDIAN OF BOTH ASTHMA = 24.8ppb Healthy controls: 5.90 (0.90) ppb, $n=17$				

Table 80: VOUTILAINEN 2013¹⁸⁷⁹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments
					Ref std +	Ref std -	Total	
Voutilainen M, Malmberg LP, Vasankari T, Haahtela T. Exhaled nitric oxide indicates poorly athlete's asthma. Clinical Respiratory Journal. 2013; 7(4):347-353. (Guideline Ref ID VOUTILAINEN2013)	<u>Study type:</u> Cross-sectional observational study <u>Setting:</u> Allergy and asthma clinic <u>Country:</u> Finland <u>Recruitment:</u> Not stated	N = 87 (study also included a group of elite athletes N=87, not included in this review) <u>Inclusion criteria:</u> Sedentary patients referred to an allergy and asthma clinic because of respiratory symptoms (cough, dyspnoea or wheeze) <u>Exclusion criteria:</u> History of sports at a competitive level	<u>Male:</u> <u>Female:</u> 26:61 <u>Mean age:</u> 23 (14-31) <u>Medications:</u> No subjects on ICS at the time of the study and beta-agonists withheld accordingly	<u>Index test</u> FeNO: measured using online single exhalation method recommended by ATS (Niox device) Cut off 30ppb. <u>Reference standard</u> Based on general guidelines including typical symptoms and the objective confirmation of variable airway obstruction documented in hospital records. Such evidence was based either on BDR ≥12%, PEFv ≥20%, BDR of PEF ≥15%, exercise challenge test ≥15% or BHR MCh PD20 or hist PD15 ≤0.4mg Time between index test and reference standard: 1 day <u>Target condition</u> Asthma FeNO levels: Asthma vs. non-asthma dx (final dx not stated)				<u>Source of funding:</u> Supported by the Vaino and Laina Kivi foundation (study sponsors did not have involvement in study design, collection, analysis or interpretation of data). <u>Limitations:</u> Random or consecutive recruitment of patients not stated <u>Additional data:</u> study also included a group of elite athletes N=87, not included in this review
					Index test +			
					Index test -			
					Total			
					Sensitivity		43%	
					Specificity		89%	
					PPV / NPV		-	
					AUC		0.79	
					FeNO levels: Asthma: 29.7ppb Non-asthma: 14.6ppb P<0.001			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
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Table 81: WOO 2012¹⁹³⁷

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments			
Woo SI, Lee JH, Kim H, Kang JW, Sun YH, Hahn YS. Utility of fractional exhaled nitric oxide (F(E)NO) measurements in diagnosing asthma. Respiratory Medicine. 2012; 106(8):1103-1109.	<u>Study type:</u> Prospective study <u>Data source:</u> Collected for study <u>Setting:</u> Department of Paediatrics <u>Country:</u> Korea <u>Recruitment:</u> Not stated	N = 245 <u>Inclusion criteria:</u> Children 8- 16 years old, presenting with non-specific respiratory symptoms e.g. cough, wheezing, shortness of breath, referred to paediatric outpatients for evaluation of asthma <u>Exclusion criteria:</u> Receiving inhaled short-acting β_2 agonist in previous 8 hours; receiving regular treatment with controller medications for 3	<u>Male: Female</u> Overall: 163:82 Atopic asthma: 92:37; atopic non-asthma: 42:18; non-atopic asthma: 20:18; non-atopic non-asthma: 9:9 <u>Mean age:</u> Atopic asthma: 11.7 (2.4) yr; atopic non-asthma: 12.6 (2.6) yr; non-atopic asthma: 11.6 (2.7) yr; non-atopic non-asthma 11.4 (2.0) yr	<u>Index test</u> FeNO: chemiluminescence (NIOX MINO device); flow rate 50mL/s; mean of 2 values. Optimal cut off 22ppb <u>Reference standard</u> History + reversible airflow obstruction ($\geq 12\%$ improvement in FEV1 with inhaled β -agonist) and/or airway hyper-responsiveness (methacholine PC20 ≤ 8 mg/mL) Time between index test and reference standard: same time <u>Target condition</u> Asthma vs. non-asthma (not airway hyper-responsiveness (cut off for	Total study population	Ref std +	Ref std -	Total	<u>Source of funding:</u> Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology <u>Limitations:</u> Unclear if treatment naive <u>Additional data:</u> None
					Index test +	95	10	105	
					Index test -	72	68	140	
					Total	167	78	245	
					Sensitivity		56.9%		
					Specificity		87.2%		
					PPV	90.5%			
NPV	48.6%								
PLR									
NLR									
Accuracy	64.5%								

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
(Guideline Ref ID WOO2012)		month or more before enrolment		methacholine PC20 of 8mg/mL) or reversible airflow obstruction (12% improvement in FEV1 with inhaled β-agonist); final diagnoses not stated. Asthma and non-asthma groups also sub-divided by atopic vs. non-atopic	AUC		0.76, p<0.001		
					Atopic only	Ref std +	Ref std -	Total	
					Index test +	93	9	102	
					Index test -	36	51	87	
					Total	129	60	189	
					Sensitivity		72.1%		
					Specificity		85.0%		
					PPV	91.2%			
					NPV	58.6%			
PLR									
NLR									
Accuracy									
AUC		0.85, p<0.001							
Geometric mean FeNO levels: asthma: 23.4 ppb (95% CI 20.9 to 26.2), n=167		Non-asthma: 12.6 ppb (95% CI 10.9 to 14.5), n=78, p<0.001							

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
					<p>Atopic asthma sub-group: 29.6 (26.6 to 32.8) ppb, n=129, p<0.001 vs. atopic non-asthma, non-atopic asthma and non-atopic non-asthma</p> <p>Non-atopic asthma sub-group: 10.6 (8.6 to 13.0) ppb, n=38</p>	<p>vs. asthma</p> <p>Atopic non-asthma sub-group: 13.6 (11.6 to 15.9) ppb, n=60, p<0.05 vs. non-atopic asthma and non-atopic no asthma</p> <p>Non-atopic non-asthma sub-group: 9.7 (7.1 to 13.3) ppb, n=18</p>

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Table 82: ZIETKOWSKI 2006A¹⁹⁸⁰

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
Zietkowski et al., 2006. Comparison of exhaled nitric oxide measurement	<p><u>Study type:</u> Case-control study</p> <p><u>Data source:</u> Collected for this study</p> <p><u>Setting:</u> Medical</p>	<p>N = 140 (inc. 39 healthy controls)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Steroid-naïve patients with mild to moderate asthma (56 allergic and 45 nonallergic) • Asthma Dx according to GINA • Stable condition free from 	<p><u>Male: Female</u> 57:83</p> <p><u>Mean () age:</u> Allergic asthma (n=56) 32 (12)</p> <p>Non-allergic</p>	<p><u>Index test</u> FeNO: chemiluminescence analyser; measurements were performed at an expiratory flow of 50 mL/s. Repeat measurements were performed until the 3 values agreed to within 10% of the mean. The mean value of the 3 measurements was recorded</p>	<p>FeNO levels</p> <p>Allergic asthma: 84.0±51.4 Non-allergic asthma: 45.8±32.6 MEDIAN OF BOTH ASTHMA = 64.9ppb</p> <p>Healthy controls: 12.9 ±4.6</p>	<p><u>Source of funding:</u> Not reported</p> <p><u>Limitations:</u></p> <p><u>Additional data:</u></p>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
<p>Backer V, Nepper-Christensen S, Ulrik CS, von Linstow ML, Porsbjerg C. Factors associated with asthma in young Danish adults. Ann Allergy Asthma Immunol. 2002 Aug;89(2):148-54.</p> <p>BACKER2002</p>	<p><u>Study type:</u> Cross-sectional</p> <p><u>Data source:</u> Registry</p> <p><u>Setting:</u> General population</p> <p><u>Country:</u> Denmark</p> <p><u>Recruitment:</u> Children and adolescents living in the area surrounding Rigshospitalet were drawn from the civil registration list who were born between 1969 and 1979.</p>	<p>N = 624</p> <p>103 people with asthma and 521 people who do not have asthma</p> <p><u>Inclusion criteria:</u> Children and adolescents</p> <p><u>Exclusion criteria:</u> Not to use theophylline or antihistamine for at least 24 hours before the test, not to use astemizole for 6 weeks before testing, oral beta-2-agonist for 12 hours before the tests. Pregnant women and breast feeding mothers were excluded from the histamine challenge and pregnant women did not undergo skin prick testing.</p>	<p><u>Male</u> N=279 <u>Female</u> N=345</p> <p><u>Age:</u> 19 to 29 years</p> <p><u>Severity of asthma:</u> Current asthma vs. those who do not have asthma.</p> <p><u>Current smokers:</u> 35 to 53%</p> <p><u>Current anti-asthma:</u> Inhaled or oral corticosteroid</p> <p><u>Drop-outs/missing values:</u> 940 were eligible; 624 participated.</p>	<p><u>Index test</u> Peripheral blood eosinophils</p> <ul style="list-style-type: none"> • Venous blood sample and put into a tube containing EDTA, and the number of eosinophil leukocytes was counted in billions per litre. <p><u>Reference standard</u> N/A</p> <p><u>Target condition</u> NA</p>	<p>Blood eosinophil count. (Factor associated with asthma in young adults). Billions per litre.</p>	<p>Non-asthma: 0.19 (0.1) versus. Asthma 0.26 (0.2)</p> <ul style="list-style-type: none"> • P<0.01 different between two groups. 	<p><u>Source of funding:</u> Danish Lung Association. Glaxo Wellcome and ALK-Abello.</p> <p><u>Limitations:</u> Overall - LOW/UNCLEAR RISK OF BIAS.</p> <p><u>Additional data</u> Those that had asthma had higher eosinophil counts.</p>

Table 84: HALVANI 2012⁶³⁴

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments			
Abolhasan Halvani, Fatemeh Tahghighi, and Hossein Hadi Nadooshan. Evaluation of correlation between airway and serum inflammatory markers in asthmatic patients. <i>Lung India</i> 29 (2):143-146, 2012. HALVANI 2012	<u>Study type:</u> Case-control	N = 98 (includes 37 healthy) <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Mild to moderate persistent asthma (GINA criteria) Non-smokers without history of RTI or exacerbation of asthma during previous 6 weeks. Healthy: no history of smoking, heart disease or other diseases; normal pulmonary function tests. <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Heart disease Diabetes Cancer Obesity Systemic inflammatory disorders. 	<u>Male: Female</u> 55%/45% <u>Mean age:</u> 37.8 years. <u>Diagnoses:</u> <ul style="list-style-type: none"> 1. Healthy controls: n=37 2. Asthma ICS user: n=31 3. Asthma non-ICS user: n=30. <u>Current smokers:</u> None reported. <u>Current anti-asthma Tx:</u> N=31 ICS users. <u>Drop-outs/missing values:</u> None reported.	<u>Index test</u> Peripheral blood eosinophils <ul style="list-style-type: none"> Not reported. CUT-OFF: N/A <u>Reference standard</u> N/A <u>Time between index test and reference standard:</u> N/A <u>Target condition</u> <ul style="list-style-type: none"> Asthma. 	Population (baseline)	Eosinophils, median No./μL	<u>Source of funding:</u> None reported. <u>Limitations:</u> Overall - LOW/UNCLEAR RIK OF BIAS. <u>Additional data:</u> N/A			
	<u>Data source:</u> Asthma pts from clinic – details not reported, and age and sex matched healthy controls.							<u>Setting:</u> Outpatients (secondary care).	<u>Healthy controls</u>	211
	<u>Country:</u> Iran							<u>Asthma – ICS user</u>	402	
	<u>Recruitment:</u> Not reported.							<u>Asthma – non-ICS user</u>	517	
					<ul style="list-style-type: none"> Asthma non-ICS user group: SS more PBE than asthma ICS users and healthy controls. 					

Table 85: HUNTER 2002⁷²¹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
C. J. Hunter, C. E. Brightling, G. Woltmann, A. J. Wardlaw, and I. D. Pavord. A comparison of the validity of different diagnostic tests in adults with asthma. <i>Chest</i> 121 (4):1051-1057, 2002. HUNTER 2002	<u>Study type:</u> Case-control	N = 110 (includes n=21 healthy controls)	<u>Male: Female</u> 47%:53%	<u>Index test</u> Peripheral blood eosinophils • Standard haematological techniques. CUT-OFF: N/A <u>Reference standard</u> N/A <u>Time between index test and reference standard:</u> N/A <u>Target condition</u> • Asthma. • Physician Dx based on clinical features and tests.	Population	Eosinophils, mean (SEM) %	<u>Source of funding:</u> None reported. <u>Limitations:</u> Overall - LOW/UNCLEAR RIK OF BIAS. <u>Additional data:</u> N/A
	<u>Data source:</u> Patients attending Dept of Respiratory medicine, staff, and volunteers.	<u>Inclusion criteria:</u> • Asthma: consistent clinical features, symptomatic, FEV1 >65% predicted, and one or more of other criteria. • Healthy controls: no symptoms suggesting past or current asthma, non-smokers. • Pseudoasthma: people referred to hospital with Dx of asthma by GP, clinical features considered atypical and symptoms not deteriorate upon withdrawal of Tx. Symptoms improved after Tx of underlying condition.	<u>Mean age:</u> 39 years (range 14-76). <u>Diagnoses:</u> • Asthma: n=69 • Pseudoasthma: n=20 • Healthy control: n=21		Healthy controls	1.9 (0.6)	
	<u>Setting:</u> Patients (secondary care) and general population.		<u>Current smokers:</u> 8%		Pseudoasthma	2.0 (0.3)	
	<u>Country:</u> UK		<u>Current anti-asthma Tx:</u> 28%. Mean Tx time = 2 years (0-29 yrs). <u>Drop-outs/missing values:</u> None reported.		Asthma	4.3 (0.6)	
	<u>Recruitment:</u> Dates not reported.	<u>Exclusion criteria:</u> None reported.			Test results for eosinophil vs. healthy controls: • Normal range = <6.3% • sens 21% (11-31) • spec 100 Most tests were less specific when the reference population consisted of people with pseudoasthma.		

Table 86: KHAKZAD 2009⁸⁵⁶

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments	
M. R. Khakzad, M. Mirsadraee, M. Sankian, A. Varasteh, and M. Meshkat. Is serum or sputum eosinophil cationic protein level adequate for diagnosis of mild asthma? <i>Iran.J.Allergy Asthma Immunol.</i> 8 (3):155-160, 2009. KHAKZAD 2009	<u>Study type:</u> Case-control <u>Data source:</u> Subjects with asthma and controls (no other details reported). <u>Setting:</u> Not reported. <u>Country:</u> Iran <u>Recruitment:</u> Not reported.	N = 62 (includes 12 healthy) <u>Inclusion criteria:</u> <ul style="list-style-type: none"> • Asthma: history of cough, dyspnoea, wheeze and airway hyperresponsiveness; symptoms increased during nights and some seasons; Spirometry showing obstructive pattern with >12% increase with bronchodilator or PC20 <8 mg/ml. • All were new cases or pts who had withheld their drugs for a long time. • Healthy: no history of asthma or other allergic disorders; PC20 >8 mg/ml. <u>Exclusion criteria:</u> <ul style="list-style-type: none"> • Healthy people with : evidence of peripheral blood eosinophilia, abnormal chest X-ray, history of smoking, systemic or ICS usage, recent infection. 	<u>Male: Female</u> 40%/60% <u>Mean age:</u> 39.5 years (range 9-76). <u>Diagnoses (GINA criteria):</u> <ul style="list-style-type: none"> • 1. Healthy controls: n=12 • 2. Asthma Mild intermittent: n=6. • 3. Asthma mild persistent: n=16. • 4. Asthma moderate persistent: n=13 • 5. Asthma severe: n=15 <u>Current smokers:</u> None reported. <u>Current anti-asthma Tx:</u> None reported. <u>Drop-outs/missing values:</u> None reported.	<u>Index test</u> Peripheral blood eosinophils <ul style="list-style-type: none"> • Automated cell counter (Sysmex). CUT-OFF: N/A <u>Reference standard</u> N/A <u>Time between index test and reference standard:</u> N/A <u>Target condition</u> <ul style="list-style-type: none"> • Asthma. 	Population (baseline) Healthy controls All asthma Asthma Mild intermittent Asthma mild persistent Asthma moderate persistent Asthma severe	Eosinophils, median % 1.2 1.0 2.0 3.6 3.2 3.2	<u>Source of funding:</u> Islamic Azad University. <u>Limitations:</u> Overall - LOW/UNCLEAR RISK OF BIAS. <u>Additional data:</u> N/A	
						• Asthma: SS higher PBE than healthy controls.		

Table 87: KOTANIEMI 2002⁹¹⁷

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Anne Kotaniemi-Syrjanen, Tiina M. Reijonen, Kaj Korhonen, and Matti Korppi. Wheezing requiring hospitalization in early childhood: predictive factors for asthma in a six-year follow-up. <i>Pediatr.Allergy Immunol.</i> 13 (6):418-425, 2002. KOTANIEMI 2002	<p><u>Study type:</u> Case series (prospective)</p> <p><u>Data source:</u> Prospective study: 6-year follow-up of children with infection-related wheeze; data used for 6 years only to see at 6 years the % who have asthma.</p> <p><u>Setting:</u> Outpatients (secondary care)</p> <p><u>Country:</u> Finland</p> <p><u>Recruitment:</u> 6 year follow-up data January to March 1999 (original baseline study December 1992-1993)</p>	<p>N = 82 (FINAL Dx: N=33 asthma; N=49 non-asthma)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Children from previous study who were available for follow-up. <p><u>Exclusion criteria:</u> None reported.</p>	<p><u>Male: Female</u> 74%:26%</p> <p><u>Median age:</u> 7.2 (5.6 - 8.8 years)</p> <p><u>Current smokers:</u> N/A</p> <p><u>Current anti-asthma Tx:</u> 30/33 asthma pts used cromones (n=18) or inhaled steroids (n=12) for maintenance medication for asthma.</p> <p><u>Drop-outs/missing values:</u> N=18 from the original 100</p>	<p><u>Index test</u> Peripheral blood eosinophils</p> <ul style="list-style-type: none"> Method not reported. <p>CUT-OFF: $\geq 0.45 \times 10^9/l$.</p> <p><u>Reference standard</u> Clinical Dx – clinical history and questionnaire (symptoms), and exercise challenge test (pulmonary testing before and after exercise using flow-volume spirometry and FEV₁ – positive = auscultatory wheezing post-exercise and/or $\geq 15\%$ fall in FEV₁).</p> <p>Asthma diagnosed if:</p> <ol style="list-style-type: none"> On continuous maintenance Tx-asthma suffered from repeated (≥ 2) episodes of wheezing and/or prolonged cough (≥ 4 wks) apart from infection during previous 12 months reported by parents. positive exercise challenge test. <p>Non-Asthma diagnosed if: wheezing or prolonged cough but negative exercise challenge OR positive exercise test but no asthma symptoms.</p> <p>Time between index test and reference standard: unclear</p> <p><u>Target condition:</u> Asthma.</p>	<p>Population</p> <p>False positives: 8, false negatives: 15, true positives: 18, true negatives: 41</p> <p>Sensitivity: 18/33 Specificity: 41/49 PPV: 18/26 (69% reported in the paper) NPV: 41/56</p>	<p>% with Eosinophil counts $\geq 0.45 \times 10^9/l$</p>	<p><u>Source of funding:</u> Ida Montin Foundation, Kerttu and kale Viik Fund, Kuopio University Hospital.</p> <p><u>Limitations:</u> Overall - LOW/UNCLEAR RISK OF BIAS.</p> <p><u>Additional data:</u> N/A</p>

Table 88: KROEGEL 1998⁹³⁰

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
C. Kroegel, M. Schuler, M. Forster, R. Braun, and P. R. Grahmann. Evidence for eosinophil activation in bronchiectasis unrelated to cystic fibrosis and bronchopulmonary aspergillosis: discrepancy between blood eosinophil counts and serum eosinophil cationic protein levels. <i>Thorax</i> 53 (6):498-500, 1998. KROEGEL 1998	<u>Study type:</u> Case-control	N = 56 (n=14 asthma) <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Proven or new bronchiectasis (persistent cough, recurrent pneumonias and frequent haemoptysis, large quantities of partially foul purulent sputum production, positive sputum cultures >3 years, and radiological evidence of bronchiectasis) COPD or asthma (diagnostic criteria previously published) All pts without clinical signs of current infectious exacerbation in previous 4 weeks Healthy controls – no pulmonary disease. No family history of similar lung disease. <u>Exclusion criteria:</u> <ul style="list-style-type: none"> None reported. 	<u>Male: Female</u> N=8/N=6	<u>Index test</u> Peripheral blood eosinophils <ul style="list-style-type: none"> Standard cytometry. CUT-OFF: N/A <u>Reference standard</u> N/A <u>Time between index test and reference standard:</u> N/A <u>Target condition</u> <ul style="list-style-type: none"> Allergic asthma. 	Population (baseline)	Eosinophils, median x10⁷/l	<u>Source of funding:</u> County of Thuringia, Germany. <u>Limitations:</u> Overall - LOW/UNCLEAR RISK OF BIAS. <u>Additional data:</u> N/A
	<u>Data source:</u> Consecutive pts with bronchiectasis, plus age and sex matched control groups (allergic asthma, COPD and healthy).		<u>Mean age:</u> 54.8 years (range 31-78).	<u>Standard cytometry.</u>	Healthy controls	10.1 (range 1.6-21.4)	
	<u>Setting:</u> Secondary care.		<u>Diagnoses:</u> <ul style="list-style-type: none"> 1. Healthy controls: n=14 2. Bronchiectasis: n=14 3. COPD: n=14 4. Allergic asthma: n=14. 	CUT-OFF: N/A	Bronchiectasis	10.2 (1.0-32.0)	
	<u>Country:</u> Germany		<u>Current smokers:</u> None reported.	<u>Reference standard</u> N/A	COPD	11.7 (range 0.6-31.5)	
	<u>Recruitment:</u> Jan 1992 – August 1994.		<u>Current anti-asthma Tx:</u> Not reported.	<u>Time between index test and reference standard:</u> N/A	Allergic asthma	30.5 (range 12.3-69.3)	
	<u>Drop-outs/missing values:</u> None reported.	<u>Target condition</u> <ul style="list-style-type: none"> Allergic asthma. 			<ul style="list-style-type: none"> Allergic asthma: SS more PBE than all other groups NS difference in PBE count between bronchiectasis and healthy controls or COPD. 		

Table 89: LABBE 2001⁹⁵⁴

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
A. Labbe, B. Aublet-Cuvelier, L. Jouaville, G. Beaugeon, L. Fiani, I. Petit, L. Ouchchane, and M. Doly. Prospective longitudinal study of urinary eosinophil protein X in children with asthma and chronic cough. <i>Pediatr.Pulmonol.</i> 31 (5):354-362, 2001.	<u>Study type:</u> Case-control	N = 143 (N=88 asthma, N=22 severe)	<u>Male: Female</u> 64%/36%	<u>Index test</u> Peripheral blood eosinophils • Method not reported. CUT-OFF: N/A <u>Reference standard</u> N/A <u>Time between index test and reference standard:</u> N/A <u>Target condition</u> • Asthma.	Population (baseline)	Eosinophils, median x10 ⁹ /L	<u>Source of funding:</u> Pharmacia.
	<u>Data source:</u> Children seen in outpts by paediatric pulmonologist . <u>Setting:</u> Outpatients (secondary care). <u>Country:</u> France <u>Recruitment:</u> Feb 1997- March 1999.	<u>Inclusion criteria:</u> • Asthma: a) recent onset, not receiving any Tx except B-2 agonists if needed. b) severe asthma, taking ICS regularly for at least 12 months. • Healthy: admitted to dept for non-infectious, non-respiratory disorder. No history of asthma or atopic disease. • Chronic cough: referred for chronic cough (>3months duration/year), or recurrent cough (>3 episodes/year, each lasting >15 days). Experienced no episodes of wheezing or dyspnoea.	<u>Mean age:</u> 7.0 years (range 1.1 - 16.5). <u>Diagnoses (GINA criteria):</u> • 1. Healthy controls: n=34. • 2. Chronic cough: n=21. • 3. Asthma: n=88 <u>Current smokers:</u> N/A. <u>Current anti-asthma Tx:</u> Some pts.	<u>Healthy controls</u> 0.25	<u>Chronic cough</u> 0.21	<u>Asthma</u> 0.40	<u>Limitations:</u> Overall - LOW/UNCLEAR RIK OF BIAS. <u>Additional data:</u> N/A
LABBE 2001		<u>Exclusion criteria:</u> • None reported.	<u>Drop-outs/missing values:</u> None reported.				

Table 90: METSO 2000¹¹³⁹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Metso T, Kilpiö K, Björkstén F, Kiviranta K, Haahtela T. Detection and treatment of early asthma. Allergy. 2000 May;55(5):505-9. METSO 2000	<p><u>Study type:</u> Case-control study (pt groups within this were randomly assigned to Tx groups for 6 weeks)).</p> <p><u>Data source:</u> Hospital staff recruited patients</p> <p><u>Setting:</u> Hospital</p> <p><u>Country:</u> Finland</p> <p><u>Recruitment:</u> 80 consecutive patients</p>	<p>N = 190 (N=30 control and N=160 asthma – N=39 budesonide, N=39 terbutaline).</p> <p><u>Inclusion criteria:</u> Subjective symptoms for <1 year. At least one of the following lung-function test outside the reference range: FEV1 improvement >15% after inhaled beta2 agonist PEF diurnal variation >15% and PEF increase of >15% after inhaled beta2-agonist at least once during a 2 week period</p> <p><u>Exclusion criteria:</u> treatment with anti-inflammatory medication, lung diseases other than asthma, and respiratory tract infection in the previous 4 weeks. Past and present long-term respiratory diseases including asthma, respiratory tract infections and preceding 4 weeks and hyper responsiveness to histamine.</p>	<p><u>Male: Female</u> Budesonide 32/7 Terbutaline 31/10 Controls 28/2</p> <p><u>Age:</u> 16-60</p> <p><u>Severity of asthma:</u> Mild/Moderate Budesonide 31/8 Terbutaline 30/11 Controls 0/0</p> <p><u>Current smokers:</u> Budesonide 14 Terbutaline 9 Controls 0</p> <p><u>Current a-asthma Tx:</u></p> <p><u>Drop-outs/missing values:</u> NA</p>	<p><u>Index test</u> Peripheral blood eosinophils</p> <p>CUT-OFF: NA</p> <p><u>Reference standard</u> N/A</p> <p><u>Target condition</u> <u>NA</u></p>	<p>Blood eosinophils 10⁹/L</p>	<p>Control: 0.13</p> <p><u>Budesonide group:</u> Pre-Tx:0.20 Post-Tx (6 wks): 0.11**</p> <p><u>Terbutaline group</u> Pre-Tx: 0.16 Post-Tx (6 wks): 0.14</p> <p>Post-Tx (6 wks terbutaline + 2 ks budesonide): 0.12**</p> <p>** p<0.05 vs baseline</p>	<p><u>Source of funding:</u> Research institute of Helsinki University Central Hospital and the Finnish Allergy Research Foundation.</p> <p><u>Limitations:</u> Overall - LOW/UNCLEAR RISK OF BIAS.</p> <p><u>Additional data:</u> N/A</p>

Table 91: NORDLUND 2012¹²⁵⁷

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
<p>Nordlund B, Konradsen JR, Kull I, Borres MP, Önell A, Hedlin G, Grönlund H. IgE antibodies to animal-derived lipocalin, kallikrein and secretoglobulin are markers of bronchial inflammation in severe childhood asthma. Allergy. 2012 May;67(5):661-9.</p> <p>NORDLUND 2012</p>	<p><u>Study type:</u> Case-series</p> <p><u>Data source:</u> Hospital based paediatric clinics</p> <p><u>Setting:</u> Outpatients (secondary care)</p> <p><u>Country:</u> Denmark</p> <p><u>Recruitment:</u> Hospital based paediatric clinics</p>	<p>N = 39 (mild to moderate)</p> <p><u>Inclusion criteria:</u> Children from 7 to 18 years of age with diagnosed asthma according to the Global initiative for asthma (GINA). At least 6 months of regular treatment with ICS, min 800 microgram of budesonide or equivalent for problematic severe asthma and 100-400 microgram budesonide or equivalent for children with mild to moderate asthma. Physician diagnosed asthma.</p> <p><u>Exclusion criteria:</u> children with lung or neurological diseases, as well as those born prematurely (gestational age <36 weeks) were excluded.</p>	<p><u>Male:female</u> 59: 41</p> <p><u>Age:</u> 13.8±2.9 years</p> <p><u>Severity of asthma:</u> Controlled mild to moderate. And severe patients were included.</p> <p><u>Current smokers:</u> 35 to 53%</p> <p><u>Current anti-asthma</u> Inhaled or oral corticosteroid</p> <p><u>Drop-outs/missing values:</u> Unclera</p>	<p><u>Index test</u> Peripheral blood eosinophils</p> <ul style="list-style-type: none"> • Venous blood sample and the number of eosinophil were measured. <p><u>Reference standard</u> N/A</p> <p><u>Target condition</u> NA</p>	<p>Blood count of eosinophils ($10^9 \times 1^{-1}$, mean SD)</p>	<ul style="list-style-type: none"> • Mild to moderate asthma 0.25± 0.19 	<p><u>Source of funding:</u> Freemason Child House Foundation Swedish Asthma and Allergy Associations Research Fund and Swedish Heart and Lung Foundation</p> <p><u>Limitations:</u> Overall - LOW/UNCLEAR RISK OF BIAS.</p> <p><u>Additional data:</u> N/A</p>

Table 92: PIIPPOSAVOLAINEN 2007¹³⁵⁸

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
E Piippo-Savolainen, S Remes, and M Korppi. Does blood eosinophilia in wheezing infants predict later asthma? A prospective 18-20-year follow-up. <i>Allergy Asthma Proc.</i> 28 (2):163-169, 2007. PIIPPOSAVOLAINEN 2007	<p><u>Study type:</u> Case-series (prospective)</p> <p><u>Data source:</u> Infants hospitalised for bronchiolitis.</p> <p><u>Setting:</u> Hospital (secondary care).</p> <p><u>Country:</u> Finland.</p> <p><u>Recruitment:</u> 1981-1982.</p>	<p>N = 83</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Infants (<2 years) hospitalised for bronchiolitis • Bronchiolitis: respiratory wheezing and/or prolonged expirum during lower respiratory infection. <p><u>Exclusion criteria:</u> None reported.</p>	<p><u>Male: Female</u> Not reported.</p> <p><u>Mean age:</u> <2 years (mean or range not given).</p> <p><u>Diagnoses:</u> N/A at baseline.</p> <p><u>Current smokers:</u> N/A</p> <p><u>Current anti-asthma Tx:</u> Not reported.</p> <p><u>Drop-outs/missing values:</u> None reported.</p>	<p><u>Index test</u> Peripheral blood eosinophils</p> <ul style="list-style-type: none"> • Fuchs-Rosenthal counting chamber. <p>CUT-OFF: N/A</p> <p><u>Reference standard</u> N/A</p> <p><u>Time between index test and reference standard:</u> N/A</p> <p><u>Target condition</u></p> <ul style="list-style-type: none"> • Asthma 	<p>BASELINE VALUES Population: wheezing</p> <p>Wheezing (all 83 pts)</p>	<p>Eosinophils, median (25th-75th percentile) counts</p>	<p><u>Source of funding:</u> None reported.</p> <p><u>Limitations:</u> Overall - LOW/UNCLEAR RIK OF BIAS.</p> <p><u>Additional data:</u> N/A</p>
						<p>0.1 x 10⁹/L (0.028 – 0.321)</p>	

Table 93: POPOVIC 2002¹³⁸¹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
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Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Asthma	Ref std +	Ref std -	Total	
<p>S. Popovic-Grle, M. Mehulic, F. Pavicic, I. Babic, and Z. Beg-Zec. Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. <i>Coll. Antropol.</i> 26 Suppl:119-127, 2002.</p> <p>POPOVIC 2002</p>	<p><u>Study type:</u> Diagnostic Cross-sectional study</p> <p><u>Data source:</u> Outpatients with dyspnoea, treated for breathlessness; referred by GP due to suspected asthma.</p> <p><u>Setting:</u> Outpatients (secondary care)</p> <p><u>Country:</u> Croatia</p> <p><u>Recruitment:</u> Not reported</p>	<p>N =195 (FINAL Dx: N=141 asthma, N=17 COPD, N=29 rhinitis/sinusitis, N=8 unsolved so further examined)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> Outpatients treated for breathlessness <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> None reported. 	<p>ASTHMA pts</p> <p><u>Male:</u> Female 48%:52%</p> <p><u>Mean age:</u> 39 years</p> <p><u>Current smokers:</u> 20%</p> <p><u>Current anti-asthma Tx:</u> Not mentioned</p> <p><u>Drop-outs/missing values:</u> None</p>	<p><u>Index test</u> Peripheral blood eosinophils</p> <ul style="list-style-type: none"> Method not mentioned <p>CUT-OFF: positive = not reported.</p> <p><u>Reference standard</u> Physician Dx (pulmonologist)</p> <p>Based on questionnaire (medical history of occasional asthma attacks with wheezing and nocturnal waking due to dyspnoea), and on the basis of bronchodilation test (reversible obstruction) with salbutamol.</p> <p>Time between index test and reference standard: unclear</p> <p><u>Target condition</u> Asthma. N=141 were people with diagnosed asthma.</p>	Asthma	Ref std +	Ref std -	Total	<p><u>Source of funding:</u> Not reported.</p> <p><u>Limitations:</u> Overall - LOW/UNCLEAR RIK OF BIAS.</p> <p><u>Additional data:</u> N/A</p>
					Eosin +	21	33	54	
					Eosin -	120	21	141	
					Total	141	54	195	
					Sensitivity	15% (21/141)			
					Specificity	39% (21/54)			
					PPV	64% (21/33)			
					NPV	74% (120/162)			
					PLR and NLR	-			
					AUC	-			
% eosinophils in asthma pts, mean (SD)	-		Not reported						

Table 94: POSTMA 1995¹³⁸⁵

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Asthma	Ref std +	Ref std	Total	
D. S. Postma and M. D. Lebowitz. Persistence and new onset of asthma and chronic bronchitis evaluated longitudinally in a community population sample of adults. <i>Arch. Intern. Med.</i> 155 (13):1393-1399, 1995. POSTMA 1995	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Adults from an epidemiologic study of obstructive airway disease. <u>Setting:</u> General population <u>Country:</u> USA <u>Recruitment:</u> Original study: 1972-1985	N =2169 (N=2130 had Dx data) (FINAL Dx: N=345 any asthma, N=303 emphysema and/or chronic bronchitis, N=124 Low 1 st FEV1, N=1358 none) <u>Inclusion criteria:</u> Age ≥20 years <u>Exclusion criteria:</u> None reported.	Reported in a separate publication (Lebowitz 1989) <u>Male: Female</u> - <u>Mean age:</u> Adults (details not reported) <u>Current smokers:</u> - <u>Current anti-asthma Tx:</u> - <u>Drop-outs/missing values:</u> -	<u>Index test</u> Peripheral blood eosinophils Stained slides counted from the 1st and 6 th surveys. CUT-OFF: eosinophilia (positive) = ≥5% 1st survey, or ≥3% 6 th survey. Based on distribution of all values in either survey. <u>Reference standard</u> Physician Dx Based on questionnaire (symptoms) and clinical evaluations (including FVC, and reversibility of airways obstruction (FEV1 before and after 5 mins after inhalation of 2 puffs of isoproterenol hydrochloride from a metered dose inhaler). Time between index test and reference standard: unclear <u>Target condition</u> Asthma. N=345 were people with diagnosed asthma.	Asthma	Ref std +	Ref std	Total	<u>Source of funding:</u> Dutch Asthma fund and National Heart, Lung and Blood Institute, USA. <u>Limitations:</u> Overall - LOW/UNCLEAR RISK OF BIAS. <u>Additional data:</u> N/A
					Eosin +	103	-	-	
					Eosin -	242	-	-	
					Total	345	1989	2130	
					Sensitivity		30% (103/345)		
					Specificity		-		
					PPV		-		
					NPV		-		
					PLR and NLR		-		
					AUC		-		
% eosinophils in asthma pts, mean (SD)		Not reported							

Table 95: RYTILA 2000¹⁴⁹⁶

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments	
P. Ryttila, T. Metso, K. Heikkinen, P. Saarelainen, I. J. Helenius, and T. Haahtela. Airway inflammation in patients with symptoms suggesting asthma but with normal lung function. <i>Eur.Respir.J.</i> 16 (5):824-830, 2000. RYTILA 2000	<u>Study type:</u> Case-control	N = 68 (includes n=43 healthy controls)	<u>Male: Female</u> 41%: 59%	<u>Index test</u> Peripheral blood eosinophils <ul style="list-style-type: none"> Method not reported. 	Population (baseline)	Eosinophils mean x10 ⁹ /l	<u>Source of funding:</u> None reported. <u>Limitations:</u> Overall - LOW/UNCLEAR RISK OF BIAS. <u>Additional data:</u> N/A	
	<u>Data source:</u> Consecutive pts with respiratory symptoms, and healthy controls.		<u>Inclusion criteria:</u> <ul style="list-style-type: none"> Pts with respiratory symptoms suggestive of asthma. At least 2/6 respiratory symptoms for >2 months and <1 year. Healthy – no respiratory symptoms or history of chronic pulmonary diseases. 	<u>Mean age:</u> 37.7 years (range 15-75).	CUT-OFF: N/A	Healthy controls		0.11
	<u>Setting:</u> Outpatients (secondary care).		<u>Exclusion criteria:</u> <ul style="list-style-type: none"> Pts treated with anti-inflammatory asthma medication. Pts or healthy pple who had clinically diagnosed respiratory infection 8 wks before study. Pts who had used histamine H2 blockers. 	<u>Diagnoses:</u> <ul style="list-style-type: none"> 1. Healthy controls (normal lung function tests): n=43 2. Respiratory symptoms (no significant airflow variability, and not hyperresponsive): n=36 3. Asthma (FEV1 increase ≥12% 15 mins after SABA, or PEF varied by >12% from morning to evening for ≥3 days during 2-week follow-up. Had increased bronchial responsiveness to inhaled histamine): n=25 	<u>Reference standard</u> N/A	Respiratory Symptoms		0.17
	<u>Country:</u> Finland		<u>Recruitment:</u> Oct 1996- March 1997.	<u>Current smokers:</u> 31% <u>Current anti-asthma Tx:</u> Not reported.	<u>Time between index test and reference standard:</u> N/A	Asthma		0.41
				<u>Drop-outs/missing values:</u> None reported.	<u>Target condition</u> <ul style="list-style-type: none"> Asthma. 	Atopic asthma		0.51
								Non-atopic asthma

Table 96: SHIELDS 1999¹⁵⁷⁹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Shields MD, Brown V, Stevenson EC, Fitch PS, Schock BC, Turner G, Taylor R, Ennis M. Serum eosinophilic cationic protein and blood eosinophil counts for the prediction of the presence of airways inflammation in children with wheezing. Clin Exp Allergy. 1999 Oct;29(10):1382-9. SHIELDS1999	<u>Study type:</u> Cross sectional study <u>Data source:</u> Wheezing children undergoing an elective surgical procedure for a non-inflammatory condition at the Hospital <u>Setting:</u> Hospital <u>Country:</u> Northern Ireland <u>Recruitment:</u> -	N = 137 <u>Inclusion criteria:</u> <ul style="list-style-type: none"> History of wheezing in the previous year Free from recent respiratory infection. <u>Exclusion criteria:</u> Alternative causes of wheezing.	Male N=48 Female N=29 <u>Age:</u> 1-15 years (mean not reported) <u>Severity of asthma:</u> Atopic asthma <u>Current smokers:</u> N/A <u>Current anti-asthma Tx:</u> 43 were taking anti-inflammatory therapy, however there was no effect on blood eosinophil counts. <u>Drop-outs/missing values:</u>	<u>Index test</u> blood eosinophils <ul style="list-style-type: none"> Blood sample taken pre-surgery. Eosinophil counts obtained from blood smears by routine methods. CUTOFF positive = 4% and 8% (elevated). <u>Reference standard</u> Physican Dx Detailed asthma and allergy history. Diagnoses: 1. Atopic asthma – symptoms triggered by known aeroallergens, who had other personal atopic features, strong family background of atopy or elevated serum IgE compared to normal values. 2. Viral-associated wheezing – no personal or family background of atopy, wheezing predominantly in winter and solely in association with viral upper RTI. <u>Target condition</u> Asthma (N=60 atopic asthma diagnosed).	Blood eosinophil % Area under curve for predicting airways inflammation Blood eosinophils >4% >8%	All patients N=77 4 (0-25) People with atopic asthma n=60 4.10 (1-25) Log serum ECP concentration = 0.75 Log blood eosinophil % = 0.76 >4% Sensitivity 62% Specificity 67% PPV % 56% PLR 1.9 >8% Sensitivity 38% Specificity 93% PPV % 78% PLR 5.4	<u>Source of funding:</u> National Asthma Campaign and the Northern Ireland Chest Heart and Stroke Association. <u>Limitations:</u> Overall - LOW/UNCLEAR RIK OF BIAS. <u>Additional data:</u> Serum eosinophil percentages in BAL and blood were lowest (NS) when last symptoms occurred more than 12 weeks previously

Table 97: SILVESTRI 2001A¹⁶⁰⁰

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes		Comments	
						Eosinophils, % and median (IQR)			
M. Silvestri, F. Sabatini, D. Spallarossa, L. Fregonese, E. Battistini, M. G. Biraghi, and G. A. Rossi. Exhaled nitric oxide levels in non-allergic and allergic mono- or polysensitised children with asthma. <i>Thorax</i> 56 (11):857-862, 2001. SILVESTRI 2001A	<p><u>Study type:</u> Case-control</p> <p><u>Data source:</u> Children with asthma referred to outpatient department.</p> <p><u>Setting:</u> Outpatients (secondary care)</p> <p><u>Country:</u> Italy</p> <p><u>Recruitment:</u> Dates not reported.</p>	<p>N = 112 (N=26 additional healthy controls, but data not given).</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Children • History of mild asthma • Positive response to methacholine challenge • Stable clinical condition • Not taken inhaled steroids at least in the year before the study <p><u>Exclusion criteria:</u> None reported.</p>	<p><u>Male: Female</u> 58%:42%</p> <p><u>Mean age (SD):</u> 10.6 (0.3), range 0-18 years.</p> <p><u>Types of asthma:</u></p> <ul style="list-style-type: none"> • Non-allergic: n=56 • Sensitised: n=56 <ul style="list-style-type: none"> ○ Monosensitised (dust mites): n=23 ○ Polysensitised (dust mites and at least one other allergen class): n=33 <p><u>Current smokers:</u> N/A</p> <p><u>Current anti-asthma Tx:</u> None reported.</p> <p><u>Drop-outs/missing values:</u> None reported.</p>	<p><u>Index test</u> Peripheral blood eosinophils</p> <ul style="list-style-type: none"> • Technicon H6000. <p>CUT-OFF: N/A</p> <p><u>Reference standard</u> N/A</p> <p><u>Time between index test and reference standard:</u> N/A</p> <p><u>Target condition</u> Asthma.</p>	Population: asthma	Eosinophils, % and median (IQR)		<p><u>Source of funding:</u> None reported.</p> <p><u>Limitations:</u> Overall - LOW/UNCLEAR RISK OF BIAS.</p> <p><u>Additional data:</u> N/A</p>	
						All allergic	7.5 (5.0-11.8)		500 (370-855)
						Mono-sensitised	6.9 (5.3-13.7)		500 (370-893)
						Poly-sensitised	8.3 (4.9-10.0)		500 (263-750)
						Non-allergic	2.5 (1.6-4.2)		125 (100-300)
<p>Children with allergic asthma had SS higher blood eosinophilia - % and absolute numbers:</p> <ul style="list-style-type: none"> • median difference %: 4.6, 95% CI 3.2-5.9; p=0.0001 • median difference cells/mm³: 375, 95% CI 237.9 – 512.1, p=0.0001 <p>There was NS difference between mono- and poly-sensitised children (p>0.1).</p>									

Table 98: SILVESTRI 2003¹⁶⁰³

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
M Silvestri, F Sabatini, R Sale, AC Defilippi, L Fregonese, E Battistini, MG Biraghi, and GA Rossi. Correlations between exhaled nitric oxide levels, blood eosinophilia, and airway obstruction reversibility in childhood asthma are detectable only in atopic individuals. <i>Pediatr.Pulmonol.</i> 35 (5):358-363, 2003. SILVESTRI 2003	<u>Study type:</u> Case-control	N = 92	<u>Male: Female</u> 65%:35%	<u>Index test</u> Peripheral blood eosinophils • Technicon H6000.	Population: asthma	% eosinophils, Median (IQR) %	<u>Source of funding:</u> None reported.
	<u>Data source:</u> Children with atopic asthma and age/gender matched children with non-atopic asthma referred to outpatient department.	<u>Inclusion criteria:</u> • Children • History of mild asthma • Atopic or non-atopic • Not have upper or lower RTIs 2 months before study	<u>Mean age (SD):</u> 10.7 (0.3) years.	<u>CUT-OFF:</u> N/A	All	5.5 (3.0-9.8)	<u>Limitations:</u> Overall - LOW/UNCLEAR RIK OF BIAS.
	<u>Setting:</u> Outpatients (secondary care)	• Atopic or non-atopic • Not taken anti-asthma Tx (except for β_2 -agonists as necessary – which were avoided 12hrs before study).	<u>Types of asthma:</u> • Atopic: n=66 • Non-atopic: n=26	<u>Reference standard</u> N/A	Atopic	6.7 (4.6-10.7)	<u>Additional data:</u> N/A
	<u>Country:</u> Italy	• Not taken anti-asthma Tx (except for β_2 -agonists as necessary – which were avoided 12hrs before study).	<u>Current smokers:</u> N/A	<u>Time between index test and reference standard:</u> N/A	Non-atopic	3.0 (1.8-4.3)	
<u>Recruitment:</u> Dates not reported.	<u>Exclusion criteria:</u> None reported.	<u>Current anti-asthma Tx:</u> None reported.	<u>Target condition</u> • Asthma. • Atopic/non-atopic diagnosed according to SPT to common aeroallergens (those sensitised to pollen were tested outside of the pollen season)	Children with atopic asthma had SS higher blood eosinophilia than non-atopic (p=0.001).			
			<u>Drop-outs/missing values:</u> None reported.	Within the atopic group, there was NS difference between mono- and poly-sensitised children (p>0.05).			

Table 99: TILEMANN 2011¹⁷⁵⁶

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Asthma	Ref std +	Ref std -	Total	
L Tilemann, L Gindner, F Meyer, J Szecsenyi, and A Schneider. Differences in local and systemic inflammatory markers in patients with obstructive airways disease. <i>Prim. care respir. j.</i> 20 (4):407-414, 2011. TILEMANN 2011	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Consecutive pts with suspected obstructive airways disease (OAD). <u>Setting:</u> Primary care <u>Country:</u> Germany <u>Recruitment:</u> Dates not mentioned.	N = 210 (FINAL Dx: N=86 asthma, N=36 COPD, N=13 partial reversibility, N=75 No OAD) <u>Inclusion criteria:</u> <ul style="list-style-type: none"> • Pts presenting for first time to GP with complaints suggestive of OAD • Symptoms: dyspnoea, coughing and/or expectoration persisting for at least 2 months. <u>Exclusion criteria:</u> <ul style="list-style-type: none"> • Respiratory tract infections in the previous 6 weeks • Well-known contraindications for bronchodilator reversibility testing or bronchial provocation – pregnancy, untreated hyperthyroidism, unstable coronary artery disease, and cardiac arrhythmia. 	<u>Male: Female</u> 45%:55% <u>Mean age:</u> 49 years <u>Current smokers:</u> 39% <u>Current anti-asthma Tx:</u> 5.2% (inhaled corticosteroids) <u>Drop-outs/missing values:</u> <ul style="list-style-type: none"> • Eosinophils: N=13 • FeNO: N=54 Pts were instructed not to use any bronchodilator or inhaled steroid and to stop smoking 12 hrs before assessments.	<u>Index test. Peripheral blood eosinophils</u> <ul style="list-style-type: none"> • Flow cytometry (ADVIA system) OPTIMAL CUT-OFF: positive = 4.15%. <u>Reference standard</u> Bronchodilation test (salbutamol) Pts with FEV ¹ <80% predicted received BDT with additional whole body plethysmography 20 mins after inhaling 400µg salbutamol. If no obstruction in the first lung function test, a BPT with methacholine was performed. Diagnoses: <ul style="list-style-type: none"> • COPD (irreversible OAD): FEV1 <12% and <200mL compared to baseline,). • Asthma: (fully reversible OAD): reversibility in FEV1 >12% and >200mL 	Eosin +	-	-	-	<u>Source of funding:</u> Federal Ministry of Education and Research, Germany. <u>Limitations:</u> Overall - LOW/UNCLEAR RISK OF BIAS. <u>Additional data:</u> N/A
					Eosin -	-	-	-	
					Total	86	124	210	
					Sensitivity	36%			
					Specificity	83%			
					PPV	59%			
					NPV	65%			
					PLR and NLR	-			
					AUC	0.602 (95% CI 0.50–0.68)			
					% eosinophils in asthma pts, mean (SD)	4.1 (3.1); 95% CI 3.3-4.7. Median 3.2			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
				<p>compared to baseline).</p> <p>Time between index test and reference standard: unclear</p> <p><u>Target condition</u> Asthma. N=86 were diagnosed with asthma.</p>			

Table 100: TOMASIAKLOZOWSKA 2012¹⁷⁷¹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
MM Tomasiak-Lozowska, Z Zietkowski, K Przeslaw, M Tomasiak, R Skiepkowski, and A Bodzenta-Lukaszyk. Inflammatory markers and	<u>Study type:</u> Case-control	110 (N=91 asthma) <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Asthma (mild allergic – all atopic and sensitised to common inhaled allergens by SPT). Healthy controls: 	<u>Male: Female:</u> 50%/50% <u>Mean age:</u> 38 years <u>Current smokers:</u> None. <u>Diagnoses (GINA criteria):</u> <ul style="list-style-type: none"> 1. Healthy controls: n=19. 2. Stable* asthma, steroid naïve (no ICS Tx in past 3 mths): n=22. 3. Stable* asthma, ICS Tx (mild to 	<u>Index test</u> Peripheral blood eosinophils <ul style="list-style-type: none"> Haematological analyser (Coulter). CUT-OFF: N/A	Population (baseline)	Eosinophils, mean cells/mm ³	<u>Source of funding:</u> Grant number given but details not specified. <u>Limitations:</u> Overall - LOW/UNCLEAR
	<u>Data source:</u> Pts and healthy volunteers.				Healthy controls	32.0	
	<u>Setting:</u> Not				Stable asthma (no ICS)	29.5	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments	
acid-base equilibrium in exhaled breath condensate of stable and unstable asthma patients. <i>Int.Arch.Allergy Immunol.</i> 159 (2):121-129, 2012. TOMASIAKLO ZOWSKA 2012	reported. <u>Country:</u> Poland. <u>Recruitment:</u> Not reported.	free of RTIs within past 3 months and other significant illness known to affect FeNO mmmts. <u>Exclusion criteria:</u> <ul style="list-style-type: none"> • Asthma exacerbation • Respiratory disease • Concomitant heart, renal, liver or collagen disease • RTI in the mouth. 	moderate, low to medium ICS dose at constant dose for ≥ 3 mths): n=35. <ul style="list-style-type: none"> • 4. Severe, unstable asthma, ICS Tx (required ≥ 1 hospitalisations for asthma and >3 oral steroid bursts in previous year. Taking high doses of ICS and LABA ≥ 6 mths): n=34. <p>*stable asthma = minimal need for rescue medication (SABA), no exacerbations and no use of systemic steroids in past 12 mths.</p> <p><u>Current anti-asthma Tx:</u> Mild to moderate asthma pts had been Tx with constant low to medium doses of ICS for ≥ 3 mths.</p> <p><u>Drop-outs/missing values:</u> None reported.</p>	<u>Reference standard</u> N/A <u>Time between index test and reference standard:</u> N/A <u>Target condition</u> <ul style="list-style-type: none"> • Asthma. 	Stable asthma (ICS)	42.4	RIK OF BIAS. <u>Additional data:</u> N/A	
						Unstable asthma (ICS)	49.8	
						No other details of results reported for eosinophil counts.		

1 **Table 101: TUCHINDA 1987¹⁷⁹⁷**

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
M. Tuchinda, S. Habananada, J. Vareenil, N. Srimaruta,	<u>Study type:</u> Case series (prospective) <u>Data source:</u>	N = 1000 measured for blood eosinophils (N=2000 whole study)	<u>Male: Female</u> 61%:39% <u>Age:</u> <13 years	<u>Index test</u> Peripheral blood eosinophils <ul style="list-style-type: none"> • Method not reported. <p>CUT-OFF: Not reported.</p>	Eosinophil counts (cells/mm³)	%	<u>Source of funding:</u> None reported.
					0 - 500	39.8	

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
and K. Piromrat. Asthma in Thai children: a study of 2000 cases. <i>Ann.Allergy</i> 59 (3):207-211, 1987.	Prospective study of 2000 children with asthma <u>Setting:</u> Outpatients (secondary care) <u>Country:</u> Thailand <u>Recruitment:</u> December 1972-1985	<u>Inclusion criteria:</u> • Age <13 years • Diagnosis of bronchial asthma. <u>Exclusion criteria:</u> None reported.	<u>Severity of asthma:</u> • Mild: 29% • Moderate: 61% • Severe: 9.6% <u>Current smokers:</u> N/A <u>Current anti-asthma Tx:</u> 7% previous CS treatment; and 23% had been hospitalised with asthma. <u>Drop-outs/missing values:</u> Not reported	<u>Reference standard :</u> N/A Time between index test and reference standard: unclear <u>Target condition</u> Asthma. 63% of pts had other allergic diseases.	501 - 1000 1001 - 1500 1501 - 2000 >2000	29.4 15.7 8.6 6.5	<u>Limitations:</u> Overall - LOW/UNCLEAR RISK OF BIAS. <u>Additional data:</u> N/A
TUCHINDA 1987							

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Table 102: VILA-INDURAIN 1999¹⁸⁶⁵

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
B. Vila-Indurain, F. Munoz-Lopez, and M. Martin-	<u>Study type:</u> Case-control <u>Data source:</u>	N = 57 (includes n=21 healthy controls)	<u>Male:</u> Female Not reported. <u>Mean age:</u>	<u>Index test</u> Peripheral blood eosinophils • Flow cytometry.	Population (baseline – pre BPT) Healthy controls	Eosinophils, mean (SD) Cells/mm³ 161 (77)	<u>Source of funding:</u> None reported. <u>Limitations:</u>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Mateos. Evaluation of blood eosinophilia and the eosinophil cationic protein (ECP) in the serum of asthmatic children with varying degree of severity. <i>Allergol.Immunopathol.(Madr)</i> . 27 (6):304-308, 1999. VILA-INDURAIN 1999	Selection of children with asthma and control healthy children. <u>Setting:</u> Not reported. <u>Country:</u> Spain <u>Recruitment:</u> Dates not reported.	<u>Inclusion criteria:</u> • Children age 8-18 years with asthma or healthy controls. <u>Exclusion criteria:</u> None reported.	Range 8-18 years. <u>Diagnoses:</u> • 1. Healthy controls (negative allergy and respiratory function tests): n=21 • 2. Asthma (favourably evolving, with normal FEV ₁): n=19 • 3. Asthma (below normal FEV ₁ that normalised with salbutamol): n=13 • 4. Asthma (below normal FEV ₁ that did not recover after bronchodilation test): n=14 <u>Current smokers:</u> N/A <u>Current anti-asthma Tx:</u> Not reported. <u>Drop-outs/missing values:</u> None reported.	<u>CUT-OFF:</u> N/A <u>Reference standard</u> N/A <u>Time between index test and reference standard:</u> N/A <u>Target condition</u> • Asthma.	1. Asthma – normal FEV ₁	509 (311)	Overall - LOW/UNCLEAR RIK OF BIAS. <u>Additional data:</u> N/A
					2. Asthma – below normal FEV ₁ normalised with SABA	397 (230)	
					3. Asthma – below normal FEV ₁ not normalise after SABA	319 (152)	

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Table 103: ZIETKOWSKI 2006A¹⁹⁸⁰

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Z. Zietkowski,	<u>Study type:</u>	140 (N=101 asthma)	<u>Male: Female</u>	<u>Index test</u>	Population	Eosinophils,	<u>Source of</u>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
A. Bodzenta-Lukaszyk, M. Tomasiak, R. Skiepmo, and M. Szmitkowski. Comparison of exhaled nitric oxide measurement with conventional tests in steroid-naive asthma patients. <i>J. Investig. Allergol. Clin. Immunol.</i> 16 (4):239-246, 2006. ZIETKOWSKI 2006A	Case-control <u>Data source:</u> Asthma pts and healthy volunteers. <u>Setting:</u> Not reported. <u>Country:</u> Poland. <u>Recruitment:</u> Not reported.	<u>Inclusion criteria:</u> <ul style="list-style-type: none"> Asthma: stable condition, free from acute exacerbations and RTIs in previous 2 mths. Healthy: FEV1 > 80% predicted. Free of RTIs for 2 mths before study and from other significant illnesses known to affect FeNO mmts. <u>Exclusion criteria:</u> <ul style="list-style-type: none"> Factors that could alter FeNO (such as smoking and nitrate rich diet, but not asthma) Features of atopy or allergic rhinitis Tx with ICS in the past. 	41%/59% <u>Mean age:</u> 35.2 years. <u>Diagnoses (GINA criteria and history of symptoms and SPT for allergic rhinitis):</u> <ul style="list-style-type: none"> 1. Healthy controls: n=39. 2. Allergic asthma: n=56. 3. Non-allergic asthma: n=45. <u>Current smokers:</u> Not reported. <u>Current anti-asthma Tx:</u> Prior to study, pts allowed to take SABA and LABA. <u>Drop-outs/missing values:</u> None reported.	<u>Peripheral blood eosinophils</u> <ul style="list-style-type: none"> Haematologic analyser (Coulter). <u>CUT-OFF:</u> N/A <u>Reference standard</u> N/A <u>Time between index test and reference standard:</u> N/A <u>Target condition</u> <ul style="list-style-type: none"> Asthma. 	(baseline)	<u>mean</u> cells/mm ³	<u>funding:</u> None reported. <u>Limitations:</u> Overall - LOW/UNCLEAR RIK OF BIAS. <u>Additional data:</u> N/A
					Healthy controls	119	
					Allergic asthma	247	
					Non-allergic asthma	211	
<ul style="list-style-type: none"> Asthma: SS higher PBE than healthy controls (P<0.05) Allergic asthma: NS higher PBE than non-allergic asthma. 							

G.12 Histamine and methacholine challenge tests for diagnosis

Table 104: ANDERSON 2009^{44,48}

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments	
					Ref std +	Ref std -	Total			
Anderson et al. 2009. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. Resp Res 10: 4. ^{44,48}	<p><u>Study type:</u> Diagnostic cross sectional study</p> <p><u>Recruitment:</u> Not mentioned</p>	<p>N = 391 (16 not included in PP analysis reported N=375)</p> <p>Adults and children/youngpeople. Sn/sp given for:</p> <ul style="list-style-type: none"> all ages <18 yrs only <p><u>Inclusion criteria:</u> Aged 6-50 yrs (BMI<35) with signs and symptoms suggestive of asthma according to the NIH questionnaire.</p> <ul style="list-style-type: none"> At least step 1 symptoms according to the NAEPPII asthma severity grading (symptoms ≤2 times per week; asymptomatic between exacerbations; exacerbations of only a few hrs to a few days; night time symptoms ≤2 times 	<p><u>Male: Female</u> 182/193</p> <p><u>Mean age:</u> 24.3 (10.2) range 6-50</p> <p>Children n=96 Adults n=279</p> <p>Medications: Withholding periods of medications summarised in table in paper for inhaled agents, oral BD, CS, other medications, foods, strenuous exercise and tobacco.</p>	<p><u>Index test</u> MCT – methacholine (Provocholine, CA) delivered from a nebulizer (DeVilbiss 646) by the dosimeter method. Concentrations were 0.0312, 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16mg/ml administered (each conc required 5 inhalations and spirometry performed within 3 minutes). PC20 calculated</p> <p>Cut-off: 16mg/ml</p> <p><u>Comparator test</u> Mannitol: mannitol test kit as per standard protocol (Aridol or Osmohale Pharmaxis Ltd). FEV1 measured 60s after each dose: 0, 5, 10, 20, 40, 80, 160, 160, 160mg). 60s after the 0mg capsule, the FEV1 was measured in duplicate at the highest value taken as baseline. PD15 calculated</p> <p>Cut-off: ≥15% fall in FEV1 ≤635mg</p>					<p><u>Source of funding:</u> Phase III clinical trial funded by Pharmaxis Ltd and involved in the design and statistics</p> <p><u>Limitations:</u></p> <ul style="list-style-type: none"> Indirect population: reported ages 6-50 yrs together. Children reported separately but age 6-18, not age 5-16 as in protocol. Not all patients included in analysis. Consecutive or random patient selection not reported. 	
					Index test +	122	34	156		
					Index test -	118	101	219		
					Total	240	135	375		
					Sensitivity		50.8%			
					Specificity		74.8%			
					PPV		78.2%			
					NPV		46.1%			
						Mann +	Mann -	Total		
					Index test +	104	52	156		
Index test -	64	155	219							
Total	168	207	375							

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
		<p>per month)</p> <ul style="list-style-type: none"> • FEV1 \geq70% predicted at screening <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> • Firm diagnosis of asthma or an exclusion of the Dx of asthma • Other pulmonary disease • Smoked >1 cigarette per week in the past yr or a \geq10pack year smoking history • Respiratory tract infection within the last 4 weeks • Skin test positive to aeroallergens present in the environment during enrolment or reported worsening symptoms when exposed to these during the study • Dx at screening visit as definitively having asthma (95-100% likelihood) or not having asthma (0-5% likelihood) • Abnormal chest x-ray or ECG 		<p>or 10% fall between consecutive doses.</p> <p><u>Reference standard</u></p> <p>Clinical Dx with objective test: made by respiratory physician at visit 5 with access to data on exercise challenge, history, examination, skin tests and BDR but not methacholine and mannitol challenge tests.</p> <p>Time between index test and reference standard: unclear</p> <p><u>Target condition</u></p> <p>Asthma</p>	<p>Sensitivity 62%</p> <p>Specificity 75%</p> <p>PPV 66.7%</p> <p>NPV 70.8%</p> <p>Children <18 yrs (n=115)</p> <p>MCT vs reference standard</p> <ul style="list-style-type: none"> • Sensitivity = 66.2% • Specificity = 62.9% 	<ul style="list-style-type: none"> • Unclear time between IT and RS <p><u>Additional data:</u></p> <p>Consisted of 5 study visits. Objective tests performed on first visit and physician assigned one of 6 asthma likelihood – those with 5-95% likelihood included. Visit 2 and 3 confirmed spirometry at screening and an exercise test. Visit 4 and 5 was randomised crossover of either mannitol or methacholine. Likelihood of asthma determined again after visit 5 – but Dx of asthma for ref standard determined by physician blinded to challenge tests.</p>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
		<ul style="list-style-type: none"> Failure to observe washout of medications 				

Table 105: HEDMAN 1998^{656,656}

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Hedman et al. 1998. A rapid dosimetric methacholine challenge in asthma diagnostic : a clinical study of 230 patients with dyspnoea, wheezing or a cough of unknown cause.	<u>Study type:</u> Diagnostic cross sectional study <u>Setting:</u> Hospital pulmonary department <u>Country:</u> Finland <u>Recruitment:</u> Consecutive patients tested with the MCT from May to Sept 1994	N = 230 Adults <u>Inclusion criteria:</u> Referred due to dyspnoea, wheezing or a cough of unknown cause <u>Exclusion criteria:</u> Previous asthma Dx; use of inhaled steroids during the preceding 4 weeks FEV1 of at least 65% before challenge test and no respiratory infection during previous 4 weeks.	<u>Male: Female</u> 90/140 <u>Mean age:</u> 44.3 (16) Current smokers n=39 Medications: - Beta2-agonist used by 58% patients with a positive MCT and 32% of patients with a negative MCT - anticholinergic drug used by 5% patients with a	<u>Index test</u> RAPID dosimetric MCT performed with a pocket turbine spirometer (MicroSpirometer, Micro Medical Instruments). An automatic, inhalation synchronised dosimeter jet nebuliser (Spira Elektro 2, Respiratory Care Centre, Finland)used for MCh delivery. After nebulisation of 33g isotonic saline, MCh delivered in four doses 80, 400, 1700, 6900µg. FEV1 measured 90s after each dose. The concentrations were 2.5, 10, 40 and 160 mg/ml. PD20 calculated Cut-off PD20≤6900µg <u>Comparator test</u> None		Ref std +	Ref std -	Total	<u>Source of funding:</u> Not reported <u>Limitations:</u> • Unclear time between IT and RS <u>Additional data:</u>
					Index test +	47	31	78	
					Index test -	14	138	152	
					Total	61	169	230	
					Sensitivity		77.0%		
					Specificity		81.7%		
					PPV	60.3%			
NPV	90.8%								
PLR									
NLR									

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
Resp Med 92: 32-39. ^{656,656}			<p>positive MCT and 21% of patients with a negative MCT</p> <p>No use of beta2-agonists for 12hrs prior to MCT, or any other asthma or antihistamine drug for 48hrs (terfenadine for 1 week and astemitsole for 4 weeks)</p>	<p><u>Reference standard</u> Physician Dx with objective test (according to guidelines of the American Thoracic Society). The person who classified the patients as having or not having asthma was blinded to MCT results. Patients had to have a documented variation in FEV or PEF of 15% or greater after medication, or repeatedly a 20% or greater spontaneous daily variation in PEF monitoring during a period of 2 weeks. In addition, a 15% or greater decrease in FEV, after a specific allergen provocation or during an exercise test was a criterion for diagnosing bronchial asthma.</p> <p>Time between index test and reference standard: unclear</p> <p><u>Target condition</u> Bronchial asthma</p>	AUC		

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Table 106: KOSKELA 2003 ^{915,915}

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Koskela et al.	<u>Study type:</u>	N=42	<u>Male: Female</u>	<u>Index test</u>	PD15 ≤1mg/ml	Ref std +	Ref std -	Total	<u>Source of funding:</u>

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					Index test +	Index test -	Total	Sensitivity Specificity	
915,915	Comparative test vs test study <u>Data source:</u> <u>Setting:</u> Outpatient clinic <u>Country:</u> <u>Finland</u> <u>Recruitment:</u> Consecutive patients with a new diagnosis of asthma over an 18 month period	Consecutive patients with a new Dx of asthma over a 18 month period <u>Inclusion criteria:</u> Asthma Dx based on patient history and clinical examination, including objective evidence of reversible airway obstruction (positive exercise challenge; BDR; PEFV or PEF improvement with BD) according to the Finnish Social Insurance Institute criteria. <u>Exclusion criteria:</u> Previous usage of inhaled or oral CS; febrile respiratory tract infection within 4 weeks; FEV1<50% predicted; if staff physician considered COPD the most probable diagnosis.	21/16 <u>Mean age:</u> 49 (44-54) Current smokers n=6 Medications: subjects refrained from taking short-acting beta2-agonists for 6 hrs, inhaled anti-cholinergic drugs for 8 hrs, and theophylline for 24 hrs prior to HCT.	HCT – administered using Spiro Elektro 2 dosimeter nebuliser (Respiratory Care Centre, Finland) . Nebulisation time 0.4s, set to start 100ms after beginning of inspiration. Starting dose 25µg with 4-fold increases until the FEV1 fallen by 15% or max dose of 1600µg administered Cut-off: PD15 ≤1mg and PD15 ≤0.4mg <u>Reference standard</u> Mannitol – spray dried powder packed in gelatin capsules containing 5, 10, 20 and 40mg (inhaled in doubling doses up to 160mg and repeated 3 times using an Inhalator). Test until 15% fall in FEV1 or cumulative dose of 635mg reached Cut-off: >15% fall in FEV1 regardless of dose Time between index test and reference standard: 2 days to 2 weeks. <u>Target condition</u> Asthma (with +ve mannitol	19	11	30	Not reported <u>Limitations:</u> Comparator test used as reference standard as all people had asthma <u>Additional data:</u> Mannitol, cold air and histamine tests given in random order within 2 weeks and at least 2 days before challenges (within 3 weeks of asthma Dx).	
					0	7	7		100% 38.9%
					19	18	37		
					PPV NPV		63.3% 100%		
					PD15 ≤0.4mg/ml	Ref std +	Ref std -		Total
					Index test +	16	2		18
					Index test -	3	16		19
					Total	19	18		37
					Sensitivity Specificity PPV NPV		84.2% 88.9% 88.9% 84.2%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables			Comments
				response)				

Table 107: KOWAL 2009^{924,924}

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
Kowal et al. Exhaled Nitric Oxide in Evaluation of Young Adults with Chronic Cough. 2009. Journal of Asthma 46: 692-698. ^{924,924}	<u>Study type:</u> Diagnostic cross sectional study <u>Data source:</u> (if it comes from records for instance) <u>Setting:</u> Asthma Clinic <u>Country:</u> Poland <u>Recruitment:</u> Patients referred by family doctors to the clinic between Sept 2000	N = 540 <u>Inclusion criteria:</u> Patients referred to the asthma clinic for evaluation of chronic cough Non smokers with non-productive cough of at least 8 weeks in duration, no abnormality on chest radiograph and baseline lung function within normal limits <u>Exclusion criteria:</u> Use of anti-asthma medication before the study; treatment with ACE inhibitors; use of codeine or other cough	<u>Male: Female</u> <u>Mean age:</u> 26.5 range 18-45 years Other Dx made were rhinitis; GERD	<u>Index test</u> HCT – doubling concentrations of histamine (aerosol generated using a DeVilbis 646 nebuliser attached to a Rosenthal French dosimeter). Five inspiratory capacity breaths of each conc. FEV1 measured 90s after each fifth inhalation. Starting at 0.62mg/ml until 20% decrease or concentration of 32mg/ml reached. Cut-off: 8mg/ml <u>Comparator test</u> FENO <u>Reference standard</u> Significant diurnal changes in PEF or significant improvement of FEV1 on administration of 200µg of		Ref std +	Ref std -	Total	<u>Source of funding:</u> <u>Limitations:</u> <ul style="list-style-type: none"> Consecutive or random patient selection not reported RS 6 months after IT Unclear if reference standard performed without knowledge of the results of the Index test <u>Additional data:</u> Data provided on a healthy
					Index test +	166	0	166	
					Index test -	12	362	374	
					Total	178	362	540	
					Sensitivity		93.3%		
					Specificity		100%		
					PPV	100%			
					NPV	96.8%			
PLR									
NLR									
AUC									

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
	and Nov2006	suppressant; upper respiratory tract infection within 4 weeks of the study; presence of any systemic disease; contradictions to HCT.		salbutamol according to the Global Initiative of Asthma (GINA) guidelines. Time between index test and reference standard: 6 months (observed for 6 months after HCT before Dx) <u>Target condition</u> Bronchial asthma		control group but not included here for calculation of sn/sp

Table 108: NIEMINEN 1992^{1241,1241}

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments			
Nieminen M.M. Unimodal Distribution of Bronchial Hyperresponsiveness to Methacholine in Asthmatic Patients. Chest: 102 (5): 1537-	<u>Study type:</u> Diagnostic cross sectional study <u>Data source:</u> <u>Setting:</u> Pulmonary Department, University Hospital	N = 791 Adults <u>Inclusion criteria:</u> dyspnoea, wheezing, prolonged cough, or a history of asthma. referred to the clinic and tested with methacholine challenge <u>Exclusion criteria:</u>	<u>Male: Female</u> 319/472 <u>Mean age:</u> 43.2 (SD 14.0) 179 current smokers Oral beta-agonists and inhaled anti-cholinergic drugs were withheld for 12	<u>Index test</u> MCT performed using a dosimeter technique with tidal breathing. An automatic, inhalation synchronised dosimeter jet nebuliser (Spira Elektro 2, Respiratory Care Centre, Finland) used for MCh delivery. Nebulisation time 0.5s, set to start 100ms after beginning of inspiration. After nebulisation of saline, MCh delivered in five cumulative doses of 18, 72, 270, 810, and 2,600 µg (concentration of MCh was 2.5 mg/ml for the doses 18 to 270µg and 25 mg/ml	Ref std +	Ref std -	Total	<u>Source of funding:</u> Supported by a grant from Suomen Astra Ltd. <u>Limitations:</u> • Unclear if reference standard performed without knowledge of	
					Index test +	283	114		397
					Index test -	36	358		394
					Total	319	472		791
					Sensitivity Specificity	88.7% 75.8%			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables		Comments
1543 ^{1241,1241} 41	<p><u>Country:</u> Finland</p> <p><u>Recruitment:</u> consecutive patients referred to pulmonary department with respiratory symptoms. March 1988 – Sept 1989</p>		hours, inhaled beta-agonists for 8 hours and theophylline compounds for 48 hours before the MCT	<p>for the doses 810 to 2,600µg). FEV1 PD20 calculated</p> <p>Cut-off: 2,600µg</p> <p><u>Comparator test</u> None</p> <p><u>Reference standard</u> Clinical Dx according to the guidelines defined by the American Thoracic Society, a typical history with chronic or repeated symptoms, and a documented variation in FEV1 or in PEFr of more than 15 percent after medication, or repeatedly 20 percent spontaneous daily variation in PEFr monitoring during a period of two weeks. In addition, a 15 percent decrease in air flow after specific allergen provocation or in an exercise test was a criterion for diagnosing bronchial asthma.</p> <p>Time between index test and reference standard: unclear</p> <p><u>Target condition</u> Bronchial asthma</p>	<p>PPV NPV PLR NLR</p>	<p>71.3% 90.9%</p>	<p>the results of the Index test.</p> <ul style="list-style-type: none"> Unclear time between IT and RS <p><u>Additional data:</u> Data provided on a healthy control group but not included here for calculation of sn/sp</p>

Table 109: POPOVIC 2012¹³⁸¹

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
					Ref st +	Ref st -	Total		
Popovic-Grle et al., 2002. Clinical validation of bronchial hyperresponsiveness, allergy tests and lung function in the diagnosis of asthma in persons with dyspnea. Collegium Antropologicum: 26 Suppl: 119-127 REF ID: POPOVIC 2002	<u>Study type:</u> Cross-sectional study <u>Setting:</u> Outpatient department, University Hospital <u>Country:</u> Croatia <u>Recruitment:</u> Random	N = 195 Adults <u>Inclusion criteria:</u> • Referred by GP with suspected asthma and symptoms of breathlessness / dyspnoea. <u>Exclusion criteria:</u> • Serious diseases of other organ systems or the lungs (apart from those of an obstructive and/or allergic nature)	<u>Male, %</u> 51% of those given an asthma Dx <u>Mean age:</u> 36.5 (6.2) in those given an asthma Dx (n=141) Medications: Not reported	<u>Index test</u> Methacholine Challenge test (initial concentration of 0.03mg/ml, increased by doubling concentrations to 8mg/ml) Cut-off: 8mg/ml suggested as highest concentration given <u>Comparator test</u> n/a <u>Reference standard</u> Dx made on the basis of questionnaire, with typical medical history data of occasional asthma attacks with wheezing and nocturnal awakening because of dyspnoea, and reversible bronchial obstruction after salbutamol test (no further details stated) Time between index test and reference standard: same time <u>Target condition</u>					<u>Source of funding:</u> Not reported <u>Limitations:</u> • Details of reference standard objective test not given • Unclear if RS results interpreted without knowledge of the IT results • Unclear if IT results interpreted without knowledge of the RS results (but objective) • Value reported in text for positive MCT result do not match other
					Index test +	137	9	146	
					Index test -	4	45	49	
					Total	141	54	195	
					Sensitivity	97.2%			
					Specificity	83.3%			
					PPV	93.8%			
					NPV	91.8%			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
				Asthma		<p>results</p> <p><u>Additional data:</u></p>

2 G.13 Mannitol challenge test for diagnosis

Table 110: ANDERSON 2009⁴⁸

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments												
Anderson et al. 2009. Comparison of mannitol and	<u>Study type:</u> Diagnostic cross sectional study	N = 391 (16 not included in PP analysis reported N=375) Adults and children/youngpeo	<u>Male: Female</u> 182/193 <u>Mean age:</u> 24.3 (10.2) range 6-50	<u>Index test</u> Mannitol: mannitol test kit as per standard protocol (Aridol or Osmohale Pharmaxis Ltd). FEV1 measured 60s after each dose: 0, 5, 10, 20, 40, 80, 160, 160, 160mg). 60s after the 0mg capsule, the	<table border="1"> <thead> <tr> <th></th> <th>Ref std +</th> <th>Ref std -</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>Index test +</td> <td>134</td> <td>34</td> <td>168</td> </tr> <tr> <td>Index test -</td> <td>106</td> <td>101</td> <td>207</td> </tr> </tbody> </table>		Ref std +	Ref std -	Total	Index test +	134	34	168	Index test -	106	101	207	<u>Source of funding:</u> Phase III clinical trial funded by Pharmaxis Ltd and involved in the design and
	Ref std +	Ref std -	Total															
Index test +	134	34	168															
Index test -	106	101	207															

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables				Comments
methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. Resp Res 10: 4. ⁴⁸	Recruitment: Not mentioned	<p>ple. Sn/sp given for:</p> <ul style="list-style-type: none"> all ages <18 yrs only <p><u>Inclusion criteria:</u> Aged 6-50 yrs (BMI<35) with signs and symptoms suggestive of asthma according to the NIH questionnaire.</p> <ul style="list-style-type: none"> At least step 1 symptoms according to the NAEPPII asthma severity grading (symptoms ≤2 times per week; asymptomatic between exacerbations; exacerbations of only a few hrs to a few days; night time symptoms ≤2 times per month) FEV1 ≥70% predicted at screening <p><u>Exclusion criteria:</u></p> <ul style="list-style-type: none"> Firm diagnosis of asthma or an 	<p>Children n=96 Adults n=279</p> <p>Medications: Withholding periods of medications summarised in table in paper for inhaled agents, oral BD, CS, other medications, foods, strenuous exercise and tobacco.</p>	<p>FEV1 was measured in duplicate at the highest value taken as baseline. PD15 calculated</p> <p>Cut-off: ≥15% fall in FEV1 ≤635mg or 10% fall between consecutive doses.</p> <p><u>Comparator test</u> Exercise: running on a treadmill whilst breathing medical grade dry air to 80-90% predicted HR (220-age) and sustained for 6 minutes. FEV1 measured 5, 10, 15 and 30 mins after and % fall in FEV1 calculated by subtracting lowest value after exercise from pre-exercise value</p> <p>Cut-off: positive if fall in FEV1 ≥10%</p> <p><u>Reference standard</u> Clinical Dx with objective test: made by respiratory physician at visit 5 with access to data on exercise challenge, history, examination, skin tests and BDR but not mannitol challenge tests.</p> <p>Time between index test and reference standard: unclear</p>	Total	240	135	375	<p>statistics</p> <p><u>Limitations:</u></p> <ul style="list-style-type: none"> Indirect population: reported ages 6-50 yrs together. Children reported separately but age 6-18, not age 5-16 as in protocol. Not all patients included in analysis. Consecutive or random patient selection not reported. Unclear time between IT and RS <p><u>Additional data:</u> Consisted of 5 study visits. Objective tests performed on</p>
					Sensitivity		55.8%		
					Specificity		74.8%		
					PPV		79.8%		
					NPV		48.8%		
						Ex +	Ex -	Total	
					Index test +	95	73	168	
					Index test -	68	136	204	
					Total	163	209	372	
					Sensitivity		58.6%		
Specificity		65.2%							
PPV		56.5%							
NPV		66.7%							

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
		exclusion of the Dx of asthma <ul style="list-style-type: none"> • Other pulmonary disease • Smoked >1 cigarette per week in the past yr or a ≥10pack year smoking history • Respiratory tract infection within the last 4 weeks • Skin test positive to aeroallergens present in the environment during enrolment or reported worsening symptoms when exposed to these during the study • Dx at screening visit as definitively having asthma (95-100% likelihood) or not having asthma (0-5% likelihood) • Abnormal chest x-ray or ECG • Failure to observe washout of 		<u>Target condition</u> Asthma	Children <18 yrs (n=115) Mannitol vs reference standard <ul style="list-style-type: none"> • Sensitivity = 63.2% • Specificity = 81.4% Mannitol vs Exercise <ul style="list-style-type: none"> • Sensitivity = 60.1% • Specificity = 58.5% 	first visit and physician assigned one of 6 asthma likelihood – those with 5-95% likelihood included. Visit 2 and 3 confirmed spirometry at screening and an exercise test. Visit 4 and 5 was randomised crossover of either mannitol or methacholine. Likelihood of asthma determined again after visit 5 – but Dx of asthma for ref standard determined by physician blinded to challenge tests.

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Statistical measures and 2x2 tables	Comments
		medications				

G.14 Exercise challenge test for diagnosis

Table 111: AVITAL2000^{81,82}

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures		Effect sizes		Comments
					Asthma	Ref std +	Ref std -	Total	
Exercise, methacholine, and adenosine 5'-monophosphate challenge s in children with asthma: relation to severity of the disease.	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Paediatric pulmonology clinic <u>Setting:</u> Secondary care <u>Country:</u>	N = 135 <u>Inclusion criteria:</u> • American Thoracic Society definition of asthma; <u>Exclusion criteria:</u> Upper or lower respiratory tract infection in last 4 weeks	<u>Male: Female</u> Not stated <u>Mean age:</u> 12.4 (3.9) range 6 to 25 years	<u>Index test</u> Exercise test 6 minute treadmill CUT-OFF: positive = minimum fall in FEV1 of 8.2% <u>Reference standard</u> Clinical Dx Methacholine challenge (PC20 ≤8mg/mL) Time between index test and reference standard: within 30 days <u>Target condition</u> Asthma	Asthma	Ref std +	Ref std -	Total	<u>Source of funding:</u> Not stated <u>Limitations:</u> None <u>Additional data:</u> None
					Exercise +	95	1	96	
					Exercise -	37	2	39	
					Total	132	3	135	
					Sensitivity	72%			
Specificity	67%								

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Pediatric Pulmonology: 30: 207-214 Avital A, Godfrey S, and Springer C 2000. REF ID: AVITAL2000.	Israel <u>Recruitment:</u> Not stated						

1

Table 112: EGGLESTON1979^{468,468}

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
A comparison of the asthmatic response to methacholine and exercise. Journal of Allergy and Clinical Immunology: 63: 104-110	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> University School of Medicine <u>Setting:</u> Secondary care	N = 45 <u>Inclusion criteria:</u> • Young adults with asthma <u>Exclusion criteria:</u> None given	<u>Male: Female</u> 27:18 <u>Mean age:</u> Range 16 to 30 years	<u>Index test</u> Exercise test 5 minutes treadmill CUT-OFF: positive = ΔFEV1 ≥18% (cut off for 2SD from mean normal response) <u>Reference standard</u> Clinical Dx Methacholine Time between index test and reference standard: same time <u>Target condition</u>	Asthma	Ref std +	Ref std -	Total	<u>Source of funding:</u> Not stated <u>Limitations:</u> No patients were methacholine-negative so specificity cannot be calculated <u>Additional data:</u> None
					Exercise +	36	0	36	
					Exercise -	9	0	9	
					Total	45	0	45	
					Sensitivity Specificity	80% Not estimable			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Eggleston PA 1979. REF ID: EGGLESTON1979.	<u>Country:</u> USA <u>Recruitment:</u> Not stated			Asthma			

Table 113: KERSTEN2009^{852,852}

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
Kersten ETG et al. Mannitol and exercise challenge tests in asthmatic children. Pediatric Pulmonology 2009; 44: 655-661. KERSTEN2009	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Outpatients <u>Setting:</u> Secondary care <u>Country:</u> The Netherlands <u>Recruitment:</u>	N = 25 <u>Inclusion criteria:</u> <ul style="list-style-type: none"> Children with a history of allergic asthma and exercise induced bronchoconstriction recruited from outpatient clinic; clinically stable, otherwise healthy; FEV1 at least 70% predicted normal value; able to run on treadmill and perform reproducible spirometry 	<u>Male: Female</u> 17: 8 <u>Mean age:</u> Mean 12.4 (2.0) years	<u>Index test</u> Exercise challenge running with nose clip on treadmill in cold air at ice ring (temperature 1°C) for 6 minutes CUT-OFF: positive = ΔFEV1%init >15% for both tests <u>Reference standard</u> Mannitol challenge up to cumulative dose 6.35mg Time between index test and reference standard: within 4 weeks <u>Target condition</u> Asthma	Asthma	Ref std +	Ref std -	Total	<u>Source of funding:</u> Pediatric Research Foundation Enschede, The Netherlands <u>Limitations:</u> None <u>Additional data:</u> None
					Cold air exercise +	9	1	10	
					Cold air exercise -	4	11	15	
					Total	13	12	25	
					Sensitivity Specificity		69% 92%		

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Not stated	<u>Exclusion criteria:</u> None given					

Table 114: KLEPACPULANIC2004⁸⁸⁷

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
Exercise and allergic diseases. Arhiv Za Higijenu Rada i Toksikologiju: 55: 197-204 Klepac-Pulanic T, Macan J, Plavec D, and Kanceljak-Macan B 2004. REF ID: KLEPACPULANIC2004.	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Institute for Medical Research and Occupational Health <u>Setting:</u> Secondary care <u>Country:</u> Croatia <u>Recruitment:</u>	N = 35 <u>Inclusion criteria:</u> <ul style="list-style-type: none"> GINA definition of asthma; asthma symptoms and/or taking asthma medication; all positive to histamine; all met EAACI definition of allergic asthma and had positive skin prick tests to at least 1 inhalatory allergen. Allergic rhinitis patients met EAACI definition; negative to histamine; positive skin prick tests to at least 1 	<u>Male: Female</u> Not stated <u>Mean age:</u> Asthma: range 15 to 48 years; allergic rhinitis: range 15 to 45 years	<u>Index test</u> Exercise test (6 minute treadmill) CUT-OFF: positive = Δ FVEV1 \geq 10% <u>Reference standard</u> Clinical Dx GINA definition of asthma; asthma symptoms and/or taking asthma medication; all positive to histamine; all met EAACI definition of allergic asthma and had positive skin prick tests to at least 1 inhalatory allergen. Allergic rhinitis patients met EAACI definition; negative to histamine; positive skin prick tests to at least 1 inhalatory allergen Time between index test and reference standard: same time <u>Target condition</u>	Asthma	Ref std +	Ref std -	Total	<u>Source of funding:</u> Not stated <u>Limitations:</u> None <u>Additional data:</u> None
					Exercise +	5	0	5	
					Exercise -	14	16	30	
					Total	19	16	35	
					Sensitivity Specificity	26% 100%			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
	Not stated	inhalatory allergen <u>Exclusion criteria:</u> Exercise test or histamine challenge contra-indicated; upper respiratory viral infection within 3 weeks		Asthma			

Table 115: LIN1991^{1018,1018}

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments		
A bronchial response comparison of exercise and methacholine in asthmatic subjects. Journal of Asthma: 28: 31-40 Lin CC, Wu JL, Huang WC, and	<u>Study type:</u> Diagnostic Cross-sectional study <u>Data source:</u> Department of Internal Medicine Chest section <u>Setting:</u> Secondary care <u>Country:</u>	N = 22 <u>Inclusion criteria:</u> <ul style="list-style-type: none"> People with stable unmedicated asthma; FEV1 >75% normal <u>Exclusion criteria:</u> None given	<u>Male: Female</u> 12:10 <u>Mean age:</u> Range 20 to 40 years	<u>Index test</u> Exercise test (10 minute treadmill) CUT-OFF: positive = ΔFEV1%init >20% <u>Reference standard</u> Clinical Dx Methacholine challenge Time between index test and reference standard: Up to 3 weeks <u>Target condition</u> Asthma	Asthma	Ref std +	Ref std –	Total	<u>Source of funding:</u> The National Science Council of China <u>Limitations:</u> None <u>Additional data:</u> None
					Exercise +	9	0	9	
					Exercise -	12	1	13	
					Total	21	1	13	
					Sensitivity Specificity	43% 100%			

Reference	Study type	Number of patients	Patient characteristics	Index test(s) and reference standard + target condition	Outcome measures	Effect sizes	Comments
Lin CY 1991. REF ID: LIN1991.	Taiwan <u>Recruitment:</u> July 1985 to December 1988						

G.15 Questionnaires to monitor asthma control

Table 116: MEER 2009^{1818,1824}

Study (subsidiary papers)	SMASHING trial: Van 2009 ^{1818,1824} (Van der meer 2010 ^{1126,1126})
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in Netherlands; Setting: GP and outpatient clinic, multicentre
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Physician Dx asthma, coded according to International Classification of Primary Care
Stratum	Adults and young people overall: Asthma patients 18- 50 years with ICS prescription, not receiving OCS
Subgroup analysis within study	Not stratified but pre-specified: Level of baseline control
Inclusion criteria	age 18-50 years; prescription of ICS for at least 3 months in the previous year; no serious cormorbid conditions interfering with asthma treatment; access to the internet at home; Dutch language.
Exclusion criteria	Receiving maintenance OCS treatment.
Recruitment/selection of patients	September 2005 to September 2006

Age, gender and ethnicity	Age - Range: 18-50 years. Gender (M:F): 61/139. Ethnicity:
Further population details	1. Education level: Moderate/high level of education (>50% with high education level). 2. Language: Non English speaking (Dutch speaking).
Extra comments	Baseline data: age mean (range): Monitoring 36 (19-50); UC 37 (18-50); FEV1%pred Monitoring 88 (34-133); UC 90 (53-118); AQLQ Monitoring 5.73 (3.66-6.94); UC 5.79 (3.03-7.00); ACQ Monitoring 1.12 (0.07-3.22); UC 1.11 (0-3.86); ICS 100%; ICS/LABA 60%.
Indirectness of population	No indirectness
Interventions	<p>(n=101) Intervention 1: Monitoring asthma control + treatment - Monitoring control questionnaires + treatment. Weekly completion of electronic ACQ and instant feedback of asthma control along with advice on how to adjust treatment according to predefined algorithm and treatment plan (treatment steps according to GINA). - Four consecutive scores ≤ 0.5 : decrease treatment according to plan- Two scores > 0.5 but < 1: increase treatment according to plan- One score ≥ 1 but < 1.5: immediately increase according to plan- One score > 1.5: immediately increase treatment and contact nurse.. Duration 12 months. Concurrent medication/care: Intervention group only - online education, face-to-face group education (two 60 min sessions) and web communications with an asthma nurse Both groups received a prior basic education session about core information on asthma, action of medications and inhaler technique instructions. All trained to measure FEV1 daily and report highest value of 3 measurements before medications. Reported daytime and nighttime symptoms and ACQ weekly. No feedback provided on ACQ or lung function. Further details: 1. Additional education training : Additional education in both groups 2. Duration of study: ≥ 6 months</p> <p>(n=99) Intervention 2: Usual care. Asthma care according to Dutch guidelines (based on GINA), recommend medical review and treatment adjustment every 2 to 4 weeks in unstable asthma and once or twice yearly for controlled asthma. Control patients had access to the part of the website on which a diary of symptoms and exacerbations was kept, but not ACQ.. Duration 12 months. Concurrent medication/care: Both groups received a prior basic education session about core information on asthma, action of medications and inhaler technique instructions. All trained to measure FEV1 daily and report highest value of 3 measurements before medications. Reported daytime and nighttime symptoms and ACQ weekly. No feedback provided on ACQ or lung function. Further details: 1. Additional education training : Additional education in both groups 2. Duration of study: ≥ 6 months</p>
Funding	Academic or government funding (Netherlands organisation for health research and development, ZonMw, and Netherland Asthma Foundation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ONGOING MANAGEMENT BASED ON ACQ SCORE versus USUAL CARE	

<p>Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people overall: AQLQ at 12 months; MD 0.38 (95%CI 0.2 to 0.56) (P<0.001) AQLQ 1-7 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people overall: Emergency treatment, hospitalisation or OCS course at 12 months; HR 1.18 (95%CI 0.51 to 2.74) Reported; Risk of bias: High; Indirectness of outcome: Serious indirectness</p>	
<p>Protocol outcome 3: Asthma control questionnaires at End of Treatment - Actual outcome for Adults and young people overall: ACQ at 12 months; MD -0.47 (95%CI -0.64 to -0.3) (P<0.001) ACQ 0-6 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people with uncontrolled asthma: ACQ at 12 months; MD -0.82 (95%CI -1.1 to 0.55) ACQ 0-6 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Adults and young people overall: Mean daily ICS use, µg at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people with controlled asthma: Mean daily ICS use, µg at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people with uncontrolled asthma: Mean daily ICS use, µg at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 5: Lung Function at End of Treatment - Actual outcome for Adults and young people overall: FEV1 L at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 6: Symptom free days at End of Treatment - Actual outcome for Adults and young people overall: % symptom free days in previous 2 weeks at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Rescue medication at End of Treatment; Time of school/work at End of Treatment

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Table 117: MEHUYS 2008^{1128,1128}

Study	Mehuys 2008 ^{1128,1128}
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=201)
Countries and setting	Conducted in Belgium; Setting: Pharmacy, multicentre
Line of therapy	Mixed line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Asthma patients
Stratum	Adults and young people overall: Asthma patients treated for asthma for ≥ 12 months (not including fully controlled or severely uncontrolled)
Subgroup analysis within study	Not applicable: na
Inclusion criteria	Aged 18-50 years; treated for asthma for ≥ 12 months; using controller medication; regular visitor to the pharmacy.
Exclusion criteria	Smoking history of >10 pack-years; suffering from another severe disease and ACT at screening of <15 (indicating seriously uncontrolled asthma) or equalling 25 (complete asthma control).
Recruitment/selection of patients	Consecutive recruitment in 66 pharmacies from Jan 2006 - April 2006.
Age, gender and ethnicity	Age - Range: 18-50. Gender (M:F): 94/107. Ethnicity:
Further population details	1. Education level: Not applicable / Not stated / Unclear 2. Language: Non English speaking (Non English speaking but Dutch version of ACT used).
Extra comments	Baseline data: Mean (range) age: Monitoring: 35.2 (19-51); Usual care: 36.3 (17-51). ACT mean (range): Monitoring: 19.7 (11-25); Usual care: 19.3 (10-25). ICS %: Monitoring: 25%; Usual care: 23.1%; LABA/ICS %: Monitoring: 64.5%; Usual care: 70.8%.
Indirectness of population	No indirectness
Interventions	(n=107) Intervention 1: Monitoring asthma control + treatment - Monitoring control questionnaires + treatment. Pharmacist intervention including initial education on inhaler technique, asthma, medication. Pharmacist advice at 1 month and 3 months based on ACT score of the patient (direct physician feedback). -ACT <15 (uncontrolled asthma): immediate referral to GP or specialist-ACT 15-19 (insufficiently controlled asthma): review inhaler technique and check controller adherence-ACT >19 (well-controlled): no advice, inform patient asthma is well-controlled. Duration 6 months. Concurrent medication/care: Education session from pharmacist at the start of the intervention in the intervention group Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Duration of study: ≥ 6 months (n=94) Intervention 2: Usual care. Usual pharmacist care. Duration 6 months. Concurrent medication/care: No education at start of study as in intervention group.

	Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Duration of study: >= 6 months
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ONGOING MANAGEMENT BASED ON ACT SCORE versus USUAL PHARMACIST CARE</p> <p>Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people overall: AQLQ at 6 months; Group 1: mean 6 (SD 0.7); n=80, Group 2: mean 5.8 (SD 0.9); n=70; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people overall: Exacerbation (ER visit, hospitalisation or course of OCS) at 6 months; Group 1: 10/80, Group 2: 8/70; Risk of bias: Very high; Indirectness of outcome: Serious indirectness</p> <p>Protocol outcome 3: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people overall: ER visit or hospitalisation at 6 months; Group 1: 1/80, Group 2: 5/70; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Asthma control questionnaires at End of Treatment - Actual outcome for Adults and young people overall: ACT final values at 3 months; Group 1: mean 20.3 (SD 3.2); n=99, Group 2: mean 20 (SD 3.8); n=84; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people overall: ACT final values at 6 months; Group 1: mean 20.2 (SD 3.5); n=80, Group 2: mean 19.7 (SD 4.8); n=70; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people overall: ACT, no. of patients controlled (score 20-25) at 3 months; Group 1: 61/99, Group 2: 52/84; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people overall: ACT, no. of patients controlled (score 20-25) at 6 months; Group 1: 54/80, Group 2: 42/70; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people overall: ACT, no. of patients partially controlled (score 15-19) at 3 months; Group 1: 32/99, Group 2: 23/84; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people overall: ACT, no. of patients partially controlled (score 15-19) at 6 months; Group 1: 19/80, Group 2: 17/70; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people overall: ACT, no. of patients uncontrolled (score <15) at 3 months; Group 1: 5/99, Group 2: 9/84; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people overall: ACT, no. of patients uncontrolled (score <15) at 6 months; Group 1: 7/80, Group 2: 11/70; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	

<p>Protocol outcome 5: Rescue medication at End of Treatment</p> <p>- Actual outcome for Adults and young people overall: puffs/day final values at 3 months; Group 1: mean 0.68 puffs/day (SD 1.16); n=99, Group 2: mean 1.3 puffs/day (SD 2.55); n=84; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Adults and young people overall: puffs/day final values at 6 months; Group 1: mean 0.67 puffs/day (SD 1.33); n=80, Group 2: mean 0.9 puffs/day (SD 1.36); n=70; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 118: RIKKERSMUTSAERTS 2012¹⁴⁶⁴

Study	SMASHING trial: Rijkers-mutsaerts 2012 ¹⁴⁶⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Netherlands; Setting: Primary and Secondary care
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Doctor Dx of mild to severe persistent asthma; not well controlled asthma as assessed by ACQ>0.75 and/or ATAQ <1.0
Stratum	Children 5 -<16 with uncontrolled asthma: Children 12-18 years, asthma not well controlled asthma as assessed by ACQ>0.75 and/or ATAQ <1.0
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12-18 years; prescription of ICS for more than 3 months in the previous year; access to the internet; Dutch language
Exclusion criteria	Receiving maintenance OCS treatment; relevant co-morbidity.
Age, gender and ethnicity	Age - Range: 12-18 years. Gender (M:F): 45/45. Ethnicity:
Further population details	1. Education level: Not applicable / Not stated / Unclear 2. Language: Non English speaking (Dutch speaking).
Extra comments	Baseline data: Age mean (range) Monitoring: 13.4 (12-17), UC: 13.8 (12-17); FEV1%pred Monitoring: 88 (49-151), UC: 92 (49-164); AQLQ Monitoring: 5.6 (3.12-6.97), UC: 5.68 (2.87-7.0); ACQ Monitoring: 1.29 (0.22-3.0), UC: 1.19 (0-3.43); %

	ICS Monitoring: 100%, UC: 100%; % ICS/LABA Monitoring: 60.5%, UC: 65%.
Indirectness of population	Serious indirectness: Age group indirect to protocol (12-18 years); not well controlled asthma includes partially controlled and uncontrolled (not uncontrolled alone)
Interventions	<p>(n=46) Intervention 1: Monitoring asthma control + treatment - Monitoring control questionnaires + treatment. Weekly asthma control monitoring (according to ACQ score) and treatment advice. Monitoring through website, use of internet based treatment plan, online education, web communications with an asthma nurse. Weekly completion of electronic ACQ and instant feedback of asthma control along with advice on how to adjust treatment according to predefined algorithm and treatment plan (treatment steps according to GINA). Patients attended their own physician, as they would normally do, every 3–6 months and extra when needed if their asthma was deteriorating).. Duration 12 months. Concurrent medication/care: Intervention group only: online education, face-to-face group education (two 60 min sessions) and web communications with an asthma nurse. Both groups received prior basic education about asthma, medications and inhaler technique. All trained to measure FEV1 daily and report highest value of 3 measurements before medications. Reported ACQ weekly. No feedback provided on ACQ or lung function. Further details: 1. Additional education training : Additional education in both groups 2. Duration of study: >= 6 months</p> <p>(n=44) Intervention 2: Usual care. Usual care. Adolescents in the usual care group received care by their physician according to the Dutch guidelines on asthma management in children in general practice and in hospitals. Commonly, they visited their general practitioner or paediatrician every 3 months or twice per year once control of asthma had been achieved.. Duration 12 months. Concurrent medication/care: Both groups received prior basic education about asthma, medications and inhaler technique. All trained to measure FEV1 daily and report highest value of 3 measurements before medications. Reported ACQ weekly. No feedback provided on ACQ or lung function. Further details: 1. Additional education training : Additional education in both groups 2. Duration of study: >= 6 months</p>
Funding	Academic or government funding (Netherlands Asthma Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ONGOING MANAGEMENT BASED ON ACQ SCORE versus USUAL CARE + TREATMENT

Protocol outcome 1: Quality of life at End of treatment

- Actual outcome for Children 5 -<16 with uncontrolled asthma: PAQLQ at 3 months; MD 0.4 (95%CI 0.17 to 0.62) (P<0.05) PAQLQ 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

- Actual outcome for Children 5 -<16 with uncontrolled asthma: PAQLQ at 12 months; MD -0.05 (95%CI -0.5 to 0.41) (P=0.85) PAQLQ 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Exacerbation (need for OCS) at End of treatment

<p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: Exacerbation requiring OCS for 3 days or more at 12 months; Group 1: 6/35, Group 2: 6/40; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Asthma control questionnaires at End of Treatment</p> <p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: ACQ at 3 months; MD -0.32 (95%CI -0.56 to -0.079) (P<0.01) ACQ 0-6 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: ACQ at 12 months; MD -0.05 (95%CI -0.35 to 0.25) (P=0.75) ACQ 0-6 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment</p> <p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: Mean daily ICS use µg at 3 months; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: Mean daily ICS use µg at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 5: Lung Function at End of Treatment</p> <p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: FEV1 L at 3 months; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: FEV1 L at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 6: Symptom free days at End of Treatment</p> <p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: Proportion of symptom free days in the previous 2 weeks at 3 months; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: Proportion of symptom free days in the previous 2 weeks at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Rescue medication at End of Treatment; Time of school/work at End of Treatment

1 G.16 Lung function tests to monitor asthma control

2 **Table 119: Adams 2001¹⁵**

Study	Adams 2001 ¹⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=N=172 (no. randomised to each group not reported and also high attrition from ACA numbers - high ROB))

Countries and setting	Conducted in Australia; Setting: Secondary care (university public teaching hospital)
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Physician's diagnosis of asthma defined by American Thoracic Society
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 17 to 70 years; physician's diagnosis of asthma defined by American Thoracic Society; demonstrated ability to use PFM; telephone access at home; could read and sign consent form in English
Exclusion criteria	Previous life-threatening attack of asthma, current or previous written asthma action plan based on symptoms or PEF; pregnancy; poor perception of bronchoconstriction during histamine inhalation test; baseline FEV1 <1.5L preventing histamine inhalation test
Recruitment/selection of patients	Recruited from inpatient and outpatient clinics
Age, gender and ethnicity	Age - Range of means: PFM group 37.3, symptoms group 35.5 years. Gender (M:F): 52:82. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=73) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Self-management action plan activated by decrease in PEF explained by specialist pulmonologist; reinforced monthly by study coordinator. Duration 12 months. Concurrent medication/care: Started or continued on appropriate dose of inhaled corticosteroids; instructed to use bronchodilator as required Further details: 1. Additional education training : Additional education in both groups</p> <p>(n=61) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Self-management action plan activated by increase in symptoms explained by specialist pulmonologist; reinforced monthly by study coordinator. Duration 12 months. Concurrent medication/care: Started or continued on appropriate dose of inhaled corticosteroids; instructed to use bronchodilator as required Further details: 1. Additional education training : Additional education in both groups</p>
Funding	Academic or government funding (University of Adelaide, The Queen Elizabeth Hospital Research Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT

<p>Protocol outcome 1: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment</p> <p>- Actual outcome for Adults and young people (16 years and over): Hospitalisation days at 12 months; Group 1: mean 0.07 days (SD -0.3); n=48, Group 2: mean 0.1 days (SD 0.5); n=40; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Adults and young people (16 years and over): ED visits at 12 months; Group 1: mean 0.11 (SD 0.4); n=48, Group 2: mean 0.15 (SD 0.4); n=40; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 2: Asthma control questionnaires at End of Treatment</p> <p>- Actual outcome for Adults and young people (16 years and over): Severity self-rating at 12 months; Group 1: mean 3.46 None (SD 3.3); n=48, Group 2: mean 3.48 None (SD 2.5); n=40; Self-rating asthma severity 0-10 Top=High is poor outcome; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 3: Lung Function at End of Treatment</p> <p>- Actual outcome for Adults and young people (16 years and over): Pre-bronchodilator FEV1 at 12 months; Group 1: mean 2.45 L (SD 0.82); n=48, Group 2: mean 2.71 L (SD 0.86); n=40; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 4: Time of school/work at End of Treatment</p> <p>- Actual outcome for Adults and young people (16 years and over): Days off work at 12 months; Group 1: mean 5 days (SD 11); n=48, Group 2: mean 2.3 days (SD 4); n=40; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment

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Table 120: Buist 2006²⁴³

Study	Buist 2006 ²⁴³
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=296)
Countries and setting	Conducted in USA; Setting: Community
Line of therapy	Not applicable
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Physician-diagnosed asthma and had medication use suggestive of moderate-to-severe asthma; bronchodilator reversibility (> 8% of baseline FEV1)

Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 50 to 92 yr, recruited from a large managed-care organization; physician-diagnosed asthma and medication use suggestive of moderate-to-severe asthma; none was using a peak flow meter; screening criteria included bronchodilator reversibility (>8% of baseline FEV1) and demonstrated ability to keep a daily symptom diary.
Exclusion criteria	None apart from above
Recruitment/selection of patients	Screening criteria included bronchodilator reversibility (> 8% of baseline FEV1) and demonstrated ability to keep a daily symptom diary.
Age, gender and ethnicity	Age - Mean (SD): 66 (9.4) years. Gender (M:F): 142:154. Ethnicity: 94% were white, not of Hispanic origin; others not stated
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=149) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Peak flow rate (twice daily or “as needed”) for asthma monitoring; four 90-min small-group classes. Development of a personalised action plan and review of the subjects’ asthma diaries; instructed in proper use of metered dose inhalers (MDIs). Interventionists also met with participants semiannually to review MDI and peak flow technique, review daily diaries, and discuss participants’ action plans. In between these meetings, they phoned participants quarterly to review diaries and answer questions . Duration 2 years. Concurrent medication/care: Not stated Further details: 1. Additional education training :</p> <p>(n=147) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Symptoms for asthma monitoring; four 90-min small-group classes. Development of a personalised action plan and review of the subjects’ asthma diaries; instructed in proper use of metered dose inhalers (MDIs). Interventionists also met with participants semiannually to review MDI and peak flow technique, review daily diaries, and discuss participants’ action plans. In between these meetings, they phoned participants quarterly to review diaries and answer questions . Duration 2 years. Concurrent medication/care: Not stated Further details: 1. Additional education training :</p>
Funding	Academic or government funding (National Heart, Lung, and Blood Institute)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT

<p>Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people (16 years and over): AQLQ increase >0.5 points at 2 years; Group 1: 52/134, Group 2: 50/128; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): AQLQ decrease >0.5 points at 2 years; Group 1: 16/134, Group 2: 11/128; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Total asthma-related health care utilisation at 2 years; Group 1: mean 1.39 Events per person-year of follow-up (SD 1.98); n=148, Group 2: mean 1.5 Events per person-year of follow-up (SD 2.23); n=146; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 121: Charlton 1990³⁰⁴

Study	Charlton 1990 ³⁰⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=115 Patients (46 children and 69 adults))
Countries and setting	Conducted in United Kingdom; Setting: General practice
Line of therapy	Not applicable
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients on the repeat prescribing register who were receiving prophylactic treatment for asthma.
Stratum	Adults and young people (16 years and over)

Subgroup analysis within study	Not applicable
Inclusion criteria	Patients on the repeat prescribing register who were receiving prophylactic treatment for asthma.
Exclusion criteria	Not stated
Recruitment/selection of patients	Patients on the repeat prescribing register who were receiving prophylactic treatment for asthma.
Age, gender and ethnicity	Age - --: Not stated. Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=51) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Peak flow self-management plan. The first interview usually took 45 minutes. One week later the patients were reviewed by the nurse for a further 15 minutes, when spirometry was again performed and inhaler technique checked. Progress with self monitoring and self management were checked and treatment altered, if necessary, after discussion with the patient's general practitioner. Topics such as smoking, holidays, provoking factors, and emergency treatments were discussed in the course of the follow up visits. All the patients were reviewed every eight weeks by the nurse or more often if she considered it necessary.. Duration 12 months. Concurrent medication/care: Not stated Further details: 1. Additional education training : Additional education in both groups</p> <p>(n=64) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Symptoms self-management plan. The first interview usually took 45 minutes. One week later the patients were reviewed by the nurse for a further 15 minutes, when spirometry was again performed and inhaler technique checked. Progress with self monitoring and self management were checked and treatment altered, if necessary, after discussion with the patient's general practitioner. Topics such as smoking, holidays, provoking factors, and emergency treatments were discussed in the course of the follow up visits. All the patients were reviewed every eight weeks by the nurse or more often if she considered it necessary.. Duration 12 months. Concurrent medication/care: Not stated Further details: 1. Additional education training : Additional education in both groups</p>
Funding	Academic or government funding (Clare Wand fund, the Scientific Foundation of the Royal College of General

	Practitioners, and Vitalograph)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT</p> <p>Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people (16 years and over): Receiving oral steroids at 12 months; Group 1: 14/27, Group 2: 7/33; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : Receiving oral steroids at 12 months; Group 1: 7/19, Group 2: 0/27; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Rescue medication at End of Treatment - Actual outcome for Adults and young people (16 years and over): Requiring nebulised salbutamol at 12 months; Group 1: 3/28, Group 2: 2/37; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : Requiring nebulised salbutamol at 12 months; Group 1: 2/17, Group 2: 0/27; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

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Table 122: Cote 1997³⁶⁹

Study	Cote 1997 ³⁶⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=188)
Countries and setting	Conducted in Canada; Setting: Three tertiary care hospitals
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: The diagnosis had to be confirmed by either a documented reversibility greater than 15% in FEV1 or a methacholine PC20<8mg/ml

Stratum	Adults and young people (16 years and over): Aged 16 years or older
Subgroup analysis within study	Not applicable
Inclusion criteria	Presence of moderate to severe asthma; aged 16 years or older; the need to take daily anti-inflammatory agents (ICS, cromoglycate or nedocromil).
Exclusion criteria	Current or ex-smokers 40 years of age or older in whom the best FEV1 after salbutamol was <80% predicted; patients with significant concurrent diseases; those requiring >7.5mg/day of prednisone to control asthma symptoms, those having taken part in an asthma educational program. Subjects in whom regular OCS were needed to obtain good asthma control during the run-in period were excluded.
Recruitment/selection of patients	At time of hospitalisation or visit to the clinic between April and December 1993
Age, gender and ethnicity	Age - Range: ≥16 years. Gender (M:F): 37/58. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=50) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Self-management based on twice daily PEF. - Step 1: green zone, morning PEF ≥85% best, continue maintenance treatment- Step 2: yellow zone, for past 24 hours PEF 60-85% best, increase BDP to 4 puffs twice daily (2000mcg/day) until PEF % best returns, or if there is no increase in PEF within 48 hours proceed to step 3.- Step 3: red zone, for past 12 hours PEF <60% best, inform physician and start OCS- Step 4: red extra zone, PEF <50% best, visit physician or ER.. Duration 12 months. Concurrent medication/care: 2-6 week run-in period when medication adjusted according to the International Consensus on asthma therapy. In patients receiving budesonide, this was replaced by an equivalent dose of inhaled beclomethasone dipropionate (BDP). In patients considered unstable during run-in period (nighttime symptoms, four or more puffs/day of inhaler beta-agonist, PEFv>15%, post-BD FEV1<85%, mean PEF <85%) the dose of BDP could be doubled or theophyllines added. Subjects in whom regular OCS were needed to obtain good asthma control were excluded. Both groups received counselling with an educator during a 1 hour session.</p> <p>Further details: 1. Additional education training : Additional education in both groups</p> <p>(n=45) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Self-management based on symptoms. - Step 1: green zone, not awakened at night, using usual SABA and able to perform usual activities, continue maintenance treatment- Step 2: yellow zone, for previous 24 hours using twice as much SABA, awakened at night and unusual breathlessness with exercise, increase BDP to 4 puffs twice daily (2000mcg/day) until PEF % best returns, or if there is no increase in PEF within 48 hours proceed to step 3.- Step 3: red zone, for past 24 hours SABA relieving symptoms for <4 hours or more than 10puffs/day, inform physician and start OCS- Step 4: red extra zone, SABA relieving symptoms for <2 hours and difficulty talking, inform physician and visit ER.. Duration 12 months. Concurrent</p>

	<p>medication/care: 2-6 week run-in period when medication adjusted according to the International Consensus on asthma therapy. In patients receiving budesonide, this was replaced by an equivalent dose of inhaled beclomethasone dipropionate (BDP). In patients considered unstable during run-in period (nighttime symptoms, four or more puffs/day of inhaler beta-agonist, PEFv>15%, post-BD FEV1<85%, mean PEF <85%) the dose of BDP could be doubled or theophyllines added. Subjects in whom regular OCS were needed to obtain good asthma control were excluded. Both groups received counselling with an educator during a 1 hour session.</p> <p>Further details: 1. Additional education training : Additional education in both groups</p>
Funding	Study funded by industry (Supported by a grant from Glaxo Canada, Mississauga (Ontario))
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT</p> <p>Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people (16 years and over): OCS courses at 12 months; Group 1: mean 0.7 number of events (SD 1.4); n=50, Group 2: mean 0.9 number of events (SD 1.3); n=45; Risk of bias: Very high; Indirectness of outcome: Serious indirectness</p> <p>Protocol outcome 2: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Hospitalisation at 12 months; Group 1: mean 0.04 number of events (SD 0.28); n=50, Group 2: mean 0.09 number of events (SD 0.27); n=45; Risk of bias: Very high; Indirectness of outcome: Serious indirectness - Actual outcome for Adults and young people (16 years and over): ER visits at 12 months; Group 1: mean 0.7 number of events (SD 1.4); n=50, Group 2: mean 0.7 number of events (SD 1.3); n=50; Risk of bias: Very high; Indirectness of outcome: Serious indirectness</p> <p>Protocol outcome 3: Time of school/work at End of Treatment - Actual outcome for Adults and young people (16 years and over): Mean number of days lost from school or work at 12 months; Group 1: mean 2.2 number of days lost (SD 12.7); n=50, Group 2: mean 2.9 number of days lost (SD 12.7); n=45; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment

Table 123: Cowie 1997³⁷⁴

Study	Cowie 1997 ³⁷⁴
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Canada; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Adult and adolescent patients who had received urgent treatment for their asthma in the preceding 12 months and used asthma medication
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult and adolescent patients who had received urgent treatment for their asthma in the preceding 12 months and used asthma medication
Exclusion criteria	Not stated
Recruitment/selection of patients	Subjects were recruited by contacting those who had been treated for an exacerbation of asthma in an emergency department in one of the teaching hospitals in the city of Calgary. Subjects were also recruited from those attending a university asthma clinic when they gave a history of having received urgent treatment for their asthma in the previous 12 months.
Age, gender and ethnicity	Age - Range of means: 36.4 to 39.1 years. Gender (M:F): 56:83. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=48) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Patients were given a peak flowmeter and brief instructions in its use and in recording the data. Their action plan included peak flow measurements that were estimated from their measured and predicted peak expiratory flows. Peak flow readings at or below which each step should be initiated were written into each subject's action plan. Doubling of their inhaled corticosteroid was recommended when the peak expiratory flow was <70% of their estimated best reading or when the diurnal variation was >20%. Initiation of the third step (prednisone) was advised at <50%, and the fourth step (urgent treatment in an emergency department) at <30% of their estimated best peak expiratory flow.. Duration 6 months. Concurrent medication/care: Not stated</p> <p>Further details: 1. Additional education training :</p> <p>(n=50) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. The instructions for the symptom-based plan listed common symptoms of asthma, including waking at night or a persistent cough and</p>

	<p>symptoms of a common cold as indications for doubling their inhaled corticosteroid. The third step required the introduction of prednisone if their relief following the use of a bronchodilator lasted <2 h or if they became short of breath doing their normal daily activities. The fourth step required them to seek urgent treatment if their bronchodilator provided relief for <30 min or if their breathing made it difficult for them to speak.. Duration 6 months. Concurrent medication/care: Not stated</p> <p>Further details: 1. Additional education training :</p>
Funding	Academic or government funding (Foothills Hospital Calgary)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT</p> <p>Protocol outcome 1: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment</p> <p>- Actual outcome for Adults and young people (16 years and over): Visits for urgent treatment of asthma at 6 months; Group 1: 5/46, Group 2: 14/45; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Adults and young people (16 years and over): Hospital admissions at 6 months; Group 1: 2/46, Group 2: 2/45; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	<p>Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment</p>

Table 124: Kaya 2009⁸³⁵

Study	Kaya 2009 ⁸³⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Turkey; Setting: Secondary care
Line of therapy	Not applicable
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients with persistent asthma; had been receiving care for at least 1 year in specific asthma clinic; classified by GINA guidelines on illness severity

Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with persistent asthma; had been receiving care for at least 1 year in specific asthma clinic; classified by GINA guidelines on illness severity
Exclusion criteria	Significant co-morbid conditions; illiteracy; hearing and visual defects; mental retardation; psychotic disorders
Recruitment/selection of patients	Specific asthma clinic
Age, gender and ethnicity	Age - Mean (SD): 43 (10.48) years. Gender (M:F): 13:50. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=31) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. PEF-based self-management. Duration 12 months. Concurrent medication/care: Standard education programme on asthma self-management prepared according to GINA recommendations given to patients with booklet for keeping daily records Further details: 1. Additional education training : Additional education in both groups</p> <p>(n=32) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Symptom-based self-monitoring. Duration 12 months. Concurrent medication/care: Standard education programme on asthma self-management prepared according to GINA recommendations given to patients with booklet for keeping daily records Further details: 1. Additional education training : Additional education in both groups</p>
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT

Protocol outcome 1: Quality of life at End of treatment

- Actual outcome for Adults and young people (16 years and over): SF-36 physical score at 3 months; Group 1: mean 58.81 None (SD 21.98); n=31, Group 2: mean 65.3 None (SD 21.31); n=32; SF-36 Physical 0-100 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness
 - Actual outcome for Adults and young people (16 years and over): SF-36 mental score at 3 months; Group 1: mean 62.39 None (SD 19.1); n=31, Group 2: mean 74.17 None (SD 15.51); n=32; SF-36 Mental 0-100 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Lung Function at End of Treatment

- Actual outcome for Adults and young people (16 years and over): FEV1 (%) at 6 months; Group 1: mean 87.74 % (SD 19.02); n=31, Group 2: mean 87.35 % (SD 21.25); n=32; Risk of bias: Very high; Indirectness of outcome: No indirectness

- Actual outcome for Adults and young people (16 years and over): PEF (% personal best) at 6 months; Group 1: mean 84.93 % (SD 14.32); n=31, Group 2: mean 79.62 % (SD 14.92); n=32; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 125: Letz 2004⁹⁹⁶

Study	Letz 2004 ⁹⁹⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in USA; Setting: Allergy, asthma and immunology clinic
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 3 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed with mild to severe persistent asthma (symptoms at least 2 times per week, FEV1<80% and FEV1 or PEF variability 12% or greater). Diagnosis made on the basis of history, examination and pre/post-BD lung function testing.
Stratum	Children 5 -<16 : 6-12 years
Subgroup analysis within study	Not applicable
Inclusion criteria	6-12 years, diagnosed with mild to severe persistent asthma (symptoms at least 2 times per week, FEV1<80% and FEV1 or PEF variability 12% or greater), new diagnosis and initiation of daily ICS.
Exclusion criteria	nr
Recruitment/selection of patients	Consecutive recruitment at 2 week follow up after diagnosis and initiation of ICS.
Age, gender and ethnicity	Age - Range of means: 8.9-9.4. Gender (M:F): 32/18. Ethnicity: Caucasian
Further population details	
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Action plan based on

	<p>patient's measured and predicted PEF values. Yellow zone recommended when PEF 60-80%, red zone when PEF <60%. Best of 3 consecutive PEF readings recorded daily. Baseline therapy with ICS (green zone), step-up of ICS and beta-agonists used every 4 hours (yellow zone), call office or present to emergency room (red zone). . Duration 3 months. Concurrent medication/care: All provided with asthma education session from a nurse including use of the action plan. Further details: 1. Additional education training : Additional education in both groups</p> <p>(n=25) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Action plan based on symptoms only. Common symptoms including persistent cough, symptoms of common cold, dyspnoea as indications for initiating yellow zone. Red zone if relief following a BD lasted less than 2 hours. Baseline therapy with ICS (green zone), step-up of ICS and beta-agonists used every 4 hours (yellow zone), call office or present to emergency room (red zone).. Duration 3 months. Concurrent medication/care: All provided with asthma education session from a nurse including use of the action plan. Further details: 1. Additional education training : Additional education in both groups</p>
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT</p> <p>Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : Required a course of OCS at 3 month; Group 1: 1/12, Group 2: 1/12; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	<p>Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment</p>

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Table 126: Lopez-vina 2000¹⁰³⁹

Study	Lopez-vina 2000¹⁰³⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Spain

Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Satisfied the ATS definition of asthma, with symptoms of episodic wheezing, cough and shortness of breath responding to bronchodilators, and reversible airflow obstruction documented on at least one previous pulmonary function study (>20% increase in FEV1 or PEF following salbutamol 0.2mg). In patients with normal spirometry and lac of functional assessment of asthma previously, a methacholine test was performed.
Stratum	Adults and young people (16 years and over): 17-65 years of age
Subgroup analysis within study	Not applicable
Inclusion criteria	17-65 years of age; required treatment in an ED of acute-care hospitals over an 18-month period because of an episode of acute asthma exacerbation; symptomatic disease during the previous year; satisfied the ATS definition of asthma with BDR or BHR.
Exclusion criteria	Concurrent chronic diseases (COPD, emphysema, cystic fibrosis, severe rheumatoid arthritis, neoplasia etc)
Recruitment/selection of patients	Consecutive patients who required treatment in an ED over an 18-month period
Age, gender and ethnicity	Age - Range: 17-65. Gender (M:F): 49/51. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=75) Intervention 1: Monitoring lung function + treatment - Monitoring PEF and symptoms + treatment. Self-management plan with a card of colour codes based on symptoms, medication and PEF. Physician assessment at 15 days, 1 month and then every 3 months at which treatment adjusted according to symptoms, spirometric data and variability in PEF (less than 10% variability considered irrelevant). Duration 12 months. Concurrent medication/care: Medical regimes tailored to each patient and included the administration of beta-agonists when needed in mild asthma; inhaled salbutamol 0.2mg or terbutaline 0.5mg and budesonide 400mcg every 12 hours in moderate to severe asthma with FEV1>80%; and inhaled salbutamol 0.2mg or terbutaline 0.5mg and budesonide 800mcg every 8 hours or when needed and prednisone 40mg/day for 14 days in moderate to severe asthma with FEV1<80%. Patients in both groups received asthma education.</p> <p>Further details: 1. Additional education training : Additional education in both groups</p> <p>(n=75) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Self-management plan based on symptoms only. Physician assessment at 15 days, 1 month and then every 3 months at which treatment adjusted according to symptoms and spirometric data only.. Duration 12 months. Concurrent medication/care: Medical regimes tailored to each patient and included the administration of beta-agonists when needed in mild asthma; inhaled</p>

	salbutamol 0.2mg or terbutaline 0.5mg and budesonide 400mcg every 12 hours in moderate to severe asthma with FEV1>80%; and inhaled salbutamol 0.2mg or terbutaline 0.5mg and budesonide 800mcg every 8 hours or when needed and prednisone 40mg/day for 14 days in moderate to severe asthma with FEV1<80%. Patients in both groups received asthma education. Further details: 1. Additional education training : Additional education in both groups
Funding	Academic or government funding (Supported in part by grant FISS 92/372)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF, MEDICATION AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOMS + TREATMENT</p> <p>Protocol outcome 1: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Number of patients with visits to an emergency ward at 12 months; Group 1: 3/56, Group 2: 0/44; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): Number of patients with a hospital admission at 12 months; Group 1: 2/56, Group 2: 0/44; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): FEV1% predicted at 12 months; Group 1: mean 80.9 % (SD 2.3); n=56, Group 2: mean 80.8 % (SD 2.8); n=44; FEV1 %pred 0-100 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Time of school/work at End of Treatment - Actual outcome for Adults and young people (16 years and over): Number of patients with absenteeism school/work at 12 months; Group 1: 2/56, Group 2: 0/44; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment

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Table 127: Turner 1998¹⁸⁰³

Study	Turner 1998¹⁸⁰³
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=117)

Countries and setting	Conducted in Canada; Setting: Primary care
Line of therapy	Not applicable
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: PC20 methacholine < 8 mg/ml
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Between 18 and 55 yr of age with moderate to moderately severe asthma. The authors defined asthma severity by including only patients with a baseline PC20 methacholine < 8 mg/ml and a daily requirement for inhaled corticosteroids to manage their asthma symptoms. Patients were either newly prescribed inhaled corticosteroids independently by their family physician or were currently using inhaled corticosteroids.
Exclusion criteria	Exclusion criteria included significant comorbid conditions that would impact on QOL measurements, current use of a PFM, inability to use a PFM, and inability to communicate in English.
Recruitment/selection of patients	Potential study patients were identified from the clinic computer database, and the clinic physicians were encouraged to refer patients meeting study criteria. The authors displayed a poster board and flyer advertisements in the clinic to encourage volunteers. All patients had written permission from their physician to participate.
Age, gender and ethnicity	Age - Mean (SD): PEF group: 34.1 (10.5); symptoms group: 34.1 (9.4) years. Gender (M:F): 43:49. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=53) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. The asthma nurse reviewed patients monthly for 6 mo after the initial visit (seven total visits). The self-management plans and use of a PFM were reviewed in detail after randomization. Monthly visits documented morbidity outcomes, reinforced and evaluated use of the self-management plan, and provided ongoing education. Duration 6 months. Concurrent medication/care: Not stated Further details: 1. Additional education training :</p> <p>(n=64) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. The asthma nurse reviewed patients monthly for 6 mo after the initial visit (seven total visits). The self-management plans were reviewed in detail after randomization. Monthly visits documented morbidity outcomes, reinforced and evaluated use of the self-management plan, and provided ongoing education. Duration 6 months. Concurrent medication/care: Not stated Further details: 1. Additional education training :</p>

Funding	Study funded by industry (Glaxo Wellcome Canada Inc.)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT</p> <p>Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people (16 years and over): Asthma Quality of Life Questionnaire at 6 months; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people (16 years and over): Prednisone treatments at 6 months; Group 1: 3/44, Group 2: 6/48; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Unscheduled doctor visits at 6 months; Group 1: 17/44, Group 2: 12/48; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): Hospitalisation at 6 months; Group 1: 0/44, Group 2: 1/48; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): ED visits at 6 months; Group 1: 6/44, Group 2: 2/48; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): FEV1 % pred at 6 months; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): PEF at 6 months; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 5: Time of school/work at End of Treatment - Actual outcome for Adults and young people (16 years and over): Time off school/work at 6 months; Group 1: 9/44, Group 2: 8/48; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment

Table 128: Wensley 2004¹⁹⁰⁶

Study	Wensley 2004 ¹⁹⁰⁶
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in United Kingdom; Setting: Recruitment in primary care and secondary care.
Line of therapy	Not applicable
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Physician-diagnosed asthma and at least step 2 of the British Thoracic Society Guidelines for Asthma Management (regular inhaled corticosteroid therapy)
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria were (1) age 7–14 years, (2) physician-diagnosed asthma, (3) at least step 2 of the British Thoracic Society Guidelines for Asthma Management (regular inhaled corticosteroid therapy), (4) stable treatment for 1 month, (5) no other respiratory problem, (6) competent at spirometry, and (7) a successful 4-week run-in period.
Exclusion criteria	None stated
Recruitment/selection of patients	Withdrawals after run-in phase (n=27) due to refusal, poor comprehension or poor compliance, technical problems, equipment failure or GP advice
Age, gender and ethnicity	Age - Median (range): Symptoms group: 12 (7–14); PEF group: 11 (7–14) years. Gender (M:F): 48:42. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Monitoring lung function + treatment - Monitoring PEF + treatment. Group PF based on symptoms plus PEF. A written symptom diary was completed each morning, and spirometry was performed twice daily. The spirometers of those children randomized to the PF group were reprogrammed so that the PEF value for any maneuver (but not other spirometric values) was visible to them at any time. The child and the main caregiver were taught self-management at a training session, which also included training in spirometry and symptom recording and which lasted 30–90 minutes according to need. A printed plan incorporating the child’s own medication regime was color coded: green, PEF more than 70%, few symptoms (carry on as usual); yellow, PEF 50–70% after beta2 agonist (double-inhaled corticosteroid as well as taking additional beta2-agonist therapy); and red, PEF less than 50% after taking additional inhaled beta2 agonist, severe symptoms (commence oral prednisolone and/or seek medical help). The PEF levels for action were based on the child’s best previous PEF.. Duration 12 weeks. Concurrent medication/care: Not stated Further details: 1. Additional education training :

	(n=46) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Group S based on symptoms alone; the S group did not have access to any lung function results throughout the study.. Duration 12 weeks. Concurrent medication/care: Not stated Further details: 1. Additional education training :
Funding	Study funded by industry (United Kingdom National Asthma Campaign and Glaxo SmithKline, United Kingdom.)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF + TREATMENT versus MONITORING SYMPTOMS + TREATMENT</p> <p>Protocol outcome 1: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Children 5 <-16 : Emergency GP visits at 12 weeks; Group 1: 10/44, Group 2: 11/45; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children 5 <-16 : Hospital admissions at 12 weeks; Group 1: 1/44, Group 2: 0/45; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children 5 <-16 : Attendance at A&E at 12 weeks; Group 1: 1/44, Group 2: 0/45; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Children 5 <-16 : FEV1 at 12 weeks; Group 1: mean 87.3 % of best value (SD 1.33); n=44, Group 2: mean 86.9 % of best value (SD 1.54); n=45; Percentage 0-100% Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 <-16 : PEF at 12 weeks; Group 1: mean 83.4 % (SD 1.39); n=44, Group 2: mean 80.6 % (SD 1.74); n=45; Percentage 0-100% Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Symptom free days at End of Treatment - Actual outcome for Children 5 <-16 : Proportion of symptom-free days at 12 weeks; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Time of school/work at End of Treatment - Actual outcome for Children 5 <-16 : Time off school at 12 weeks; Group 1: 15/44, Group 2: 13/45; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment

Table 129: Yoos 2002¹⁹⁶³

Study	Yoos 2002¹⁹⁶³
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Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=168)
Countries and setting	Conducted in USA; Setting: 11 primary care settings
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: All school-aged children who carried a diagnosis of asthma
Stratum	Children 5 -<16 : Aged 6-19 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 6-19 years with a diagnosis of asthma, more that 3 asthma-related healthcare visits in the previous 12 months, English speaking, the child had not used a PEF meter in the previous 6 months.
Exclusion criteria	Children with mild asthma who were rarely symptomatic (had not had more than 3 asthma related healthcare visits in the previous 12 months).
Recruitment/selection of patients	All school-aged children who carried a diagnosis of asthma identified through computerised data sets.
Age, gender and ethnicity	Age - Range: 6-19 years. Gender (M:F): 99/69. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=57) Intervention 1: Monitoring lung function + treatment - Monitoring PEF and symptoms + treatment. Personal action plan zones based on symptoms and PEF. Green zone, yellow zone (rescue medication) and red zone (contact healthcare provider).. Duration 3 months. Concurrent medication/care: Both groups received asthma education and a personal action plan. Two week run-in period with allocated self-management method and at the end of this period the nurse established zones based on PEF best and developed a personal action plan based on PEF and symptoms. Further details: 1. Additional education training : Additional education in both groups</p> <p>(n=56) Intervention 2: No lung function monitoring + treatment - Monitoring symptoms + treatment. Personal action plan zones based on symptoms only. Green zone, yellow zone (rescue medication) and red zone (contact healthcare provider).. Duration 3 months. Concurrent medication/care: Both groups received asthma education and a personal action plan. Two week run-in period with allocated self-management method and at the end of this period the nurse established zones based on symptoms and developed a personal action plan based on symptoms. Further details: 1. Additional education training : Additional education in both groups</p>

Funding	Academic or government funding (Supported by NIH grants)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING PEF AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOMS + TREATMENT	
Protocol outcome 1: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : FEV1 % predicted at 3 months; Group 1: mean 88 % (SD 20.6); n=57, Group 2: mean 90 % (SD 21); n=56; FEV1 %pred 0-100 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

1 G.17 FeNO to monitor asthma control

2 **Table 130: Calhoun 2012²⁶⁴**

Study	BASALT trail trial: Calhoun 2012²⁶⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=342)
Countries and setting	Conducted in USA; Setting: Secondary - adjustments of inhaled corticosteroids made at outpatient visits
Line of therapy	Mixed line
Duration of study	Intervention time: 9 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All patients had a physician diagnosis of asthma, and either reversible airflow limitation ($\geq 12\%$ improvement in forced expiratory volume in the first second of expiration [FEV1] after 360 mcg of albuterol), or airway hyperresponsiveness (provocative concentration of methacholine [$< 8\text{mg/ml}$] causing a 20% drop in FEV1)
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Mild to moderate persistent asthma, acceptable control of asthma (i.e. a score of 0 or 1 on each of the 3

	questions on the Asthma Evaluation Questionnaire and predicted bronchodilator FEV1 >70%), and patients who demonstrated at least 75% adherence (i.e. those patients that could tolerate 2 puffs twice daily of beclomethasone HFA (40 mcg/puff)) during the run-in period
Exclusion criteria	Poorly controlled, severe asthma
Recruitment/selection of patients	Participants were recruited cooperatively with a concurrent Asthma Clinical Research Network trial
Age, gender and ethnicity	Age - Mean (SD): 35 (11.83). Gender (M:F): 105/237. Ethnicity: White: 216, Black: 69, Hispanic: 38, Asian/Pacific Islander:13, Other: 5, American Indian/Alaska Native: 1
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=114) Intervention 1: No FeNO monitoring + treatment - Monitoring symptoms and lung function + treatment. Dose of inhaled corticosteroids was adjusted by an investigator according to a strategy based on National Heart, Lung, and Blood Institute guidelines (PABA). Dose adjustments of inhaled corticosteroids were made at the time of clinic visits (every 6 weeks). Treatment step down - PABA: Physician assessment-based adjustment, inhaler A (1). Fev1 ≥85% at baseline, plus symptoms in past 2 wk ≤2 d/wk (all AEQ of 0); control status: well controlled; inhaler dose change: down 1 level. (2). Fev1 ≥85% at baseline, plus symptoms no worse than mild (AEQ scores of 0 or 1 on each question); control status: controlled; inhaler dose change: maintain current level. (3). Fev1 <85% at baseline, moderate symptoms (any AEQ score of 2 or 3), or meets criteria for treatment failure; control status: under controlled; inhaler dose change: up 1 level. . Duration 9 months. Concurrent medication/care: During the prerandomisation period, patients were given 3 inhalers coded as A, B, and C. Inhaler A contained beclomethasone HFA (40 mcg/puff), and inhalers B and C contained placebo. An albuterol inhaler was provided for use as needed for asthma symptoms. Participants were instructed to use 2 puffs twice daily from inhalers A and B, and to use 2 puffs from inhaler C each time they used 2 puffs of albuterol for symptom relief. Participants who demonstrated 75% adherence were randomised to one of the adjustment strategies (PABA, BBA, or SBA (occurrence of symptoms - data not extracted)). Beclomethasone HFA was provided at a dosage of 2 puffs twice daily (40 mcg/puff) before randomisation, corresponding to level 3 treatment. Hence, inhaled corticosteroid therapy could be intensified or deintensified during the trial. Following randomisation, beclomethasone HFA was contained only in inhaler A for PABA participants, only in inhaler B for BBA patients, and only in inhaler C for SBA participants. Thereafter, inhalers were adjusted according to the strategy assigned (i.e. PABA or BBA). Subsequent visits occurred at 2, 4, 6, 12, 18, 24, 30, and 36 weeks after randomisation.</p> <p>Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to decrease ICS in controlled patients (To evaluate different approaches to dose adjustment of inhaled corticosteroids in a 3-group trial during 9 months in adults with mild to moderate asthma that was well controlled with low-dose inhaled corticosteroids).</p>

(n=115) Intervention 2: Monitoring FeNO + treatment. Dose of inhaled corticosteroids was adjusted by an investigator according to exhaled nitric oxide (BBA). Dose adjustments of inhaled corticosteroids were made at the time of clinic visits (every 6 weeks). BBA: Biomarker-based adjustment, inhaler B. Fraction of exhaled nitric oxide, ppb: (1). <22; control status: well controlled; inhaler dose change: down 1 level. (2). 22-35; control status: controlled; inhaler dose change: maintain current level. (3). >35; control status: under controlled; inhaler dose change: up 1 level. Inhaled corticosteroids dose level: (1) none, na; (2) 80 (2 puffs), once daily (am); (3) 160 (2 puffs), twice daily; (4) 320 (4 puffs), twice daily; (5) 640 (8; 4 puffs at double strength), twice daily.. Duration 9 months. Concurrent medication/care: During the prerandomisation period, patients were given 3 inhalers coded as A, B, and C. Inhaler A contained beclomethasone HFA (40 mcg/puff), and inhalers B and C contained placebo. An albuterol inhaler was provided for use as needed for asthma symptoms. Participants were instructed to use 2 puffs twice daily from inhalers A and B, and to use 2 puffs from inhaler C each time they used 2 puffs of albuterol for symptom relief. Participants who demonstrated 75% adherence were randomised to one of the adjustment strategies (PABA, BBA, or SBA (occurrence of symptoms - data not extracted)). Beclomethasone HFA was provided at a dosage of 2 puffs twice daily (40 mcg/puff) before randomisation, corresponding to level 3 treatment. Hence, inhaled corticosteroid therapy could be intensified or deintensified during the trial. Following randomisation, beclomethasone HFA was contained only in inhaler A for PABA participants, only in inhaler B for BBA patients, and only in inhaler C for SBA participants. Thereafter, inhalers were adjusted according to the strategy assigned (i.e. PABA or BBA). Subsequent visits occurred at 2, 4, 6, 12, 18, 24, 30, and 36 weeks after randomisation.

Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to decrease ICS in controlled patients (To evaluate different approaches to dose adjustment of inhaled corticosteroids in a 3-group trial during 9 months in adults with mild to moderate asthma that was well controlled with low-dose inhaled corticosteroids).

Funding

Academic or government funding (Study was conducted with the support of the Institute for Translational Sciences at the University of Texas Medical Branch, supported in part by a Clinical and Translational Science Award from the National Center for Advancing Translational Sciences, National Institutes of Health. The study was also supported by National Institutes of Health grants that were awarded by the National Heart, Lung, and Blood Institute. Teva Pharmaceuticals provided the study drug and matching placebo.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT

Protocol outcome 1: Quality of life at End of treatment

<p>- Actual outcome for Adults and young people (16 years and over): AQLQ at 9 months; MD 0.00 (SE 0.11); Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 2: Exacerbation (need for OCS) at End of treatment</p> <p>- Actual outcome for Adults and young people (16 years and over): Asthma exacerbation (including multiple episodes) at 36 weeks; HR InHR -0.095 (SE 0.429); Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 3: Asthma control questionnaires at End of Treatment</p> <p>- Actual outcome for Adults and young people (16 years and over): ACQ at 9 months; MD -0.04 (SE 0.08); Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 4: Rescue medication at End of Treatment</p> <p>- Actual outcome for Adults and young people (16 years and over): Rescue medication - albuterold rescue use (puffs) at 9 months; MD -0.06 (SE 0.034119); Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 5: Dose of regular asthma treatment (SABA, ICS) at End of Treatment</p> <p>- Actual outcome for Adults and young people (16 years and over): Dose of regular asthma therapy (ICS, beclomethasone HFA (40 mcg/puff)) at 36 weeks; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 6: Lung Function at End of Treatment</p> <p>- Actual outcome for Adults and young people (16 years and over): Lung function - am peak flow 2-week average prior to visit 4, L/min at 9 months; MD 2.3 (SE 7.2); Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Adults and young people (16 years and over): Lung function - pm peak flow 2-week average prior to visit 4, L/min at 9 months; MD 3.8 (SE 7.04); Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Adults and young people (16 years and over): Lung function - prebronchodilator FEV1 at 9 months; MD 0.98 (SE 0.96); Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 7: Time of school/work at End of Treatment</p> <p>- Actual outcome for Adults and young people (16 years and over): Time off school/work (no. of patients) at 36 weeks; OR InOR 0.693 (SE 0.273); Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcomes not reported by the study</p>	<p>Mortality at End of Treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Symptom free days at End of Treatment</p>

Table 131: de Jongste 2009⁴⁰²

Study	CHARISM (Children with Asthma subjected to Respiratory Inflammatory Status Monitoring) trial: De jongste 2009 ⁴⁰²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in Netherlands; Setting: Secondary (clinic visits, data transmitted daily to centre, telephone contact).
Line of therapy	Mixed line
Duration of study	Intervention time: 30 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed according to GINA guidelines
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Age: 6-18 years; stable mild-moderate atopic asthma, diagnosed according to GINA guidelines; treatment with 200-1000 mcg of inhaled budesonide or equivalent daily for 2 months before randomisation; and RAST class 2 or higher or a positive skin prick test for at least one airborne allergen.
Exclusion criteria	Exclusion criteria were as follows: active smoking, previous admission to an intensive care unit for asthma, and concomitant disease that might affect FeNO.
Recruitment/selection of patients	Participants were recruited from 5 academic centres and 12 general hospitals.
Age, gender and ethnicity	Age - Mean (SD): 11.7 (3.538). Gender (M:F): 100/51. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Monitoring FeNO + treatment - Monitoring FeNO and symptoms + treatment. Children in the FeNO group received an airway inflammation monitor (NIOX MINO; Aerocrine, Solna, Sweden) that measures FeNO. Measurements were performed daily. Measurement time was recorded by the device. Data was transmitted to the coordinating centre. All parents were phoned every 3 weeks between visits, and medication was adapted according to geometric mean FeNO over the preceding 3 weeks and cumulative symptom scores. Algorithm: (a) symptom score, high; FeNO, high; adjustment, increase; (b) symptom score, high; FeNO, low; adjustment, no change; (c) symptom score, low; FeNO, high; adjustment, increase; (d) symptom score, low; FeNO, low; adjustment, decrease or discontinue. Cut-off level for symptom score - high score: >60, low score ≤60 cumulative in 3 weeks. Cut-off levels for FeNO were 20 ppb for children aged 6-10 years and 25 ppb for older children. . Duration 30 weeks. Concurrent medication/care: Monitored children with atopic asthma for 30 weeks. Children were randomised at first visit, stratified by centre. ICS doses were adjusted every 3 weeks on the basis of either FeNO and symptoms, or symptom

	<p>scores alone. All children recorded asthma symptoms in a palmtop diary. Entries were transmitted daily to the coordinating centre. Children in both groups were seen at randomisation and at 3, 12, 21, and 30 weeks. Doses were changed according to predefined steps for each type of inhaled steroid, for example, budesonide at 100, 200, 400, 800, and 1,200 mcg. Maximal allowed dose: 1200 mcg of budesonide or equivalent. If a combination of ICS and long-acting beta-agonist (LABA) was used, the LABA was stopped whenever decrease was required at the lowest ICS dose, before stopping ICS. Steroids were stopped for 6 weeks with low symptom scores at the lowest steroid dose level. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear</p> <p>(n=74) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms + treatment. All parents were phoned every 3 weeks between visits. Algorithm: symptom score: above average (adjustment - increase); in range (no change); below range (decrease or discontinue). Cut-off level: the "normal range" was 10-60. Duration 30 weeks. Concurrent medication/care: Monitored children with atopic asthma for 30 weeks. Children were randomised at first visit, stratified by centre. ICS doses were adjusted every 3 weeks on the basis of either FeNO and symptoms, or symptom scores alone. All children recorded asthma symptoms in a palmtop diary. Entries were transmitted daily to the coordinating centre. Children in both groups were seen at randomisation and at 3, 12, 21, and 30 weeks. Doses were changed according to predefined steps for each type of inhaled steroid, for example, budesonide at 100, 200, 400, 800, and 1,200 mcg. Maximal allowed dose: 1200 mcg of budesonide or equivalent. If a combination of ICS and long-acting beta-agonist (LABA) was used, the LABA was stopped whenever decrease was required at the lowest ICS dose, before stopping ICS. Steroids were stopped for 6 weeks with low symptom scores at the lowest steroid dose level. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear</p>
<p>Funding</p>	<p>Study funded by industry (Supported by a research grant from Aerocrine AB (Solna, Sweden). Conflict of interest statement: authors received travel grants, research grants and lectured at scientific meetings for the following: GlaxoSmithLine, Merck Sharp & Dohme, Altana Pharma, Aerocrine, Abbott, Valeas, Chiesi and Roche. Also note that the Department of Paediatrics/Erasmus MC Holding received research grants from GlaxoSmithKline, AstraZeneca, Aerocrine, Roche, Freisland Foods, Transave, Chiron, and Pfizer.)</p>
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOMS + TREATMENT</p> <p>Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Children 5 -<16 : PACQLQ(S) - Paediatric Asthma Caregiver Quality of Life Questionnaire with Standardised Activities at 30 weeks; Group 1: mean</p>	

6.2 (SD 0.8); n=75, Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : Exacerbation - OCS, prednisone course at 30 weeks; Group 1: 9/75, Group 2: 12/72; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcome 3: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Children 5 -<16 : UHU at 30 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcome 4: Rescue medication at End of Treatment - Actual outcome for Children 5 -<16 : Rescue medication - beta agonist puffs per 3 weeks at 30 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcome 5: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Dose of regular therapy - ICS, budesonide at 30 weeks; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcome 6: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : Lung function - FEV1 at 30 weeks; Group 1: mean 95 % (SD 14); n=75, Group 2: mean 94 % (SD 14); n=72; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcome 7: Symptom free days at End of Treatment - Actual outcome for Children 5 -<16 : % symptom free days over last 12 weeks at 30 weeks; MD 0.3 (95%CI -10 to 11); Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Asthma control questionnaires at End of Treatment; Time of school/work at End of Treatment

Table 132: Fritsch 2006⁵²⁸

Study	Fritsch 2006 ⁵²⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=47)
Countries and setting	Conducted in Austria; Setting: Secondary care - Paediatric Pulmonology outpatient clinic
Line of therapy	Mixed line
Duration of study	Intervention time: 6 months

Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A paediatrician, trained in paediatric pulmonology and allergology, diagnosed participants asthma according to ATS criteria.
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 6-18 years, with mild to moderate persistent asthma. All participants had a positive skin prick test or radioallergosorbent test (RAST >1) to at least one of seven common aeroallergens (cat, dog, house dust mite, alternaria, birch-, hazelnut-, and mixed grass-pollen) in their past medical history or at the time of recruitment.
Exclusion criteria	Participants who had received oral or IV steroid treatment 4 weeks prior to the first visit were excluded from the study.
Recruitment/selection of patients	Recruited from the Paediatric Pulmonology outpatient clinic of the University Children's Hospital Vienna.
Age, gender and ethnicity	Age - Mean (SD): 11.73 (3.121). Gender (M:F): 28/19. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=25) Intervention 1: No FeNO monitoring + treatment - Monitoring symptoms and lung function + treatment. Children in the control group were treated considering parameters of asthma control (symptoms, short-acting beta agonist use, and lung function) recommended in current asthma guidelines. A step down in therapy was performed if FEV1 % predicted was $\geq 80\%$ and there was no or mild symptoms over the last 4 weeks and beta agonist use was <6 puffs over the last 12 days. A step up was performed in every other case. . Duration 6 months. Concurrent medication/care: Following a run-in period of 4 weeks participants were randomly assigned to a control group or a FeNO group at the first visit. The trial included five visits (6 weeks intervals) over a period of 6 months. Doses - Low dose ICS: (2X 100 mcg fluticasone or 2x 200 mcg budesonide); Low dose ICS + leukotriene receptor agonists: (2x 100 mcg fluticasone or 2x 200 mcg budesonide + 5 mg montelukast once daily p.o.); Low dose ICS + long acting beta-agonist (2x 100 mcg fluticasone + 2x 50 mcg salmeterol or 2x 200 mcg Budesonide + 2x 12 mcg formeterol); High dose ICS + leukotriene receptor agonist (2x 250 mcg fluticasone or budesonide 2x 400 mcg + 1 daily 5 mg montelukast p.o.); High dose ICS + long acting beta-agonist (2x 250 mcg fluticasone + 2x 50 mcg salmeterol or 2x 400 mcg budesonide + 2x 12 mcg formeterol).</p> <p>Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear</p> <p>(n=22) Intervention 2: Monitoring FeNO + treatment - Monitoring FeNO, symptoms and lung function + treatment. FeNO group therapy was based on symptoms, beta agonist use, lung function, and FeNO. A step down in therapy was performed if FEV1 % predicted was $\geq 80\%$ and there was no or mild symptoms over the last 4 weeks and beta agonist use was <6 puffs over the last 14 days. A step up was performed in every other case. Treatment was further adjusted</p>

	<p>according the FeNO cut-off point, >20 ppb. In participants with stable asthma increased FeNO was considered a sign of insufficient anti-inflammatory treatment. These patients were provided with 2-week diary cards to record daily symptoms, beta agonists use and controller medication requirement, and telephone calls were regularly performed to check adherence to therapy. Asymptomatic patients on therapy with beta-agonist on demand only, with normal lung function but increased FeNO were prescribed low dose steroids. Step up was performed irrespective of FeNO level if FEV1% predicted was <80% and/or there were severe symptoms over the last 4 weeks and/or beta-agonist use was ≥6 puffs over the last 14 days. If FeNO was raised in these patients, they received 2-week diary cards as well. Step down was performed if FEV1% predicted was ≥80% and there were no or mild symptoms over the last 4 weeks and beta-agonist use was <6 puffs over the last 14 days and FeNO was ≤20 ppb.. Duration 6 months. Concurrent medication/care: Following a run-in period of 4 weeks participants were randomly assigned to a control group or a FeNO group at the first visit. The trail included five visits (6 weeks intervals) over a period of 6 months. Doses - Low dose ICS: (2X 100 mcg fluticasone or 2x 200 mcg budesonide); Low dose ICS + leukotriene receptor agonists: (2x 100 mcg fluticasone or 2x 200 mcg budesonide + 5 mg montelukast once daily p.o.); Low dose ICS + long acting beta-agonist (2x 100 mcg fluticasone + 2x 50 mcg salmeterol or 2x 200 mcg Budesonide + 2x 12 mcg formeterol); High dose ICS + leukotriene receptor agonist (2x 250 mcg fluticasone or budesonide 2x 400 mcg + 1 daily 5 mg montelukast p.o.); High dose ICS + long acting beta-agonist (2x 250 mcg fluticasone + 2x 50 mcg salmeterol or 2x 400 mcg budesonide + 2x 12 mcg formeterol).</p> <p>Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear</p>
Funding	Study funded by industry (Aerocine provided technical support and help with data analyses)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO, SYMPTOMS AND LUNG FUNCTION + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT</p> <p>Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : Exacerbation - OCS at 6 months; Group 1: 2/22, Group 2: 2/25; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Dose of regular treatment - ICS dose at 6 months; Other: ; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 133: Honkoop 2014⁷⁰⁰

Study	Asthma Control Cost-Utility Randomised Trial Evaluation (ACCURATE) trial: Honkoop 2014 ⁷⁰⁰
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	1 (n=647)
Countries and setting	Conducted in Netherlands; Setting: Primary
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Doctor diagnosed asthma according to Dutch national guidelines
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	18-50 years old, doctor-diagnosed asthma according to the Dutch national guidelines, a prescription for ICSs for at least 3 months in the previous year, and asthma being managed in primary care
Exclusion criteria	Significant comorbidity (at the GPs discretion), inability to understand Dutch, and a prescription for oral corticosteroids in the previous month
Recruitment/selection of patients	General practices from both rural and urban areas in The Netherlands were invited to participate
Age, gender and ethnicity	Age - Mean (SD): 39.42 (9.633). Gender (M:F): 191/420 . Ethnicity: Not specified
Further population details	
Indirectness of population	No indirectness
Interventions	(n=205) Intervention 1: Monitoring FeNO + treatment - Monitoring FeNO and symptoms + treatment. Treatment strategy: aiming at FeNO-driven controlled asthma (FCa strategy). In all strategies, patients visited the practice nurse of their general practice every 3 months over the course of 1 year. During these visits, the practice nurse assessed current medication use and asthma control status by using the 7-item asthma control questionnaire that includes lung function. In addition, FeNO measurement was performed in the FCa strategy. Duration 12 months. Concurrent medication/care: At each visit, a patient's asthma control status was classified based on the ACQ score as controlled (ACQ score ≤ 0.75), partly controlled ($0.75 < ACQ \leq 1.5$), or uncontrolled (ACQ score > 1.5); and additionally in the FCa strategy as 3 subcategories of FeNO: low/absence of airway inflammation for values at 25 ppb or less, intermediate at 26 to 50 ppb, and high/presence of airway inflammation at greater than 50 ppb. Treatment decisions were based on a dedicated algorithm for each strategy. (1)Strategy aimed at Ca = asthma controlled status Ca (ACQ ≤ 0.75): 3mo: no change, 6mo: step down; asthma controlled status PCa ($0.75 > ACQ \leq 1.5$): step up, treatment choice open; asthma

controlled status uncontrolled (ACQ >1.5): step up, treatment choice open. (2)Strategy aimed at FCa, low FeNO (<25 ppb) = asthma controlled status Ca (ACQ ≤0.75): step down, treatment choice open; asthma controlled status PCa (0.75 > ACQ ≤1.5): 3 mo: no change/change within current step to LABA, 6mo: step down to ICS; asthma controlled status uncontrolled (ACQ >1.5): 3 mo: step up LABA, 6mo: revise asthma diagnosis. (3)Strategy aimed at FCa, intermediate FeNO (25-50 ppb) = asthma controlled status Ca (ACQ ≤0.75): no change; asthma controlled status PCa (0.75 > ACQ ≤1.5): step up, treatment choice open; asthma controlled status uncontrolled (ACQ >1.5): treatment choice open. (4)Strategy aimed at FCa, high FeNO (>50 ppb) = asthma controlled status Ca (ACQ ≤0.75): step up/change within current step to ICS; asthma controlled status PCa (0.75 > ACQ ≤1.5): step up, 1 X ICS; asthma controlled status uncontrolled (ACQ >1.5): step up, 2 X ICS. Current medication use and all measurements were entered into an online decision support tool, which subsequently automatically generated treatment advice based on the appropriate algorithm for each of the treatment strategies. Patients' current medication use was classified as an asthma treatment step ranging from 0 (only short-acting beta agonists) to 5 (oral prednisone) based on the US National Asthma Education and Prevention Programme guideline. When treatment was to be adjusted, in the Ca strategy professionals and patients could choose any (combination of) type or types of asthma medication they preferred within a certain treatment step, whereas the FCa strategy offered more guidance toward adding/removing LABAS or ICSs.

Further details: 1. Additional education training : No education in both groups 2. Aim of intervention: Not applicable / Not stated / Unclear

(n=210) Intervention 2: No FeNO monitoring + treatment - Monitoring symptom control questionnaires + treatment. Treatment strategy: aiming at controlled asthma (Ca strategy). In all strategies, patients visited the practice nurse of their general practice every 3 months over the course of 1 year. During these visits, the practice nurse assessed current medication use and asthma control status by using the 7-item asthma control questionnaire that includes lung function. . Duration 12 months. Concurrent medication/care: At each visit, a patient's asthma control status was classified based on the ACQ score as controlled (ACQ score ≤0.75), partly controlled (0.75 <ACQ ≤1.5), or uncontrolled (ACQ score >1.5); and additionally in the FCa strategy as 3 subcategories of FeNO: low/absence of airway inflammation for values at 25 ppb or less, intermediate at 26 to 50 ppb, and high/presence of airway inflammation at greater than 50 ppb. Treatment decisions were based on a dedicated algorithm for each strategy. (1)Strategy aimed at Ca = asthma controlled status Ca (ACQ ≤0.75): 3mo: no change, 6mo: step down; asthma controlled status PCa (0.75 > ACQ ≤1.5): step up, treatment choice open; asthma controlled status uncontrolled (ACQ >1.5): step up, treatment choice open. (2)Strategy aimed at FCa, low FeNO (<25 ppb) = asthma controlled status Ca (ACQ ≤0.75): step down, treatment choice open; asthma controlled status PCa (0.75 > ACQ ≤1.5): 3 mo: no change/change within current step to LABA, 6mo: step down to ICS; asthma controlled status uncontrolled (ACQ >1.5): 3 mo: step up LABA, 6mo: revise asthma diagnosis. (3)Strategy aimed at FCa, intermediate FeNO (25-50 ppb) = asthma controlled status Ca (ACQ ≤0.75): no change; asthma controlled status PCa (0.75 > ACQ ≤1.5): step up, treatment choice open; asthma controlled status uncontrolled (ACQ >1.5): treatment choice open. (4)Strategy aimed at FCa, high FeNO (>50 ppb) =

	<p>asthma controlled status Ca (ACQ \leq0.75): step up/change within current step to ICS; asthma controlled status PCa (0.75 > ACQ \leq1.5): step up, 1 X ICS; asthma controlled status uncontrolled (ACQ >1.5): step up, 2 X ICS. Current medication use and all measurements were entered into an online decision support tool, which subsequently automatically generated treatment advice based on the appropriate algorithm for each of the treatment strategies. Patients' current medication use was classified as an asthma treatment step ranging from 0 (only short-acting beta agonists) to 5 (oral prednisone) based on the US National Asthma Education and Prevention Programme guideline. When treatment was to be adjusted, in the Ca strategy professionals and patients could choose any (combination of) type or types of asthma medication they preferred within a certain treatment step, whereas the FCa strategy offered more guidance toward adding/removing LABAs or ICSs.</p> <p>Further details: 1. Additional education training: No education in both groups 2. Aim of intervention: Not applicable / Not stated / Unclear</p>
Funding	<p>Study funded by industry (Study was funded by the Netherlands Organisation for Health Research and Development and the Netherlands Asthma Foundation, and nonfinancial support was received from Aerocrine. Author holds stock in Grace Bros and received consultancy fees from Astra-Zeneca, GlaxoSmithKline, and Novartis, as well as grants funding from ACME Pharmaceutical.)</p>
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOM CONTROL QUESTIONNAIRES + TREATMENT</p> <p>Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people (16 years and over): Exacerbation (severe, defined as hospitalisation, emergency care or use of OCS) at 12 months; Risk of bias: High; Indirectness of outcome: Serious indirectness</p> <p>Protocol outcome 2: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Adults and young people (16 years and over): UHU - hospitalisation (from the exacerbation outcome) at 12 months; Group 1: 1/189, Group 2: 2/203; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): UHU - ED visit (from the exacerbation outcome) at 12 months; Group 1: 2/189, Group 2: 3/203; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Asthma control questionnaires at End of Treatment - Actual outcome for Adults and young people (16 years and over): ACQ-7 score at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): Lung function (FEV1 % predicted) at 12 months; Risk of bias: High; Indirectness of outcome: No</p>	

indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 134: Peirsman 2013¹³³¹

Study	Peirsman 2013 ¹³³¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=99)
Countries and setting	Conducted in Belgium; Setting: Secondary
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Not stated - children with persistent allergic asthma
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with persistent allergic asthma. Mild to severe persistent asthma according to GINA guidelines, for a period of at least 6 months, and allergic sensitisation (i.e., a positive skin prick test and/or specific IgE antibodies against inhalant allergens).
Exclusion criteria	Exclusion criteria comprised significant comorbidity, an acute exacerbation or the administration of experimental medication 4 weeks prior to the screening visit, hospitalisation and/or systematic corticosteroids 12 weeks prior to the screening visit or oral corticosteroids dependence.
Recruitment/selection of patients	Secondary - visits were organised by physicians from seven Belgian hospitals.
Age, gender and ethnicity	Age - Mean (SD): 10.65 (2.151). Gender (M:F): 66/33. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=49) Intervention 1: Monitoring FeNO and symptoms + treatment. In the intervention group, FeNO measurements were primarily used to adjust the treatment. Goal was to keep FeNO below 20 ppb, the rounded 95% upper limit of

	<p>FeNO values in healthy children, deduced from previous trials. Controlled asthma = NO \leq20 ppb and controlled; ICS (dosage in budesonide or equivalent) = ICS step down - 100 mcg/day, below 100 mcg/day: stop and add LTRA; LTRA = stay the same; ICS + LTRA = ICS step down: -100 mcg/day, below 100 mcg/day: stop ICS; ICS + LABA = stop LABA. Partly controlled asthma = NO \leq20 ppb and partly controlled or uncontrolled; ICS (dosage in budesonide or equivalent) = consider + LTRA; consider + ICS 100 mcg/day (max 200 mcg/day); ICS + LTRA = consider ICS step up + 100 mcg/day (max 400 mcg/day, then add LABA); ICS + LABA = consider + LTRA. Uncontrolled asthma = NO $>$20 ppb regardless of symptoms; ICS (dosage in budesonide or equivalent) = +LTRA; LTRA = +ICS 100 mcg/day (max 200 mcg/day); ICS + LTRA = ICS step up: 100 mcg/day, (max 400 mcg/day, then add LABA); ICS + LABA = replace LABA with LTRA.. Duration 12 months. Concurrent medication/care: Five visits, one every 3 months.</p> <p>Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear</p> <p>(n=50) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms and lung function + treatment. In the control group, control and treatment adjustments during each visit were determined by the reporting of symptoms (i.e., limitation of activities, daytime and nocturnal symptoms), the need for rescue treatment during the two preceding weeks and spirometry (FEV1), based on GINA guidelines.. Duration 12 months. Concurrent medication/care: Five visits, one every 3 months.</p> <p>Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear</p>
<p>Funding</p>	<p>Study funded by industry (Research supported in part by a research grant from the Investigator Initiated Studies Program of Merck & Co., Inc. NO analysers were provided by Aerocrine, Solna, Sweden.)</p>
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT</p> <p>Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : exacerbation (OCS) at 12 months; Group 1: 2/49, Group 2: 3/50; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Children 5 -<16 : UHU - number of unscheduled asthma-related contacts at 12 months; Group 1: 6/44, Group 2: 15/43; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : UHU - number of children with \geq1 hospital admission at 12 months; Group 1: 1/43, Group 2: 1/43; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : UHU - number of children with \geq1 emergency room admission at 12 months; Group 1: 2/45, Group 2: 4/46; Risk of bias: Very</p>	

high; Indirectness of outcome: No indirectness	
Protocol outcome 3: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Dose of regular therapy - change in daily ICS dose at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcome 4: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : lung function - FEV1 (mean % predicted) [≥ 6 mo] at 12 months; Group 1: mean 93.9 mean % predicted (SD 15.5); n=49, Group 2: mean 91.2 mean % predicted (SD 12.3); n=50; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : lung function - FEV1 (mean % predicted) [< 6 mo] at 3 months; Group 1: mean 92.2 (SD 14.1); n=49, Group 2: mean 90.7 (SD 13.2); n=50; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcome 5: Symptom free days at End of Treatment - Actual outcome for Children 5 -<16 : % symptom free days at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcome 6: Time of school/work at End of Treatment - Actual outcome for Children 5 -<16 : time off school/work - number of children missed school at 12 months; Group 1: 10/46, Group 2: 12/46; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment

Table 135: Petsky 2014¹³⁵⁴

Study	Petsky 2014 ¹³⁵⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Australia, Hong Kong (China); Setting: Secondary care
Line of therapy	Unclear
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Under the care of a paediatrician
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged >4 years with persistent asthma, prescribed anti-inflammatory asthma treatment, and receiving their

	care primarily through the clinical service at Royal Children’s Hospital, Brisbane or Prince of Wales Hospital, Hong Kong.
Exclusion criteria	Children who had underlying cardio-respiratory illness such as bronchiectasis or tracheomalacia, inability to take ICS or long acting beta-2-agonists (LABA) or previous poor adherence to medications (as documented in clinic notes).
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Median (IQR): 10.17 (6.56,12.69) years FeNO; 10.08 (6.25, 12.44) years controls. Gender (M:F): 31:32. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=31) Intervention 1: Monitoring FeNO + treatment. Management based on FeNO levels and atopic status. If FeNO was low for two consecutive visits, medications were stepped down. Elevated FeNO was defined ≥ 10ppb in children with no positive skin prick test (SPT), ≥ 12ppb in children with one positive SPT, and ≥ 20ppb in children with ≥ 2 positive SPT. Treatment steps were modified from the Australian National Asthma Council guidelines and GINA guidelines.. Duration 1 year. Concurrent medication/care: 2-week run-in period when the children were maintained on their current treatment. If they were unstable (based on clinician review and diary cards) their medications were adjusted by their treating physician and a further run-in period was undertaken Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear</p> <p>(n=32) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms + treatment. Management based on clinical symptoms. Treatment decisions were made on symptoms as recorded on the asthma symptom diary card. Control was considered inadequate and treatment increased if scores increased by more than or equal to 15% since the previous visit. Treatment was stepped down if the child’s scores totalled < 10 in recent week. Treatment steps were modified from the Australian National Asthma Council guidelines and GINA guidelines.. Duration 1 year. Concurrent medication/care: 2-week run-in period when the children were maintained on their current treatment. If they were unstable (based on clinician review and diary cards) their medications were adjusted by their treating physician and a further run-in period was undertaken Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear</p>
Funding	Academic or government funding (Asthma Foundation of Queensland 2008, Royal Children’s Hospital Foundation, NHMRC)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS + TREATMENT

<p>Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Children 5 -<16 : Asthma QOL score at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : 1 or more exacerbations at 12 months; Group 1: 6/27, Group 2: 15/28; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Children 5 -<16 : Hospitalisation at 12 months; Group 1: 0/27, Group 2: 0/28; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Fluticasone dose at 12 months; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 5: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : FEV1 % predicted at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 136: Pijnenburg 2005¹³⁵⁹

Study	Pijnenburg 2005 ¹³⁵⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=85)
Countries and setting	Conducted in Netherlands
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: States participants were children with atopic asthma, and fulfilled ATS criteria for asthma.
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients had been using inhaled corticosteroids (ICS) at a constant dose for at least 3 months preceding the study. All

	patients were atopic, defined as RAST class 2 or higher for at least 1 airborne allergen ever.
Exclusion criteria	None specified.
Recruitment/selection of patients	Participants were recruited from the outpatient clinic of Erasmus MC - Sophia Children's Hospital.
Age, gender and ethnicity	Age - Mean (SD): 12.28 (2.868). Gender (M:F): 55/30. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=42) Intervention 1: Monitoring FeNO + treatment - Monitoring FeNO and symptoms + treatment. In the intervention group, ICS doses were determined by FeNO and symptoms according to the following algorithm: FeNO >30ppb, regardless of symptoms = ICS increased; FeNO ≤30ppb AND symptoms > 14 = ICS stays same; FeNO ≤30 AND symptoms ≤14 = ICS decreased.. Duration 12 months. Concurrent medication/care: After a 2-week run-in period, participants were randomly allocated to one of two groups stratified for baseline FeNO (≥ 30 or <30 ppb) and dose of ICS (≥ 400 or <400 mcg budesonide or equivalent daily dose). Study duration was 12 months, with five visits at 3-month intervals. FeNO was measured at each visit, and the ICS dose was then adapted to FeNO and/or symptom scores recorded during the previous 2 weeks. Throughout the study, 2000 mcg per day budesonide (or equivalent dose of other ICS) was the maximum allowed dose. The study design was such that the patients' physician was allowed to deviate from the recommended ICS dose. Lung function and bronchoprovocation tests with methacholine were performed at visits 1 and 5. At all visits, inhaler technique was checked and optimised. ICS doses: 100 mcg: increase to 200 mcg, decrease to 0 mcg; 200 mcg: increase to 400 mcg, decrease to 100 mcg; 400 mcg: increase to 800 mcg, decrease to 200 mcg; 500 mcg: increase to 1000 mcg, decrease to 250 mcg; 800 mcg: increase to 1200 mcg, decrease to 400 mcg; 1000 mcg: increase to 1500 mcg, decrease to 500 mcg; 1200 mcg: increase to 1600 mcg, decrease to 800 mcg; 1600 mcg: increase to 2000 mcg, decrease to 1200 mcg; 2000 mcg: no further increase, decrease to 1000 mcg.</p> <p>Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear</p> <p>(n=47) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms + treatment. In the control group, only symptoms influenced ICS dosing. Symptoms >14 = ICS increased; symptoms ≤ 14, first time = ICS stays same; symptoms ≤14, second time = ICS decreased. . Duration 12 months. Concurrent medication/care: After a 2-week run-in period, participants were randomly allocated to one of two groups stratified for baseline FeNO (≥ 30 or <30 ppb) and dose of ICS (≥ 400 or <400 mcg budesonide or equivalent daily dose). Study duration was 12 months, with five visits at 3-month intervals. FeNO was measured at each visit, and the ICS dose was then adapted to FeNO and/or symptom scores recorded during the previous 2 weeks. Throughout the study, 2000 mcg per day budesonide (or equivalent dose of other ICS) was the maximum allowed dose. The study design was such that the patients' physician was allowed to deviate from the recommended ICS dose. Lung function and bronchoprovocation tests with</p>

	<p>methacholine were performed at visits 1 and 5. At all visits, inhaler technique was checked and optimised. ICS doses: 100 mcg: increase to 200 mcg, decrease to 0 mcg; 200 mcg: increase to 400 mcg, decrease to 100 mcg; 400 mcg: increase to 800 mcg, decrease to 200 mcg; 500 mcg: increase to 1000 mcg, decrease to 250 mcg; 800 mcg: increase to 1200 mcg, decrease to 400 mcg; 1000 mcg: increase to 1500 mcg, decrease to 500 mcg; 1200 mcg: increase to 1600 mcg, decrease to 800 mcg; 1600 mcg: increase to 2000 mcg, decrease to 1200 mcg; 2000 mcg: no further increase, decrease to 1000 mcg.</p> <p>Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear</p>
Funding	Other (Supported by grant from the Kroger Foundation/Sophia Children's Hospital Foundation. Authors note in conflict of interest statement that the Department of Paediatrics of Erasmus University received research grants and payments for consultancy services from Aerocine (manufacturer of NO analysers).)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOMS + TREATMENT</p> <p>Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : Exacerbation - need for OCS (prednisone course) at 12 months; Group 1: 7/39, Group 2: 10/46; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Dose of regular treatment (mean daily ICS dose score, at 3 months) at 3 months; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : Lung function - FEV1 at 12 months; MD 2.3 (95%CI -1.8 to 6.3); Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 137: Pike 2012¹³⁶⁰

Study	Pike 2012 ¹³⁶⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in United Kingdom; Setting: Secondary - hospital
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Asthma diagnosis was based upon a history of typical symptoms, $\geq 15\%$ increase in FEV1 with bronchodilator or diurnal PEF variability of $\geq 15\%$.
Stratum	Children 5 - <16
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants were age 6-17 years, clinical diagnosis of asthma and treatment with ≥ 400 mcg/day beclomethasone/budesonide or ≥ 200 mcg/day fluticasone.
Exclusion criteria	Inability to perform spirometry or FeNO measurement, cigarette smoking, poor treatment adherence, life-threatening exacerbation or need for maintenance oral prednisolone.
Recruitment/election of patients	Participants were recruited from outpatient clinics at Southampton University Hospital; St Mary's Hospital, Portsmouth; St Mary's Hospital, Isle of Wight; and, the Royal Hampshire County Hospital, Winchester.
Age, gender and ethnicity	Age - Mean (SD): 10.98 (2.695). Gender (M:F): 51/39. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: No FeNO monitoring + treatment - Monitoring symptoms, BD use and lung function + treatment. Therapy decisions were taken by an independent clinician following a simple algorithm reflecting symptom control for standard management subjects. Under standard management, therapy was increased if symptoms were poorly controlled and decreased if symptoms were well controlled for 3 months as per the SIGN/BTS (Scottish Intercollegiate Guidelines Network/British Thoracic Society) guidelines. Algorithm for managing asthma: Standard management group: (a) poorly controlled asthma - increase inhaled corticosteroids or add LABA and/or LTRA as directed by stepwise approach to therapy SIGN/BTS; (b) asthma controlled – no change in inhaled corticosteroids; (c) well-controlled asthma – if well-controlled for 3 months reduced if inhaled corticosteroids if dose ≤ 400 mcg, reduce LABA. Duration 12 months. Concurrent medication/care: Participants asthma was stabilised if necessary over 4-16 weeks prior to randomisation. Participants were assessed 2 monthly for 12 months. Participants' asthma was

categorised as well controlled (symptoms and reliever inhaler <1 per week and FEV1 ≥90% predicted); controlled (symptoms or reliever inhaler use 1-2 days per week or FEV1 ≥80% predicted); or poorly controlled (symptoms or reliever inhaler use >2 days per week or FEV1 <80% predicted). Step 1: no inhaled corticosteroid (option 1); no inhaled corticosteroid (option 2); no inhaled corticosteroid (option 3). Step 2: Beclometasone 50 mcg twice a day via spacer (option 1); Budesonide 50 mcg twice a day via spacer (or tubohaler) (options 2); Fluticasone 50 mcg once a day via spacer (or accuhaler) (option 3). Step 3: Beclometasone 100 mcg twice a day via spacer (option 1); Budesonide 100 mcg twice a day via spacer (or tubohaler) (options 2); Fluticasone 50 mcg twice a day via spacer (or accuhaler) (option 3). Step 4: Beclometasone 200 mcg twice a day via spacer (option 1); Budesonide 200 mcg twice a day via spacer (or tubohaler) (options 2); Fluticasone 100 mcg once a day via spacer (or accuhaler) (option 3). Step 5: Trial of LABA, if ineffective consider trial of LTRA (options 1, 2, 3). Step 6: Fluticasone 125 mcg twice a day via spacer (options 1, 2, 3). Step 7: Fluticasone 250 mcg twice a day via spacer (options 1, 2, 3). Step 8: Consider a short course of prednisolone or other therapeutic options (options 1, 2, 3).

Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear

(n=46) Intervention 2: Monitoring FeNO + treatment - Monitoring FeNO and symptoms + treatment. Therapy decisions were taken by an independent clinician following a simple algorithm reflecting FeNO measurements in addition to symptom control for FeNO group. ICS was decreased if FeNO ≤15 ppb and symptoms were controlled or well controlled for 3 months in similar steps as for the standard management group. Where asthma was poorly controlled and FeNO was <25ppb in the FeNO group, long-acting beta-agonist (LABA) therapy was maximised before ICS was increased. ICS was increased if FeNO ≥25 ppb or FeNO doubled from baseline. If FeNO remained raised after increasing by two SIGN/BTS steps, ICS was not further increased unless participants were poorly controlled. Algorithm for managing asthma: FeNO group: (a) ≥25 ppb or FeNO more than twice baseline: poorly controlled asthma - increase inhaled corticosteroids or add LTRA if already at SIGN/BTS step 4 (if after increasing by two SIGN/BTS steps FeNO remains high do not increase therapy further); asthma controlled/well-controlled asthma – increase inhaled corticosteroids or add LTRA if already at SIGN/BTS step 4. (b) >15 to <25 ppb: poorly controlled asthma - increase LABA therapy (if dose maximal, increase corticosteroids or add LTRA if already at SIGN/BTS step 4); asthma controlled/well-controlled asthma – continue current treatment. (c) ≤15 ppb: poorly controlled asthma – increase LABA (if does maximal, increase corticosteroids or add LTRA if already at SIGN/BTS step 4); asthma controlled/well-controlled asthma – if asthma controlled for 3 months, reduce inhaled corticosteroids (if dose ≤400 mcg, reduce LABA).. Duration 12 months. Concurrent medication/care: Participants asthma was stabilised if necessary over 4-16 weeks prior to randomisation. Participants were assessed 2 monthly for 12 months. Participants' asthma was categorised as well controlled (symptoms and reliever inhaler <1 per week and FEV1 ≥90% predicted); controlled (symptoms or reliever inhaler use 1-2 days per week or FEV1 ≥80% predicted); or poorly controlled (symptoms or reliever inhaler use >2 days per week or FEV1 <80% predicted). Step 1: no inhaled corticosteroid (option 1); no inhaled corticosteroid (option 2); no inhaled corticosteroid (option 3). Step 2: Beclometasone 50 mcg twice a day via spacer

	<p>(option 1); Budesonide 50 mcg twice a day via spacer (or tubohaler) (options 2); Fluticasone 50 mcg once a day via spacer (or accuhaler) (option 3). Step 3: Beclometasone 100 mcg twice a day via spacer (option 1); Budesonide 100 mcg twice a day via spacer (or tubohaler) (options 2); Fluticasone 50 mcg twice a day via spacer (or accuhaler) (option 3). Step 4: Beclometasone 200 mcg twice a day via spacer (option 1); Budesonide 200 mcg twice a day via spacer (or tubohaler) (options 2); Fluticasone 100 mcg once a day via spacer (or accuhaler) (option 3). Step 5: Trial of LABA, if ineffective consider trial of LTRA (options 1, 2, 3). Step 6: Fluticasone 125 mcg twice a day via spacer (options 1, 2, 3). Step 7: Fluticasone 250 mcg twice a day via spacer (options 1, 2, 3). Step 8: Consider a short course of prednisolone or other therapeutic options (options 1, 2, 3). Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Not applicable / Not stated / Unclear</p>
Funding	Other (Funding was provided by Sparks)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOMS + TREATMENT</p> <p>Protocol outcome 1: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Children 5 -<16 : UHU - severe, requiring ≥8 hr hospital admission at 12 months; Group 1: 5/46, Group 2: 3/44; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Dose of regular therapy - final inhaled corticosteroid dose at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 138: Shaw 2007¹⁵⁷⁴

Study	Shaw 2007 ¹⁵⁷⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=118)
Countries and setting	Conducted in United Kingdom; Setting: Secondary - visits took place at hospital
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants had a diagnosis of asthma recorded in their general practitioner's (GP) notes. Participants attended hospital for tests to characterise their asthma: exhaled nitric oxide levels measured at flow of 50 ml/second, FEV1, and forced vital capacity (FVC), methacholine challenge test to determine the concentration of methacholine required to provoke a 20% fall in FEV1, induced sputum analysis, and skin prick tests.
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	GP diagnosis of asthma. Participants were eligible if they had received at least one prescription for any antiasthma medication in the last 12 months. Study was restricted to current non-smokers with a past smoking history of less than 10 packs-years.
Exclusion criteria	Participants were excluded if they were considered by their physician to be poorly compliant or had had a severe asthma exacerbation, requiring a course of prednisolone, within 4 weeks of study entry.
Recruitment/selection of patients	Recruited from primary care - all suitable participants on the registers (held in general practices around Leicester, UK) who responded to an invitation from their GP to be contacted by the research team were invited to participate in the study.
Age, gender and ethnicity	Age - Mean (range): Intervention group: 50 (20-75). Control group: 52 (24-81).. Gender (M:F): 54/64. Ethnicity: Not specified
Further population details	
Indirectness of population	No indirectness
Interventions	(n=58) Intervention 1: Monitoring FeNO + treatment - Monitoring FeNO and symptoms + treatment. At each visit, patients asthma control was determined using a validated Juniper asthma control questionnaire, which scores asthma control from 0 to 6; a score of greater than 1.57 was used to identify poorly controlled asthma. Assessment of asthma control was made per protocol by investigators who were unaware of the participants' randomisation status. In the

FeNO group, treatment was adjusted following a set protocol according to both the FeNO and Juniper scores. If the FeNO was greater than 26 ppb, inhaled corticosteroid treatment was increased; if it was less than 16 ppb or less than 26 ppb on two consecutive occasions, treatment was decreased. Bronchodilator therapy was increased if symptoms were uncontrolled, despite a FeNO of less than 26 ppb. *Hierarchy of Anti-Inflammatory Treatment: 1) Low dose inhaled steroid (100-200µg BDP bd). 2) Moderate dose inhaled steroid (200-800µg BDP bd). 3) High dose inhaled steroid (800-2000µg BDP bd). 4) High dose inhaled steroid (800-2000µg BDP bd) plus leukotriene antagonist. 5) Higher dose inhaled steroid (2000µg BDP bd) plus leukotriene antagonist. 6) Higher dose inhaled steroid (2000µg BDP bd) plus leukotriene antagonist plus oral Prednisolone 30mg. 2/52, then titrating dose reducing by 5mg/week **Hierarchy of Bronchodilator Treatment: 1) PRN short acting β₂-agonists. 2) Long acting β₂ agonist. 3) Long acting β₂ agonist plus theophylline. 4) Long acting β₂-agonist plus theophylline plus nebulised bronchodilator.. Duration 12 months. Concurrent medication/care: Participants were seen 2 weeks following characterisation of their asthma, and then every month for 4 months; they were seen every 2 months for a further 8 months. Each visit occurred at the same time of day and consisted of assessment of exhaled nitric oxide, spirometry, and post-bronchodilator FEV₁, 20 minutes after 400 mcg albuterol at the end of every visit. Peak flow and symptom diaries were analysed and compliance assessed by monitoring adherence to prescription script collection. Participants were issued with self-management plans based on their baseline peak flow from the first 2 weeks of the study; if their peak flow fell to less than 70% of their best peak flow for 48 hours during the study, or their asthma deteriorated, they were asked to attend the hospital where they were assessed by a physician. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to decrease ICS in controlled patients

(n=60) Intervention 2: No FeNO monitoring + treatment - Monitoring symptom control questionnaires + treatment. At each visit, patients asthma control was determined using a validated Juniper asthma control questionnaire, which scores asthma control from 0 to 6; a score of greater than 1.57 was used to identify poorly controlled asthma. Assessment of asthma control was made per protocol by investigators who were unaware of the participants' randomisation status. In the control group, treatment was doubled if the score was more than 1.57, and treatment was halved if the score was less than 1.57 for 2 consecutive months. Step 1: SABA as required. Step 2: Add inhaled steroid 200 to 800mcg/day BDP equivalent. Step 3: Add inhaled LABA. Step 4: Increase ICS up to 2000mcg/day and addition of 4th drug, e.g. LTRA, theophylline, LABA. Step 5: Oral prednisolone, high does ICS, refer to specialist care.. Duration 12 months. Concurrent medication/care: Participants were seen 2 weeks following characterisation of their asthma, and then every month for 4 months; they were seen every 2 months for a further 8 months. Each visit occurred at the same time of day and consisted of assessment of exhaled nitric oxide, spirometry, and post-bronchodilator FEV₁, 20 minutes after 400 mcg albuterol at the end of every visit. Peak flow and symptom diaries were analysed and compliance assessed by monitoring adherence to prescription script collection. Participants were issued with self-management plans based on their baseline peak flow from the first 2 weeks of the study; if their peak flow fell to less than 70% of their best peak flow for 48 hours during the study, or their asthma deteriorated, they

	<p>were asked to attend the hospital where they were assessed by a physician. Further details: 1. Additional education training: Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to decrease ICS in controlled patients</p>
Funding	<p>Academic or government funding (Trial supported by a grant from Asthma UK. Conflict of interest statement: authors received grants (research and travel) from Glaxo SmithKline and lecture fees from Astra eneca.)</p>
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO AND SYMPTOMS + TREATMENT versus MONITORING SYMPTOM CONTROL QUESTIONNAIRES + TREATMENT</p> <p>Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people (16 years and over): Exacerbation - course of oral steroids or antibiotics at 12 months; Group 1: 12/58, Group 2: 19/60; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Dose of regular therapy - ICS, expressed as equivalent dose to BDP at 12 months; MD -338 (95%CI - 640 to -37); Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	<p>Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment</p>

Table 139: Smith 2005¹⁶²⁸

Study	Smith 2005 ¹⁶²⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in New Zealand; Setting: Primary care
Line of therapy	Unclear
Duration of study	Intervention time: Phase 1 stabilisation on optimum therapy (mean 22 and 25 weeks in the 2 groups); phase 2 dose adjustment using FeNO or control: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Chronic asthma
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	12 to 75 years of age with chronic asthma, managed in primary care, regular inhaled corticosteroids for six months or more with no change in dose in last 6 weeks
Exclusion criteria	Four or more courses of oral prednisone in the previous 12 months; admission to the hospital because of asthma in the previous 6 months or to the intensive care unit because of asthma at any time in the past; and cigarette smoking, either current or past, with a history of more than 10 pack-years.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): 44.8 (12 to 73) years. Gender (M:F): 41:69. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Monitoring FeNO + treatment. Dose adjustment based on FeNO. Visits every 2 months for 1 year. Cut-off 15ppb (at an exhaled flow rate of 250 ml per second), above which an increase in the dose of inhaled corticosteroid was prescribed; this FeNO value is equivalent to 35 ppb at a flow rate of 50 ml per second. Subjects in the FeNO group had a predetermined "safety buffer" by which an upward (one-step) adjustment in the dose was provided to deal with deteriorating asthma in the absence of a rise in measured FeNO. Duration 12 months. Concurrent medication/care: 5 patients on LABA. Two-week run-in period. At the second visit, all patients were started on inhaled fluticasone. During phase 1, the dose of inhaled fluticasone was titrated downward in a stepwise manner until the optimal dose was deemed to have been achieved. Subjects received 750 µg per day to start (or 500 µg per day if their inhaled-corticosteroid requirement before enrolment was less than 200 µg per day of fluticasone or the equivalent).

	<p>Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to increase ICS in uncontrolled patients</p> <p>(n=49) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms, BD use and lung function + treatment. Dose adjustments were based on predetermined thresholds in regard to symptoms, bronchodilator use, diurnal peak flows, and spirometry with an algorithm based on Global Initiative for Asthma 2002 criteria. Visits every 2 months for 1 year.. Duration 12 months. Concurrent medication/care: 8 patients on LABA. Two-week run-in period. At the second visit, all patients were started on inhaled. During phase 1, the dose of inhaled fluticasone was titrated downward in a stepwise manner until the optimal dose was deemed to have been achieved. Subjects received 750 µg per day to start (or 500 µg per day if their inhaled-corticosteroid requirement before enrolment was less than 200 µg per day of fluticasone or the equivalent).</p> <p>Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to increase ICS in uncontrolled patients</p>
Funding	Academic or government funding (Otago Medical Research Foundation, Dunedin School of Medicine, University of Otago)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT

Protocol outcome 1: Exacerbation (need for OCS) at End of treatment
 - Actual outcome for Adults and young people (16 years and over): Number of patients requiring at least one course of OCS at 12 months; Group 1: 13/46, Group 2: 15/48; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Rescue medication at End of Treatment
 - Actual outcome for Adults and young people (16 years and over): Bronchodilator mean puffs/day (past 7 days) at 12 months; Group 1: mean 0.4 puffs/day (SD 1.04); n=46, Group 2: mean 0.4 puffs/day (SD 0.88); n=48; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Dose of regular asthma treatment (SABA, ICS) at End of Treatment
 - Actual outcome for Adults and young people (16 years and over): Dose of fluticasone at 12 months; Group 1: mean 370 microg/day (SD 370); n=46, Group 2: mean 641 microg/day (SD 407); n=48; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Lung Function at End of Treatment
 - Actual outcome for Adults and young people (16 years and over): FEV1 % predicted at 12 months; MD 3.8 (SE 4.4); Risk of bias: High; Indirectness of outcome: No indirectness

<p>- Actual outcome for Adults and young people (16 years and over): PEF am (mean previous 7 days) at 12 months; MD 1.0 (SE 13.2); Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 5: Symptom free days at End of Treatment</p> <p>- Actual outcome for Adults and young people (16 years and over): Percentage of symptom-free days at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Time of school/work at End of Treatment

Table 140: Syk 2013¹⁷¹¹

Study	Syk 2013 ¹⁷¹¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=181)
Countries and setting	Conducted in Sweden; Setting: Primary care.
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Physician's diagnosis of asthma, had been on prescribed ICS treatment for at least 6 months, and had confirmed IgE sensitisation to at least 1 major airborne perennial allergen (dog, cat, or mite).
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible participants had a physician's diagnosis of asthma, had been on prescribed ICS treatment for at least 6 months, and had confirmed IgE sensitisation to at least 1 major airborne perennial allergen (dog, cat, or mite). In addition: age 18-64 years old, non-smokers since at least 1 year earlier and with a smoking history of <10 packs years.
Exclusion criteria	Not stated
Recruitment/selection of patients	Participants recruited from 17 primary health care centres in 7 different autonomous health care regions in central and southern Sweden.
Age, gender and ethnicity	Age - Mean (SD): 41 (12.4). Gender (M:F): 94/87. Ethnicity: Not stated

Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=93) Intervention 1: Monitoring FeNO + treatment. In the FeNO-guided group, the anti-inflammatory treatment (ICS and leukotriene receptor antagonist [LTRA]) was adjusted according to an algorithm based on exhaled NO levels (FeNO <19ppb (men), <21ppb (women) - decrease one step; FeNO 19-23 (men), 21-25 (women) - no change; FeNO ≥24ppb (men), ≥26ppb (women) - increase one step (no change in treatment step if on step 4 or 5 and using ≤2 inhalations of short-acting beta2 agonist per week); FeNO ≥30ppb (men), ≥32ppb (women)- increase two steps (only if one treatment step 1); grey zone of 5ppb applied to avoid frequent dose changes) and 6 fixed treatment steps (Steps 1-6: Budesonide (mcg/day): 0, 200, 400, 800, 800+LTRA, 1600+LTRA; Fluticasone (mcg/day): 0, 100, 250, 500, 500+LTRA; 1000+LTRA; Mometasone (mcg/day): 0, 100, 200, 400, 400+LTRA, 800+LTRA).. Duration 12 months. Concurrent medication/care: Capillary blood was sampled to confirm perennial allergy by using ImmunoCAP Rapid Wheeze/Rhinitis Child. All participants currently being treated with combination inhalers (corticosteroid plus LABA) were required to switch to the corresponding single corticosteroid inhaler to withdraw the LABA component. All patients switched SABA to a salbutamol inhaler which incorporates a dose counter. Venous blood was sampled for serum IgE All participants received a logbook to take home, in which they noted contacts with health care, changes in drug therapy, sick leave, or other problems between scheduled visits.</p> <p>Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to decrease ICS in controlled patients (The goal of the asthma treatment was to achieve and maintain clinical control, which implies that the patients should be free from symptoms; maintain normal activity levels, including physical exercise; maintain pulmonary function as close to normal as possible; avoid adverse effects of asthma medication; and have little or no need for reliever medication, all according to the Swedish Medical Product Agency recommendations.).</p> <p>(n=88) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms, BD use and lung function + treatment. In the control group, FeNO measurement was done but blinded to both operator and patient, and treatment was adjusted according to usual care, that is, based on patient-reported symptoms, SABA use, physical examination, and results of pulmonary function tests. In the control group, only the treatment steps (as described for the intervention group) were allowed, but changes in treatment steps were entirely at the discretion of the treating physician, and immediate changes over several steps were allowed. Permissible treatment steps (as described for the intervention group) basically followed the prevailing national guidelines at the time of the study start, issued in 2002 by the Swedish Medical Product Agency, with the exception that only LTRA was used as an add-on treatment.. Duration 12 months. Concurrent medication/care: Capillary blood was sampled to confirm perennial allergy by using ImmunoCAP Rapid Wheeze/Rhinitis Child. All participants currently being treated with combination inhalers (corticosteroid plus LABA) were required to switch to the corresponding single corticosteroid inhaler to withdraw the LABA component. All patients switched SABA to a salbutamol inhaler which incorporates a dose counter. Venous</p>

	<p>blood was sampled for serum IgE analysis. All participants received a logbook to take home, in which they noted contacts with health care, changes in drug therapy, sick leave, or other problems between scheduled visits. Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to decrease ICS in controlled patients (The goal of the asthma treatment was to achieve and maintain clinical control, which implies that the patients should be free from symptoms; maintain normal activity levels, including physical exercise; maintain pulmonary function as close to normal as possible; avoid adverse effects of asthma medication; and have little or no need for reliever medication, all according to the Swedish Medical Product Agency recommendations.).</p>
Funding	<p>Academic or government funding (Study was funded by the Stockholm country council (PickUp), Centre for Allergy Research, Korlinska Institutet, and the Research Foundation of the Swedish Asthma and Allergy Association. Support also from Aerocine AB (NIOX MINO instruments), Phadia AB (ImmunoCAP Rapid), Meda AB (Buventol Easyhaler), and MSD Sweden (small grant). Authors not conflicts of interest: grants from Aerocrine AB and Research Council for Working Life and Social Research; stock/stock options as employee and co-founder of Aerocine, etc.)</p>

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT

Protocol outcome 1: Exacerbation (need for OCS) at End of treatment

- Actual outcome for Adults and young people (16 years and over): Exacerbation - severe (≥ 1 event, course of OCS) at 12 months; Group 1: 8/93, Group 2: 6/88; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Asthma control questionnaires at End of Treatment

- Actual outcome for Adults and young people (16 years and over): ACQ - clinically important improvement (≥ 0.5) at 12 months; Group 1: 29/81, Group 2: 19/74; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: Rescue medication at End of Treatment

- Actual outcome for Adults and young people (16 years and over): Rescue medication (SABA use per week, at 8-12 months, i.e. ≥ 6 months) at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment

- Actual outcome for Adults and young people (16 years and over): Dose of regular therapy (Budesonide equivalent dose) at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 5: Lung Function at End of Treatment

- Actual outcome for Adults and young people (16 years and over): Lung function - FEV1 (litres) at 12 months; Group 1: mean -0.034 litres (SD 0.28); n=88, Group 2: mean -0.006 litres (SD 0.28); n=78; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 141: Szefler 2008¹⁷¹²

Study	Szefler 2008 ¹⁷¹²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=546)
Countries and setting	Conducted in USA; Setting: 10 centres
Line of therapy	Unclear
Duration of study	Intervention time: 46 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Physician diagnosis
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 12 to 20 years, with asthma; residents of urban census tracts in which at least 20 percent of households had incomes below the federal poverty threshold. Individuals receiving long-term control therapy were required to have symptoms of persistent asthma or evidence of uncontrolled disease. Individuals not receiving long-term control therapy were required to have both symptoms of persistent asthma and evidence of uncontrolled disease defined by NAEPP guidelines
Exclusion criteria	Excluded after the run-in if controller adherence was <25%. Participants with a urinary cotinine >100 excluded (active smokers)
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 14.4 ± 2.1 years in each group. Gender (M:F): 288:258. Ethnicity: Black: 347/546 (64%); Hispanic: 125/546 (23%); other/mixed: 74/546 (13%)
Further population details	
Indirectness of population	No indirectness
Interventions	(n=276) Intervention 1: Monitoring FeNO, lung function, BD use and symptoms + treatment. Exhaled nitric oxide

	<p>(eNO) added to guideline-based care. FENO was measured for each participant at every visit, but only influenced treatment of the FENO Group. Control level and FENO data were entered into a computer program which generated two treatment options for the blinded physician, one for the Reference Group and another for the FENO Group. The treatment options were derived from protocol-defined treatment steps. Duration 46 weeks. Concurrent medication/care: For safety reasons, FENO was not allowed to increase treatment on the third consecutive visit without elevated symptoms. Also low FENO alone was not allowed to reduce therapy without a corresponding reduction in symptoms. Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to increase ICS in uncontrolled patients</p> <p>(n=270) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms, BD use and lung function + treatment. Based on National Asthma Education and Prevention Program (NAEPP) guidelines. Duration 46 weeks. Concurrent medication/care: Not stated Further details: 1. Additional education training : Not applicable / Not stated / Unclear 2. Aim of intervention: Aim to increase ICS in uncontrolled patients</p>
Funding	Academic or government funding (National Institute of Allergy and Infectious Diseases, National Institutes of Health and National Centre for Research Resources, National Institutes of Health)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT</p> <p>Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : OCS at 46 weeks; Group 1: 89/250, Group 2: 113/244; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment - Actual outcome for Children 5 -<16 : Hospitalisation at 46 weeks; Group 1: 9/250, Group 2: 11/244; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : Unscheduled visits at 46 weeks; Group 1: 59/250, Group 2: 61/244; Risk of bias: Low; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Asthma control questionnaires at End of Treatment - Actual outcome for Children 5 -<16 : Poor control at >20% of visits at 46 weeks; Group 1: 59/267, Group 2: 63/267; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Children 5 -<16 : Asthma Control Test score in last month at 46 weeks; Group 1: mean 21.89 Not stated (SD 1.9); n=250, Group 2: mean 21.83 Not stated (SD 1.87); n=244; Asthma Control Test Not stated Top=High is good outcome; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	

<p>Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : ICS daily dose (fluticasone) at 46 weeks; MD 118.9 (95%CI 48.5 to 189.3); Risk of bias: Low; Indirectness of outcome: Serious indirectness</p>	
<p>Protocol outcome 5: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : FEV1 % pred at 46 weeks; MD 0.8 (95%CI -0.51 to 2.07); Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 6: Symptom free days at End of Treatment - Actual outcome for Children 5 -<16 : Number of symptom-days in last 2 weeks at 46 weeks; Group 1: mean 1.93 days (SD 1.42); n=250, Group 2: mean 1.89 days (SD 1.41); n=244; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 7: Time of school/work at End of Treatment - Actual outcome for Children 5 -<16 : School days missed in last 2 weeks at 46 weeks; Group 1: mean 0.19 days (SD 0.47); n=250, Group 2: mean 0.23 days (SD 0.47); n=244; Risk of bias: Low; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Rescue medication at End of Treatment

Table 142: Verini 2010¹⁸⁵⁷

Study	Verini 2010 ¹⁸⁵⁷
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	Unclear
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis was made by a paediatric respiratory physician on the basis of clinical history of repeated episodes of coughing, dyspnoea, and wheezing, according to ATS-ERS criteria
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with allergic asthma; age 6-17 years; referred to the Allergological and Pneumological Unity of the Paediatric Department, University of Chieti, Italy, between January 2005 and January 2006.
Exclusion criteria	Not stated

Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): FeNO group: 10.7 ± 2.4 years; GINA group: 11.3 ± 2.1 years, range 6-17 years. Gender (M:F): 36:28. Ethnicity: Caucasian
Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=32) Intervention 1: Monitoring FeNO + treatment. Therapy was based on symptoms, short acting β2-agonist use, and lung function and FeNO measurements. Duration 12 months. Concurrent medication/care: Not stated Further details: 1. Additional education training : 2. Aim of intervention:</p> <p>(n=32) Intervention 2: No FeNO monitoring + treatment - Monitoring symptoms and lung function + treatment. Therapy was based on symptoms, short acting β2-agonist use, and lung function. Duration 12 months. Concurrent medication/care: ot stated Further details:1. Additional education training : 2. Aim of intervention:</p>
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING FENO + TREATMENT versus MONITORING SYMPTOMS AND LUNG FUNCTION + TREATMENT</p> <p>Protocol outcome 1: Rescue medication at End of Treatment - Actual outcome for Children 5 -<16 : Number of patients with exacerbations (defined as the number of episodes of coughing, dyspnoea, and wheezing, according to ATS-ERS criteria, requiring short-acting β2-adrenergic agonist) at 12 months; Group 1: 16/32, Group 2: 26/32; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome fo Children 5 -<16 : Number of patients not using inhaled corticosteroids or anti-leukotrienes at 12 months; Group 1: 2/32, Group 2: 6/32; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

G.18 Challenge tests to monitor asthma control

Table 143: Koenig 2008⁸⁹⁵

Study	Koenig 2008 ⁸⁹⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=466)
Countries and setting	Conducted in Latvia, Multiple countries, USA; Setting: 50 sites in the US, three sites in Latin American, and two sites in Latvia.
Line of therapy	Mixed line
Duration of study	Intervention time: 40 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Either historical documentation of reversible airways disease within the last 24 months or an increase in FEV1 of at least 12% within 30 min of inhalation of 2 puffs (180 mcg) of albuterol.
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Male and female patients, 12 years of age and older; asthma for at least 3 months and had been treated during the previous month with short-acting beta2-agonists, anticholinergics, or ICS (p250 mcg daily of fluticasone propionate (FP) or equivalent). At the screening visit, all patients were required to have a forced expiratory volume in 1 s (FEV1) between 60% and 95% of predicted normal
Exclusion criteria	Pregnancy; lifethreatening asthma, hospitalization attributable to asthma within the last 6 months, current smoker or a >10 pack-year history of smoking, a recent (within 2 weeks) upper or lower respiratory tract infection, or significant concurrent diseases. Medications that could confound the evaluation of the study treatments or treatment strategies were prohibited before and throughout the study, including inhaled (up to 250 mcg FP allowed prior to randomization), oral, or parenteral corticosteroids (with the exception of protocol defined use of oral corticosteroids following second consecutive assignment to the highest dose of FP), theophylline or other bronchodilators, leukotriene modifiers, anticholinergics, cromolyn, and nedocromil
Recruitment/selection of patients	Patients underwent physical examination, pulmonary function testing, and other pre-study procedures at the screening visit
Age, gender and ethnicity	Age - Mean (range): 34.8 (12–81), 34.8 (12–81) and 33.2 (12–72) years in the three groups. Gender (M:F): 85:115. Ethnicity: White FSCBHR 124 (79%), FPBHR 120 (77%), FPREF 124 (81%); Black FSCBHR 18 (12%), FPBHR 24 (15%), FPREF 16 (10%); Other FSCBHR 14 (9%), FPBHR 12 (8%), FPREF 14 (9%)

Further population details	
Indirectness of population	No indirectness
Interventions	<p>(n=156) Intervention 1: Monitoring challenge tests + treatment - Monitoring direct challenge tests + treatment. Starting dose of treatment and adjustment of dose (at each 8 week visit for 40 weeks) based on severity class or BHR. Severity class included 4 treatment steps based on control over the past 14 days based on the highest of the following clinical measures (symptoms, BD use, PEFv, FEV1) or BHR. Treatment steps 1-no ICS (placebo); 2-FSC 100/50mcg BID; 3-FSC 250/50mcg BID; 4-500/50mcg BID. For BHR (methacholine PC20) severity class one >4mg/ml; two 1.1-4mg/ml; three 0.25-1mg/ml; four <0.25mg/ml.. Duration 40 weeks. Concurrent medication/care: SABA replaced by albuterol for study duration. ICS was fluticasone propionate using the DISKUS. If patient remained in step 4 for 2 or more visits they were given OCS. Further details: 1. Additional education training : Not applicable / Not stated / Unclear</p> <p>(n=154) Intervention 2: No challenge test monitoring + treatment - Monitoring symptoms, lung function and BD use + treatment. Starting dose of treatment and adjustment of dose (at each 8 week visit for 40 weeks) based on severity class (without BHR as a clinical measure). Severity class included 4 treatment steps based on control over the past 14 days based on the highest of the following clinical measures (symptoms, BD use, PEFv, FEV1). Treatment steps 1-no ICS (placebo); 2-FSC 100/50mcg BID; 3-FSC 250/50mcg BID; 4-500/50mcg BID. . Duration 40 weeks. Concurrent medication/care: SABA replaced by albuterol for study duration. ICS was fluticasone propionate using the DISKUS. If patient remained in step 4 for 2 or more visits they were given OCS. Further details: 1. Additional education training : Not applicable / Not stated / Unclear</p>
Funding	Study funded by industry (GlaxoSmithKline, Research Triangle Park, NC.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING DIRECT CHALLENGE TESTS + TREATMENT versus MONITORING SYMPTOMS, LUNG FUNCTION AND BD USE + TREATMENT

Protocol outcome 1: Mortality at End of Treatment

- Actual outcome for Adults and young people (16 years and over): Death at 40 weeks; Group 1: 1/105, Group 2: 0/107; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Exacerbation (need for OCS) at End of treatment

- Actual outcome for Adults and young people (16 years and over): Asthma exacerbation (not defined) at 40 weeks; Group 1: 22/105, Group 2: 26/107; Risk of bias: Very high; Indirectness of outcome: Exacerbations not defined, serious indirectness.

<p>Protocol outcome 3: Rescue medication at End of Treatment - Actual outcome for Adults and young people (16 years and over): Albuterol use (puff/day) at 40 weeks; Group 1: mean -0.8 puffs/day (SD 1.8); n=105, Group 2: mean -0.7 puffs/day (SD 1.8); n=107; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Adults and young people (16 years and over): Mean inhaled corticosteroid daily dose over treatment period (mcg) at 40 weeks; MD 131.2 (95%CI 83.2 to 178.5) (P=0.037 van Elteren tests); Risk of bias: High; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 5: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): AM PEF at 40 weeks; Group 1: mean 16.9 L/min (SD 92.2); n=105, Group 2: mean 25.5 L/min (SD 92.1); n=107; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): PM PEF at 40 weeks; Group 1: mean 16.4 L/min (SD 89.1); n=105, Group 2: mean 22.4 L/min (SD 88.9); n=107; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): Pre-dose FEV1 at 40 weeks; Group 1: mean 0.06 L (SD 0.51); n=105, Group 2: mean 0.11 L (SD 0.52); n=107; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 6: Symptom free days at End of Treatment - Actual outcome for Adults and young people (16 years and over): % symptom-free days at 40 weeks; Group 1: mean 13 % (SD 56.2); n=105, Group 2: mean 18.1 % (SD 54.9); n=107; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Time of school/work at End of Treatment

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Table 144: Lipworth 2012¹⁰³⁰

Study	STAMINA trial: Lipworth 2012 ¹⁰³⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=157)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: History of mild to moderate persistent asthma

Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Between 18 and 65 years of age and with a history of mild to moderate persistent asthma; prebronchodilator FEV ₁ was required to be > 60% predicted for the purposes of challenge testing.
Exclusion criteria	Not stated
Recruitment/selection of patients	At the time of patients' entry into the study, AHR was established through a provocative dose of mannitol causing a 10% fall in FEV ₁ (PD 10) ≤ 635 mg at the end of the step-down period. Patients initially underwent step-down of their existing treatment with follow-up every 2 weeks. Patients on combination inhalers were switched to an equivalent dose of the same ICS only. The dose of ICS was then halved every 2 weeks until patients were taking 200 mcg/d beclomethasone dipropionate equivalent or they became clinically unstable. Once unstable, patients were stepped back up to the last stable dose of ICS. All patients were then converted to an equivalent dose of the reference ICS, namely ciclesonide, to be taken throughout the rest of the study.
Age, gender and ethnicity	Age - Mean (SD): Control 53.7 (1.7); intervention 53.2 (1.6) years. Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	
Indirectness of population	Serious indirectness: Patients initially underwent step-down of their existing treatment. Patients on combination inhalers were switched to an equivalent dose of the same ICS only (unclear whether LABA was continued)
Interventions	<p>(n=80) Intervention 1: Monitoring challenge tests + treatment - Monitoring indirect challenge tests + treatment. Treatment adjusted based on mannitol AHR only, every 2 months for 12 months. ICS dose increased by one step every 2 months until they became unresponsive to mannitol (PD10>635mg). Treatment steps: ciclesonide, step 1: 80mcg once daily, step 2: 160mcg once daily, step 3: 320mcg once daily, step 4: 160mcg and 320mcg BID, step 5: 320mcg BID.. Duration 12 months. Concurrent medication/care: Initial step-down of existing treatment and those on combination inhalers switched to same ICS only. Dose of ICS halved every 2 weeks until taking 200ug/d beclomethasone dipropionate or equivalent or became unstable - put back to last stable ICS dose. All then converted to equivalent ciclesonide. Further details: 1. Additional education training : Not applicable / Not stated / Unclear</p> <p>(n=77) Intervention 2: No challenge test monitoring + treatment - Monitoring symptoms, lung function and BD use + treatment. Treatment adjusted according to BTS guidelines every 2 months for 12 months. ICS dose increased by one step if 1. fall in PEF >20% baseline; 2. fall in FEV₁ >20% baseline; 3. BD use more than 0.5puffs/day; 4. symptom score >0.5. Treatment steps: ciclesonide, step 1: 80mcg once daily, step 2: 160mcg once daily, step 3: 320mcg once daily, step 4: 160mcg and 320mcg BID, step 5: 320mcg BID.. Duration 12 months. Concurrent medication/care: Initial step-down of existing treatment and those on combination inhalers switched to same ICS only. Dose of ICS halved every 2 weeks until taking 200ug/d beclomethasone dipropionate or equivalent or became unstable - put back to last stable ICS dose. All</p>

	then converted to equivalent ciclesonide. Further details: 1. Additional education training : Not applicable / Not stated / Unclear
Funding	Study funded by industry (University Departmental grants as well as by Pharmaxis, who supplied mannitol as a gift and donated an unrestricted educational grant. Nycomed supplied the ciclesonide inhalers as a gift and also provided an unrestricted educational grant.)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING INDIRECT CHALLENGE TESTS + TREATMENT versus MONITORING SYMPTOMS, LUNG FUNCTION AND BD USE + TREATMENT</p> <p>Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people (16 years and over): mini AQLQ at 12 months; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Adults and young people (16 years and over): Severe exacerbations requiring oral corticosteroids at 12 months; Group 1: 12/61, Group 2: 13/58; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Rescue medication at End of Treatment - Actual outcome for Adults and young people (16 years and over): Reliever use (puffs/day) at 12 months; MD 0.31 (95%CI -0.12 to 0.73) (P=0.16) (final value is lower in the intervention group, therefore mean difference analysed as -0.31); Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Adults and young people (16 years and over): ciclesonide dose mcg at 12 months; MD 306 (95%CI 241.6 to 370.2); Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 5: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): AM PEF at 12 months; MD 1.5 (95%CI -37.7 to 34.7) (P=0.93); Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): FEV1% at 12 months; Group 1: mean 2 % (SD 22.3); n=61, Group 2: mean 1.7 % (SD 24.9); n=58; % 0-100 Top=High is good outcome; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): PEF% at 12 months; Group 1: mean 3.1 % (SD 25.9); n=61, Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of

	Treatment
Table 145: Nuijsink 2007¹²⁶⁰	
Study	Children Asthma Therapy Optimal (CATO) Study trial: Nuijsink 2007¹²⁶⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=210)
Countries and setting	Conducted in Netherlands; Setting: 15 centres; secondary care
Line of therapy	Mixed line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Documented clinical history of moderate persistent asthma, according to GINA guidelines.
Stratum	Children 5 -<16
Subgroup analysis within study	Not applicable
Inclusion criteria	<p>Children with clinically stable asthma living in the Netherlands, aged 6–16 yrs and with a documented clinical history of moderate persistent asthma, according to GINA guidelines. All patients gave a positive, class ≥ 1, radioallergosorbent test result for one or more airborne allergens and used ≥ 200 $\mu\text{g}/\text{day}$ fluticasone or an equivalent dose of other ICS.</p> <p>In children treated with 500 mg/day fluticasone who did not meet the criteria for randomisation after 1 month, the dose of ICS was tapered down to 200 mg/day fluticasone for a further 2 months before randomisation. After run-in, children were randomised into one of two treatment strategy arms if they showed a cumulative symptom score ≥ 14 during the last 2 weeks of the run-in period and/or a PD20<150mg.</p>
Exclusion criteria	Not stated
Recruitment/selection of patients	Selected on the basis of symptom scores and/or the presence of airway hyper-responsiveness
Age, gender and ethnicity	Age - Mean (SD): Intervention: 10.8+/-2.4 years; control: 10.9+/-2.5 years. Gender (M:F): 117:89. Ethnicity: Not stated
Further population details	
Indirectness of population	Serious indirectness: Patients initially underwent step-down of their existing treatment.
Interventions	(n=102) Intervention 1: Monitoring challenge tests + treatment - Monitoring direct challenge tests + treatment. Treatment adjusted on the basis of AHR and symptom score according to a three step medication level algorithm. AHR methacholine dosimeter method PD20.- Increase by 1: PD20<100mcg and SS<14 or PD20<300mcg and SS>=14- No

	<p>change: PD20 100-300mcg and SS<14 or PD20>=300mcg and SS>=14- Decrease by 1: PD20>300mcg and SS<14.. Duration 2 years. Concurrent medication/care: During run-in patients put on 100 or 250 FP BID depending on equivalent treatment before run-in. Further details: 1. Additional education training : Not applicable / Not stated / Unclear</p> <p>(n=104) Intervention 2: No challenge test monitoring + treatment - Monitoring symptoms + treatment. Treatment adjusted on the basis of symptom score only according to a three step medication level algorithm. Symptoms from diary 2 weeks before visit. - Increase by 1: SS>=14- No change: SS 0-14- Decrease by 1: SS=0. Duration 2 years. Concurrent medication/care: During run-in patients put on 100 or 250 FP BID depending on equivalent treatment before run-in. Further details: 1. Additional education training : Not applicable / Not stated / Unclear</p>
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING DIRECT CHALLENGE TESTS + TREATMENT versus MONITORING SYMPTOMS + TREATMENT</p> <p>Protocol outcome 1: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 : At least one exacerbation at 2 years; Group 1: 16/102, Group 2: 17/104; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Dose of regular asthma treatment (SABA, ICS) at End of Treatment - Actual outcome for Children 5 -<16 : Mean daily ICS dose for treatment period at 2 years; Group 1: mean 562 mcg/day (SD 239); n=85, Group 2: mean 478 mcg/day (SD 256); n=90; Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 3: Lung Function at End of Treatment - Actual outcome for Children 5 -<16 : FEV1 % at 2 years; MD 6.0 (95%CI 1.2 to 10.8); Risk of bias: High; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Symptom free days at End of Treatment - Actual outcome for Children 5 -<16 : % symptom-free days (in last 3 months) at 2 years; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Time of school/work at End of Treatment

Table 146: Sont 1999¹⁶⁴²

Study	AMPUL trial: Sont 1999 ¹⁶⁴²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in Netherlands; Setting: Secondary care
Line of therapy	Mixed line
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: History of episodic chest tightness and wheezing in the previous year and visiting a chest physician for their asthma.
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were visiting a chest physician for their asthma at one of the outpatient clinics of four hospitals in the Leiden area; history of episodic chest tightness and wheezing in the previous year; AHR was established through a 20% decrease in FEV1 in response to a provocative concentration of inhaled methacholine (PC20) of < 8 mg/ml; nonsmokers at the time of recruitment (> 1 yr; < 5 pack-yr), and were atopic, between 18 and 50 yr of age, and had had a history of episodic chest tightness and wheezing in the previous year. Atopy was assessed through a positive skin-prick test (> 3 mm wheal) to one or more common airborne allergen extracts. Prebronchodilator FEV1 was more than 50% predicted and > 1.5 L, whereas postbronchodilator FEV1 was within the normal range (> 80% predicted). Subjects were eligible when they had used no other medication than regular inhaled steroids and/or beta-agonists as needed for their asthma during the 6 mo before entry. All subjects gave their written informed consent
Exclusion criteria	Not stated
Recruitment/selection of patients	Outpatient clinics of four hospitals in the Leiden area
Age, gender and ethnicity	Age - Mean (SD): Intervention 31.5 (1.7); control 28.2 (1.3) years. Gender (M:F): 37:38. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Monitoring challenge tests + treatment - Monitoring direct challenge tests + treatment. Treatment adjusted at each 3 month visit based on severity class or AHR. Severity class included 4 treatment steps based on the highest of the following clinical measures (symptoms, BD use, PEFv, FEV1 or BHR). Treatment steps 1-no ICS; 2-low dose ICS; 3-intermediate dose ICS; 4-high dose ICS plus OCS course. For AHR (methacholine PC20) severity class one

	<p>>4mg/ml; two 1.0-4mg/ml; three 0.25-1mg/ml; four <0.25mg/ml.. Duration 2 years. Concurrent medication/care: SABA used as needed Further details: 1. Additional education training : Not applicable / Not stated / Unclear</p> <p>(n=41) Intervention 2: No challenge test monitoring + treatment - Monitoring symptoms, lung function and BD use + treatment. Treatment adjusted at each 3 month visit based on severity class ONLY. Severity class included 4 treatment steps based on the highest of the following clinical measures (symptoms, BD use, PEFv, FEV1). Treatment steps 1-no ICS; 2-low dose ICS; 3-intermediate dose ICS; 4-hig dose ICS plus OCS course. . Duration 2 years. Concurrent medication/care: SABA use as needed Further details: 1. Additional education training : Not applicable / Not stated / Unclear</p>
Funding	Academic or government funding (The Netherlands Asthma Foundation)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONITORING DIRECT CHALLENGE TESTS + TREATMENT versus MONITORING SYMPTOMS, LUNG FUNCTION AND BD USE + TREATMENT</p> <p>Protocol outcome 1: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): FEV1 L at 2 years; Group 1: mean 78 mL/year (SD 34); n=32, Group 2: mean -7 mL/year (SD 36); n=35; Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

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G.19 Monitoring adherence to treatment

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Table 147: BURGESS 2010²⁴⁶

Study	Burgess 2010 ²⁴⁶
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=26)
Countries and setting	Conducted in Australia; Setting: Paediatric asthma clinic, outer metropolitan general hospital
Line of therapy	Mixed line
Duration of study	Intervention time: 4 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Dx with asthma
Stratum	Children 5 -<16 with uncontrolled asthma: Children 6-14 years, asthma not well controlled despite preventative medication ('unstable asthma')
Subgroup analysis within study	Not applicable:
Inclusion criteria	Aged 6-14 years; asthma not well controlled (based on a reported history of asthma symptoms occurring more than twice a week and requiring reliever medication and/or lung function FEV1 <80%)
Exclusion criteria	nr
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Range: 6-14 years. Gender (M:F): 17/9. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Near fatal asthma attacks: Not applicable / Not stated / Unclear 4. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=14) Intervention 1: Adherence monitoring + treatment - Adherence monitoring and feedback + treatment. Electronic monitoring device (Smartinhale, Nexus 6; counts number of doses). Adherence calculated at each monthly review as a % of the number of prescribed doses registered by the smartinhale. Adherence shared with child and carer and incorporated into the management plan (direct feedback from respiratory physician). Duration 4 months. Concurrent medication/care: In both groups: personalised asthma education and generic written information. Personalised asthma management plan devised, assessment of inhaler technique. Further details: 1. Additional education training : Additional education in both groups</p> <p>(n=12) Intervention 2: Usual care + treatment - Usual care (no adherence feedback) + treatment. Adherence remains unknown to physician. Duration 4 months. Concurrent medication/care: In both groups: personalised asthma education and generic written information. Personalised asthma management plan devised, assessment of inhaler technique. Further details: 1. Additional education training : Additional education in both groups</p>

Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADHERENCE MONITORING AND FEEDBACK + TREATMENT versus USUAL CARE (NO ADHERENCE FEEDBACK) + TREATMENT</p> <p>Protocol outcome 1: Adherence at End of Treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: % of prescribed doses measured by the electronic inhaler at 4 months; Group 1: mean 84.2 % (SD 26.3); n=14, Group 2: mean 55.3 % (SD 26.3); n=12; % of prescribed doses measured by the electronic inhaler 0-100 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Exacerbation (need for OCS) at End of treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: Acute exacerbation at 4 months; Group 1: 3/14, Group 2: 1/12; Risk of bias: Very high; Indirectness of outcome: Serious indirectness</p> <p>Protocol outcome 3: Rescue medication at End of Treatment - Actual outcome for Children 5 -<16 with uncontrolled asthma: Reliever medication 3 or more times a week at 4 months; Group 1: 2/14, Group 2: 0/12; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 148: ONYIRIMBA 2003¹²⁸²

Study	Onyirimba 2003 ¹²⁸²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in USA; Setting: hospital asthma centre
Line of therapy	Mixed line
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Adults with moderate to severe asthma; referred to hospital asthma centre
Stratum	Adults and young people with uncontrolled asthma: Adults with moderate to severe asthma
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with moderate to severe asthma; referred to hospital asthma centre; low socioeconomic status; FEV1 <80% predicted and BDR of ≥15%; regular use of ICS (LABA, OCS and theophylline permissible); smokers not excluded.
Exclusion criteria	nr
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Range: >18 years. Gender (M:F): 3/16. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Near fatal asthma attacks: Not applicable / Not stated / Unclear 4. Social economic disadvantage: Low social economic status
Indirectness of population	Serious indirectness: Includes severe asthma
Interventions	(n=15) Intervention 1: Adherence monitoring + treatment - Adherence monitoring and feedback + treatment. Electronic monitoring device (MDI Chronologs and electronic recording of actuations for 10 weeks). Received direct feedback on ICS use from the clinician investigator and discussion of techniques to improve adherence (in addition to standard asthma care). Duration 10 weeks. Concurrent medication/care: In both groups: If necessary, ICS switched to a twice daily regime; 3 week intensive asthma education (four 30-60min sessions) by a nurse and/or respiratory therapist blinded to the patient group (goals of therapy, signs of worsening asthma, medications, importance of prophylactic medication, MDI technique and PEF). Physician input, therapy adjustment and implementation of a management plan based on PEF or symptoms at these sessions Further details: 1. Additional education training : Additional education in both groups

	(n=15) Intervention 2: Usual care + treatment - Usual care (no adherence feedback) + treatment. Adherence data not provided to physician. Standard asthma care only. Duration 10 weeks. Concurrent medication/care: In both groups: If necessary, ICS switched to a twice daily regime; 3 week intensive asthma education (four 30-60min sessions) by a nurse and/or respiratory therapist blinded to the patient group (goals of therapy, signs of worsening asthma, medications, importance of prophylactic medication, MDI technique and PEF). Physician input, therapy adjustment and implementation of a management plan based on PEF or symptoms at these sessions Further details: 1. Additional education training : Additional education in both groups
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADHERENCE MONITORING AND FEEDBACK + TREATMENT versus USUAL CARE (NO ADHERENCE FEEDBACK) + TREATMENT</p> <p>Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people with uncontrolled asthma: AQLQ at 10 weeks; Group 1: mean change score 1.13 (SD 0.31); n=10, Group 2: mean change score 0.76 (SD 0.33); n=9; AQLQ 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Adults and young people with uncontrolled asthma: FEV1 % at 10 weeks; Group 1: mean 0.04 L (SD 0.11); n=10, Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Adherence at End of Treatment; Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

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Table 149: OTSUKI 2009¹²⁹²

Study	Otsuki 2009 ¹²⁹²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=250)
Countries and setting	Conducted in USA; Setting: Community; recruited from paediatric ED
Line of therapy	Mixed line

Duration of study	Intervention time: 18 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Phys Dx asthma
Stratum	Children 5 -<16 with uncontrolled asthma: Children 2-12 years with asthma recruited from ED discharge records; 2 ED visits or 1 hospitalisation for asthma in previous year
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with asthma recruited from ED discharge records; 2-12 years old; had Phys Dx asthma; 2 ED visits or 1 hospitalisation for asthma in previous year; prescribed an asthma controller medication)
Exclusion criteria	nr
Recruitment/selection of patients	2001-2003
Age, gender and ethnicity	Age - Range: 2-12 years. Gender (M:F): 106/61. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Near fatal asthma attacks: Not applicable / Not stated / Unclear 4. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness: Mean age within 5-16 year age group
Interventions	<p>(n=83) Intervention 1: Adherence monitoring + treatment - Adherence monitoring and feedback + treatment. Feedback of adherence (electronic medication monitors), goal-setting and reinforcement of adherence goals and strategies for self-monitoring of med use plus home-based education as in the control group. Duration 18 months. Concurrent medication/care: In both groups: Five 30min home visits by trained asthma educators Further details: 1. Additional education training : Additional education in both groups</p> <p>(n=84) Intervention 2: Usual care + treatment - Usual care (no adherence feedback) + treatment. Home-based asthma education programme alone (review of asthma regime; training in inhaler technique; development of asthma action plan and other education materials). Duration 18 months. Concurrent medication/care: In both groups: Five 30min home visits by trained asthma educators Further details: 1. Additional education training : Additional education in both groups</p>
Funding	Academic or government funding (National Heart Lung and Blood Institute)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADHERENCE MONITORING AND FEEDBACK + TREATMENT versus USUAL CARE (NO ADHERENCE FEEDBACK) + TREATMENT	

<p>Protocol outcome 1: Adherence at End of Treatment</p> <p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: % self-reported adherence in previous 6 months at 18 months; Group 1: mean 87.33 % (SD 25.24); n=76, Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: Number of canister refills (100% adherence = 3.0) at 18 months; Group 1: mean 0.58 (SD 0.86); n=76, Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
<p>Protocol outcome 2: Exacerbation (need for OCS) at End of treatment</p> <p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: Courses of OCS in previous 6 months at 18 months; Group 1: mean 0.96 (SD 1.59); n=76, Risk of bias: High; Indirectness of outcome: Serious indirectness</p>	
<p>Protocol outcome 3: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment</p> <p>- Actual outcome for Children 5 -<16 with uncontrolled asthma: Hospitalisation in previous 6 months at 18 months; Group 1: mean 12 (SD 15.8); n=76, Risk of bias: High; Indirectness of outcome: Serious indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Quality of life at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Table 150: WILLIAMS 2010¹⁹²²

Study	Williams 2010 ¹⁹²²
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	1 (n=2698)
Countries and setting	Conducted in USA; Setting: Primary care
Line of therapy	Mixed line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: at least one physician Dx of asthma and no Dx of COPD or congestive heart failure
Stratum	Adults and young people overall: Age 5-56 years with ICS prescription
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 5-56 years; an electronic prescription for an ICS between Jan 2005 and April 2007; at least one physician Dx of asthma and no Dx of COPD or congestive heart failure; at least one visit to primary care provider in the previous year

Exclusion criteria	nr
Recruitment/selection of patients	August 2007 to July 2008
Age, gender and ethnicity	Age - Range: 5-56 years. Gender (M:F): Define. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Near fatal asthma attacks: Not applicable / Not stated / Unclear 4. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness: Mean age within adult and young person age group
Interventions	<p>(n=1335) Intervention 1: Adherence monitoring + treatment - Adherence monitoring and feedback + treatment. Physicians provided with adherence information (from refill data) when reviewing and writing prescriptions. Adherence calculated from prescription and refill data and uploaded onto the ePrescribing system every 2 weeks and could be viewed by physicians. General and detailed adherence information could be viewed. Physicians also received specific instructions on how to interpret the adherence data.. Duration 12 months. Concurrent medication/care: GP practices in both groups received information on the most recent asthma guidelines, and methods for discussing nonadherence with their patients. Further details: 1. Additional education training : No education in both groups</p> <p>(n=1363) Intervention 2: Usual care + treatment - Usual care (no adherence feedback) + treatment. GP used e Prescribing system but could not view asthma patient's adherence data.. Duration 12 months. Concurrent medication/care: GP practices in both groups received information on the most recent asthma guidelines, and methods for discussing nonadherence with their patients. Further details: 1. Additional education training : No education in both groups</p>
Funding	Academic or government funding (Grants from National Heart Lung and Blood Institute, National Institute of Allergy and Infectious Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes for Health, Fund for Henry Ford Hospital, American Asthma Foundation.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ADHERENCE MONITORING AND FEEDBACK + TREATMENT versus USUAL CARE (NO ADHERENCE FEEDBACK) + TREATMENT

Protocol outcome 1: Adherence at End of Treatment

- Actual outcome for Adults and young people overall: % adherence to prescription refills in previous 3 months at 12 months; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Exacerbation (need for OCS) at End of treatment

- Actual outcome for Adults and young people overall: OCS use at 12 months; HR 1.07 (95%CI 0.89 to 1.29) Reported; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people overall: OCS use at 12 months; RR Adjusted RR 1.11 (95%CI 0.92 to 1.34) (P=0.28 (negative binomial regression model)); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 3: UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment

- Actual outcome for Adults and young people overall: Asthma-related Hospitalisation at 12 months; HR 0.86 (95%CI 0.32 to 2.29) Reported; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people overall: Asthma-related Hospitalisation at 12 months; RR Adjusted RR 0.87 (95%CI 0.33 to 2.29) (P=0.77 (negative binomial regression model)); Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people overall: Asthma-related ED visit at 12 months; HR 1.22 (95%CI 0.83 to 1.78) Reported; Risk of bias: Very high; Indirectness of outcome: No indirectness
- Actual outcome for Adults and young people overall: Asthma-related ED visit at 12 months; RR Adjusted RR 1.12 (95%CI 0.74 to 1.69) (P=0.60 (negative binomial regression model)); Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study

Mortality at End of Treatment; Quality of life at End of treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Lung Function at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

G.20 Monitoring inhaler technique

Study	Al-showair 2007 ²⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=71)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care - patients attending an outpatient clinic
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Patients with asthma attending an outpatient clinic and receiving ICS
Stratum	Adults and young people (16 years and over)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with asthma attending an outpatient clinic; receiving ICS from an MDI without a spacer; identified with poor inhaler technique (good coordination but inhaled too fast IFR ≥ 90 l/min).
Exclusion criteria	Experienced an acute exacerbation of asthma within 4 weeks prior to recruitment; hearing problems and/or unable to distinguish between one and two tones produced by the 2TT tool; patients who started to inhale before actuating a dose (poor coordination).
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Mean (SD): Verbal group 52.6 (15.7); Verbal+2TT group 58.3 (13.7). Gender (M:F): 27/44. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Monitoring inhaler technique + feedback - Monitoring using electronic devices + feedback. Verbal training on the most desirable inhalation technique with emphasis on breathing out slowly as far as comfortable and actuating a dose at or soon after the start of a slow inhalation. Also trained on how to use the 2Tone Trainer every morning and night to obtain the one-tone sound and to use the same inhalation procedure when using their MDI.. Duration 6 weeks. Concurrent medication/care: nr Further details: 1. Additional education training : Additional education in both groups (Counselled on compliance with the prescribed medication).

	(n=36) Intervention 2: Monitoring inhaler technique + feedback - Visual monitoring + feedback. Verbal training on the most desirable inhalation technique with emphasis on breathing out slowly as far as comfortable and actuating a dose at or soon after the start of a slow inhalation.. Duration 1 visit (6 weeks follow-up). Concurrent medication/care: nr Further details: 1. Additional education training : Additional education in both groups (Counselled on compliance with the prescribed medication).
Funding	Other (2 Tone trainers donated by Canday Medical Ltd.)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VERBAL TRAINING PLUS ELECTRONIC DEVICE TO PRACTICE versus VERBAL TRAINING</p> <p>Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people (16 years and over): mini AQLQ at 6 weeks; Group 1: mean 4.6 (SD 1); n=36, Group 2: mean 4.2 (SD 1); n=35; mini AQLQ 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): FEV1 L at 6 weeks; Group 1: mean 1.93 L (SD 0.63); n=36, Group 2: mean 2.16 L (SD 0.74); n=35; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Study	Ammari 2013-1 ⁴³
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=34)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Patients with asthma who collected their MDI prescriptions from community pharmacies
Stratum	Adults and young people (16 years and over):
Subgroup analysis within study	Stratified then randomised: Adults and children
Inclusion criteria	Aged 4-45 years; prescribed at least one MDI without a spacer device including a preventer; identified with poor inhaler technique (defined as poor hand-lung coordination and an IFR ≥ 90 l/min).
Exclusion criteria	Experienced an acute exacerbation of asthma or received OCS within 4 weeks prior to recruitment; had other illnesses adversely affecting their respiratory system; hearing problems and/or unable to distinguish between one and two tones produced by the 2TT tool.
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Mean (SD): 40.7 (9.7). Gender (M:F): 11/23. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Monitoring inhaler technique + feedback - Monitoring using electronic devices + feedback. All patients selected due to a fast inhalation (most common inhaler technique problem). Verbal training + the 2 tone trainer (2TT) to achieve a slow inhalation flow rate by encouraging patients to increase the length of their inhalation period. The 2TT is an MDI-like tool without a canister that is designed to give an audible feedback depending on the inhalation speed (a high pitched two tone noise if inhalation is too fast >60 l/min). Patients then simulate this technique when using their own MDI. . Duration 6 weeks. Concurrent medication/care: Instructed to practice using the 2TT twice daily before taking their MDI Further details: 1. Additional education training : No education in both groups

	(n=17) Intervention 2: Monitoring inhaler technique + feedback - Visual monitoring + feedback. All patients selected due to a fast inhalation (most common inhaler technique problem). Verbal training to achieve a slow inhalation flow rate by encouraging patients to increase the length of their inhalation period.. Duration 1 visit (6 week follow-up). Concurrent medication/care: nr Further details: 1. Additional education training : No education in both groups
Funding	Principal author funded by industry (Author received sponsorship to carry out studies from several pharmaceutical companies. Research sponsorship also received from EPSRC and MRC)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VERBAL TRAINING PLUS ELECTRONIC DEVICE TO PRACTICE versus VISUAL TRAINING</p> <p>Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people (16 years and over): mini AQLQ at 6 weeks; Group 1: mean -0.409 (SD 1.05); n=17, Group 2: mean -0.748 (SD 1.31); n=17; miniAQLQ 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): FEV1 % pred at 6 weeks; Group 1: mean 96.3 % (SD 17.6); n=17, Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Study	Ammari 2013-2 ⁴³
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=12)
Countries and setting	Conducted in United Kingdom; Setting: Primary care
Line of therapy	Mixed line
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Patients with asthma who collected their MDI prescriptions from community pharmacies
Stratum	Children 5 -<16
Subgroup analysis within study	Stratified then randomised: Adults and children
Inclusion criteria	Aged 4-45 years; prescribed at least one MDI without a spacer device including a preventer; identified with poor inhaler technique (defined as poor hand-lung coordination and an IFR ≥ 90 l/min).
Exclusion criteria	Experienced an acute exacerbation of asthma or received OCS within 4 weeks prior to recruitment; had other illnesses adversely affecting their respiratory system; hearing problems and/or unable to distinguish between one and two tones produced by the 2TT tool.
Recruitment/selection of patients	nr
Age, gender and ethnicity	Age - Mean (SD): 10.2 (3.2). Gender (M:F): 8/4. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=6) Intervention 1: Monitoring inhaler technique + feedback - Monitoring using electronic devices + feedback. All patients selected due to a fast inhalation (most common inhaler technique problem). Verbal training + the 2 tone trainer (2TT) to achieve a slow inhalation flow rate by encouraging patients to increase the length of their inhalation period. The 2TT is an MDI-like tool without a canister that is designed to give an audible feedback depending on the inhalation speed (a high pitched two tone noise if inhalation is too fast >60l/min). Patients then simulate this technique when using their own MDI.. Duration 1 visit (6 week follow-up). Concurrent medication/care: Instructed to practice using the 2TT twice daily before taking their MDI Further details: 1. Additional education training : No education in both groups

	<p>(n=6) Intervention 2: Monitoring inhaler technique + feedback - Visual monitoring + feedback. All patients selected due to a fast inhalation (most common inhaler technique problem). Verbal training to achieve a slow inhalation flow rate by encouraging patients to increase the length of their inhalation period.. Duration 1 visit (6 week follow-up). Concurrent medication/care: nr</p> <p>Further details: 1. Additional education training : No education in both groups</p>
Funding	Principal author funded by industry (Author received sponsorship to carry out studies from several pharmaceutical companies. Research sponsorship also received from EPSRC and MRC)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VERBAL TRAINING PLUS ELECTRONIC DEVICE TO PRACTICE versus VERBAL TRAINING</p> <p>Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Children 5 -<16: PAQLQ at 6 weeks; Group 1: mean -0.362 (SD 0.52); n=6, Group 2: mean -0.391 (SD 0.69); n=6; PAQLQ 1-7 Top=High is good outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Children 5 -<16: FEV1 % pred at 6 weeks; Group 1: mean 90.9 % (SD 14.3); n=6, Risk of bias: High; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

Study (subsidiary papers)	Basheti 2007 ¹²² (Basheti 2008 ¹¹⁹)
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	(n=)
Countries and setting	Conducted in Australia; Setting: Community - pharmacy education
Line of therapy	Mixed line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Doctor Dx asthma and use of ICS
Stratum	Adults and young people (16 years and over): Aged ≥14 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients presenting with Turbuhaler or Diskus prescriptions for asthma; age ≥14 years; doctor diagnosed asthma; use of ICS with Turbuhaler or Diskus with or without LABA; no change in asthma medication or dose for 1 month.
Exclusion criteria	Did not self-administer their own medication; did not speak or understand English.
Recruitment/selection of patients	April 2003 - 2004
Age, gender and ethnicity	Age - Range: ≥14 years. Gender (M:F): nr. Ethnicity:
Further population details	1. Cognitive function: Not applicable / Not stated / Unclear 2. Disability: Not applicable / Not stated / Unclear 3. Social economic disadvantage: Not applicable / Not stated / Unclear
Indirectness of population	No indirectness
Interventions	<p>(n=56) Intervention 1: Monitoring inhaler technique + feedback - Visual monitoring + feedback. Pharmacy trained to deliver education on peak flow meter technique and inhaler technique. Assessed inhaler technique using checklists and then educated using 'show and tell' for each step on the checklist. Incorrect steps on the checklist were highlighted and attached to the patient's inhaler using a label. This was repeated at 1, 2, 3 and 6 months.. Duration 6 months. Concurrent medication/care: nr Further details: 1. Additional education training : No education in both groups</p> <p>(n=56) Intervention 2: No monitoring . Pharmacy trained to deliver education on peak flow meter technique only. Duration 1 visit (6 month follow-up). Concurrent medication/care: nr Further details: 1. Additional education training : No education in both groups</p>

Funding	Principal author funded by industry (Author grant support from GSK and AstraZenica)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VISUAL MONITORING + FEEDBACK versus NO MONITORING OF INHALER TECHNIQUE</p> <p>Protocol outcome 1: Quality of life at End of treatment - Actual outcome for Adults and young people (16 years and over): Marks AQLQ at 3 months; Group 1: mean 0.8 (SD 0.5); n=53, Group 2: mean 1.35 (SD 0.6); n=44; Marks AQLQ 0-10 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): Marks AQLQ at 6 months; Group 1: mean 0.8 (SD 0.6); n=53, Group 2: mean 1.3 (SD 0.6); n=44; Marks AQLQ 0-10 Top=High is poor outcome; Risk of bias: Very high; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: Lung Function at End of Treatment - Actual outcome for Adults and young people (16 years and over): PEFv (Min%Max) at 3 months; Group 1: mean 83.8 % (SD 8.3); n=53, Risk of bias: Very high; Indirectness of outcome: No indirectness - Actual outcome for Adults and young people (16 years and over): PEFv (Min%Max) at 6 months; Group 1: mean 78.9 % (SD 9.7); n=53, Group 2: mean 74.4 % (SD 8.9); n=44; Risk of bias: Very high; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Mortality at End of Treatment; Exacerbation (need for OCS) at End of treatment; UHU (ED visit, hospitalisation, GP out-of-hours centre) at End of Treatment; Asthma control questionnaires at End of Treatment; Rescue medication at End of Treatment; Dose of regular asthma treatment (SABA, ICS) at End of Treatment; Symptom free days at End of Treatment; Time of school/work at End of Treatment

1G.21 Tele-healthcare to monitor asthma control

2 Table 151: Baptist 2013^{100,100}

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
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Baptist, A. P., et al. (2013). A randomized controlled trial of a self-regulation intervention for older adults with asthma. <i>May. Journal of the American Geriatrics Society, 61(5), 747-753</i>	RCT	N=70		Tele	Control	3 in-person group sessions and 3 one-on-one telephone sessions. Group sessions included seven participants and a health educator who served as the leader. A health educator conducted all group and telephone sessions.	3 phone calls not related to asthma self-management. An allergist called participants randomized to the control group 1 and 2 weeks after enrolment to address any inquiries regarding information received during the asthma education session.	6 and 12 months	Hospital visits	T:0/34 C:4/36	Funding: American Academy of Allergy Asthma and Immunology
			Age, yrs	72.8	73.8				GP visits	T: 6/34 C: 14/36	
			% male:	32.4	13.9				FEV1 % predicted	T: 84.6 C: 76.3 P=0.17	
			% pred. FEV1	84.2	80.9						
			Inclusion criteria:								
<ul style="list-style-type: none"> • Outpatients aged 65 and older • Physician diagnosis of asthma • Daily controller medication • Access to a home telephone 											
Exclusion criteria:											
<ul style="list-style-type: none"> • COPD or any other primary pulmonary disorder • Current smokers or smoking history of > 20 pack-years • Mental impairment 											
									Risk of bias: <ul style="list-style-type: none"> • Randomised with number generator • Participants, physicians and assessors were blind • 90% included in final analysis • ACQ continuous data not reported 		

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Table 152: Barbanel 2003^{105,105}

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments	
Barbanel, D., Eldridge, S., & Griffiths, C. (2003). Can a	RCT	N=24		Tele	Control	After a 3-day training course on asthma care, patients were	The control group received no input from	6 months	North of England Asthma Scale – not	N/A	Funding: Not stated
	Deprived area	Tele:	Age, yrs	45	47						

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			% male:	50	41.7						
self-management programme delivered by a community pharmacist improve asthma control? A randomised trial. <i>Thorax</i> , 58(10), 851-854.	of London	N=12 Control: N=12				allocated to a pharmacist for a 45 min educational session and weekly follow-up calls for 3 months. Education included inhaler technique and PEF meter use. Patients were also given supporting literature and a management plan.	the pharmacist.		meta-analysed		<ul style="list-style-type: none"> • Risk of bias: Sequence generation unclear but concealed allocation • Blinding was not possible • One dropout in control was imputed

Table 153: Bender 2010^{150,150}

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Test of an interactive voice response intervention to improve adherence to controller medications in adults with asthma. Journal of the American	RCT	N=50 (25 in each group) 18 to 65 years; physician-diagnosed asthma for which they were prescribed daily inhaled corticosteroid treatment. Exclusion criteria: (1) any	Mean age treatment: 39.6 (12.8) years; control 43.5 (14.3) years. % male: 40% and 32%. White 56% and 60%; Hispanic 24% and 12%; African American 20% and 20%;	2 automated interactive voice response telephone calls separated by one month, with one additional call if they reported recent symptoms of poorly controlled disease or failure to fill a prescription. Calls were completed in	Participants in the control group received no calls.	10 weeks	Mean ICS adherence (dividing the number of inhaler puffs taken by the number of puffs prescribed to be taken each day and then averaged over the 10-week interval) was	64.5 (17.2) % vs. 49.1 (16.8) %, p=0.0032	Investigator-sponsored Study Program of AstraZeneca	Randomisation and allocation concealment unclear (random table generated before study initiation); investigator blind; no attrition; no selective

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Board of Family Medicine: 23: 159-165 Bender BG, Apter A, Bogen DK, Dickinson P, Fisher L, Wamboldt FS, and Westfall JM 2010.		significant disease or disorder that, in the opinion of the investigator, might influence the results of the study or the patient's ability to participate in the study (including other chronic health disorders, current substance abuse or dependence, mental retardation, or psychiatric disorder); and (2) current participation in any other asthma-related research or clinical trial.	Asian 0% and 8%. All not significantly different.	< 5 minutes and included content designed to inquire about asthma symptoms, deliver core educational messages, encourage refilling of inhaled corticosteroid prescriptions, and increase communication with providers			higher in the group receiving IVR intervention than in the control group			reporting; groups comparable at baseline
							Change in Beliefs about Medications Questionnaire (scores above 0 indicate more positive beliefs and scores below 0 indicate more negative beliefs): the group receiving IVR intervention demonstrating a greater upward shift in positive medication beliefs	0.248 (1.07) vs. -0.508 (0.913), p=0.007		
							Change in Asthma Quality of Life Questionnaire	-0.152 (0.92) vs. -0.381		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							(higher scores indicate better quality of life)	(1.06), not significant		
							Change in Asthma Control Test (higher scores indicate better control of asthma symptoms)	-1.120 (3.90) vs. -1.840 (4.14), not significant		

Table 154: Chan 2007^{298,299}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Chan, D. S., et al (2007). Internet-based home monitoring and education of children with asthma is comparable to ideal office-based	RCT Child clinic in Hawaii army centre	N=120 Tele: N=60 Control: N=60		Tele:	Control:	Virtual group patients received computers, internet connections, and in-home, Internet-based case	Office-based group patients received traditional in-person education and case management.	12 m	Hospital visits	T: 1/60 C: 1/60	Funding: US Army Medical Research Acquisition Activity Risk of bias:
			Age, yrs	10.2	9				ED visits	T: 4/60 C: 2/60	
			% male	61.7	63.3				PAQLQ child	T: 6.1 (1.1) C: 5.8 (1.2)	
			Inclusion criteria: • Children/teens aged 6-17						PAQLQ parent	T: 6.4 (1) C: 6.2 (0.8)	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
care: results of a 1-year asthma in-home monitoring trial. <i>Pediatrics</i> , 119(3), 569-578.			<ul style="list-style-type: none"> Persistent asthma Dependent of active duty or retired military personnel Could receive cable modem Willing to complete questionnaires <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Not stated 	management and received education through the study website.			FEV1 % predicted	T: 97.4 (19.2) C: 92.7 (18.1)	<ul style="list-style-type: none"> Random numbers table Un-blinded Dropout much higher in tele-health group (23%) than office group (8%)

Table 155: Chatkin 2006^{306,307}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Chatkin, J. M., et al. (2006). Impact of a low-cost and simple intervention in enhancing treatment adherence in a Brazilian asthma sample. <i>Journal of Asthma</i> , 43(4), 263-266.	RCT Physicians from all over Brazil were invited to include their patients	N=271		Tele	Control	Participants received 10 minute telephone calls every two weeks to provide asthma education with emphasis on treatment adherence. A specifically trained nursing student conducted the calls.	Routine care with a call at the beginning and end of the study to collect data.	Unknown follow-up	Adherence measures	None of interest	<p>Funding: GSK Brazil</p> <p>Risk of bias:</p> <ul style="list-style-type: none"> Minimal information regarding randomisation 10 patients were not included because they did not return their
			Age, yrs	43.3	44.4						
			% male	25.7	29						
			<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Adults/adolescents 12+ years Mod./severe asthma according to GINA <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Mild persistent asthma 								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			<ul style="list-style-type: none"> • Pregnancy or breast-feeding • Recent alcohol or drug abuse • Active medical condition 						drug disks and 8 for not responding to the telephone calls

Table 156: Christakis 2012^{325,325}

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
<p>Improving parental adherence with asthma treatment guidelines: a randomized controlled trial of an interactive website. Academic pediatrics: 12: 302-311</p> <p>Christakis DA, Garrison MM, Lozano P,</p>	RCT	N=603; 283 intervention; 320 control. Parents of children aged 2 to 10 years with asthma (at least 1 clinical encounter – clinic visit, emergency room or inpatient admission – or two prescription refills for bronchodilato	29% had mild to severe persistent asthma; 71% had mild intermittent asthma; 54% on at least one controller medication and of these, 61% took controller 5 or more days per week. Among controller users, 60% adherent in control arm and 61% in	Web-based intervention: gathers information from parents (day and night time symptoms, quick-reliever use), applies algorithm to determine asthma severity, home care practices (controller use and adherence), functional status, parental beliefs (outcomes expectation and	Control parents had similar intervention around reducing media usage among their children.	12 months	<p>Appropriate controller use: non-users converted to controller use at 6 months</p> <p>Patients who should have been on controllers at baseline (i.e. persistent asthma) but were not, who were on controllers at 6</p>	<p>15.69% control vs. 15.79% int'n, p=0.98 (denominators unclear)</p> <p>7/19 (36.84%) int'n; 5/30 (16.7%) cont; OR 2.85, 95% CI 0.63 to 14.04,</p>	National Heart, Lung and Blood Institute	Computer randomisation; 85% completed 6-month assessment and 80% at 12 months; no selective reporting; groups comparable at baseline

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Meischke H, Zhou C, and Zimmerman FJ 2012.		rs in the last year) in an HMO and a primary care clinical practice network. Had to have convenient access to internet-enable computer, speak English at home.	intervention arm at baseline.	self-efficacy), feedback on child's asthma (recommendations regarding controller use and other aspects of asthma care), allowed parent to set goals relevant to their situation. Monthly email reminders to log on. Intervention 6 months, then opt-in for further 6 months			months	p=0.17		
							Persistent asthma on controllers at baseline but discontinued at 6 months	6/42 (14%) int'n; 3/58 (5%) cont; OR 0.33, 95% CI 0.05 to 1.67, p=0.16		
							Adherence at 6 months (5 or more days per week) to controllers for those who were prescribed them at 6 months	72% int'n vs. 62% cont, OR 1.54, 95% CI 0.90 to 2.63, p=0.10		
							Adherence at 6 months (5 or more days per week) to controllers for the persistent asthma subgroup who were	77% vs. 50%, OR 3.33, 95% CI 1.20 to 10.07, p=0.01 (denominators		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							prescribed them at baseline and 6 months	unclear)		
							Outcome expectations at 6 months: positive: no difference between groups; negative: lower in intervention arm.	Positive: 124/241 (51%) int'n; 122/274 (44%) cont, p=0.12. Negative: 145/241 (60%) int'n vs. 190/274 (69%) cont, p=0.03		
							Parental self-efficacy (parents somewhat or strongly agreeing that they can give their child controller medication daily) at 6	217/241 (90%) int'n vs. 218/274 (80%) cont, p=0.001		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							months			
							Asthma symptoms and severity at 6 and 12 months: Proportions of children with stable or improved symptoms not significantly differed between groups	Data not shown		
							Proportion of children on controllers at 12 months	50% int'n vs. 57% cont, p=0.17 (denominators unclear)		
							Of those who met severity criteria for controllers at baseline, number on them at 12 months	34/53 (64%) int'n, 50/82 (60%) cont, p=0.86		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							Adherence 5 or more days/week at 12 months	69/105 (66%) int'n, 88/140 (63%) cont, p=0.69		

Table 157: Deschildre 2012^{431,431}

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Deschildre, A., et al. (2012). Home telemonitoring (forced expiratory volume in 1 s) in children with severe asthma does not reduce exacerbations. <i>European respiratory journal</i> , 39(2), 290-296.	RCT 4 paediatric clinics in France	N=50 Tele: N=25 Control: N=25		Tele	Control	Daily home spirometry transmitted to the physician via modem, and medical feedback. Depending on FEV1 results, the GP or hospital paediatrician was contacted.	12 m	Hospital visits	T: 2/21 C: 2/23	Funding: French Ministry of Health Risk of bias: <ul style="list-style-type: none"> • Unclear randomisation procedures • Un-blinded • Unbalanced attrition (higher in tele group) • Analysed with non-parametric tests
			Age, yrs (median)	11.0	11.2			Oral steroids	T: 19/21 C: 21/23	
			% male	72	76					
			FEV1 % predicted (median)	87.4	83.3					
			Inclusion criteria:							
<ul style="list-style-type: none"> • Children/teens aged 6-16 • Severe allergic asthma (3rd Paediatric Asthma Consensus) • Frequent exacerbations • reversibility of > 12%and/or 										

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			an increase of at least 200 mL • All taking LABA/ICS combo Exclusion criteria: • Congenital or acquired illness other than asthma						

Table 158: Donald 2008^{447,447}

Reference	Study type	Number of patients	Patient characteristics		Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Donald, K. J., McBurney, H., Teichtahl, H., & Irving, L. (2008). A pilot study of telephone based asthma management. <i>Australian Family Physician</i> , 37(3), 170-173.	RCT 2 teaching hospitals in Australia	N=71		Tele:	6 follow-up calls from the nurse educator about current asthma symptoms, with management advice. Patients were given a PEF meter and recording instructions, a face-to-face session with an asthma nurse educator, advice on medications, triggers and management, and an Asthma Action Plan.	The control group was encouraged to continue with self-management and usual GP care	12 m	Hospital visits	T: 1/31 C: 6/29	Funding: Unclear Risk of bias: • Unclear randomisation procedures • Researcher blinded, patients and nurses not • Low questionnaire response rate
		Tele: N=36	Age, years	36.2				ED visits	T: 7/36 C: 5/35	
		Control: N=35	% male	23.9				GP visits	T: 22/31 C: 16/29	
		Inclusion criteria: • Adults aged 18-55 • Previous asthma admission • Primary diagnosis of asthma Exclusion criteria: • Other chronic respiratory or unstable medical condition • Cognitive disability • Psychiatric illness		Oral steroids				T: 22/31 C: 21/29		
								Absence (days)	T: 2.81 (6.26) C: 5.22 (8.38)	

Table 159: Gruffydd-Jones 2005⁶⁰³

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Gruffydd-Jones, K., et al (2005). Targeted routine asthma care in general practice using telephone triage. <i>British Journal of General Practice</i> , 55(521), 918-923.	RCT 1 general practice in England	N=194		Tele:	Control:	Contacted by telephone every 6-months by a trained asthma nurse and asked the RCPs 'three questions' plus two extra questions related to a high risk of asthma death. The nurse formulated an individualised asthma action plan with the patient.	Usual care by 6-monthly check up with an asthma nurse. Symptom scores, inhaler technique, and PEF were checked and all patients issued with an asthma action plan.	6 and 12 m	AQLQ	T: 5.93 (1.64) C: 5.79 (0.90)	Funding: Asthma UK Risk of bias: • Random number tables • Un-blinded • Unbalanced attrition (higher in usual care)
		Tele: N=97	Age, years	50.8	49.6				ACQ	T: -0.18 (95% CI) (-0.38 to 0.02) C: -0.11 (-0.32 to 0.11)	
		Control: N=97	% male	51.5	39.2				Costs	T: 210.4(95% CI) (208.9 to 211.8) C: 332.7 (329.5 to 335.9)	
		Inclusion criteria: • Adults aged 17-70 • On the practice asthma list Exclusion criteria: • Housebound or no phone									

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Table 160: Guendelman 2002^{609,609}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Guendelman, S., et al (2002). Improving asthma outcomes and self-management behaviors of	RCT 1 clinic in California, USA	N=134		Tele:	Control:	Internet-based asthma self-management and education program with feedback (Health Buddy) which asked	Paper asthma diary. All children returned for 2 follow-up visits at 6 and 12 weeks when they received	3 m	Hospital visits	T: 4/62 C: 1/60	Funding: Unclear Risk of bias: • Unclear sequence generation,
		Tele: N=66	Age, years	12.0	12.2				ED visits	T: 6/62 C: 11/60	
		Control: N=68	% male	61	54						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
inner-city children: a randomized trial of the Health Buddy interactive device and an asthma diary. <i>Archives of Pediatrics & Adolescent Medicine.</i> , 156(2), 114-120.			Inclusion criteria: <ul style="list-style-type: none"> • Children/teens aged 8-16 • Persistent asthma • English speaking with a telephone in the house Exclusion criteria: <ul style="list-style-type: none"> • In another asthma study • Mental or physical challenges that affected the program • Co-morbid conditions that might affect quality of life 	every day about asthma status, PEF and medication. Responses were downloaded to the nurse co-ordinator overnight.	further standardised teaching from the nurse co-ordinator				concealed with envelopes <ul style="list-style-type: none"> • Un-blinded • Low attrition

Table 161: Gustafson 2012^{617,617}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Gustafson, D., et al (2012). The effects of combining web-based eHealth with telephone nurse case management for pediatric asthma control: A randomized	RCT USA	N=301		Tele:	Control:	Automated management software with monthly calls from nurse (CHES+CM). Based on self-determination theory and designed to improve competence, social support,	Treatment as usual plus asthma information	12 m	ACQ	MD -0.31; 95% CI -0.56 to -0.06; 0=0.01	Funding: National Institute of Nursing Research Risk of bias: <ul style="list-style-type: none"> • Sequence generation fine and well concealed • Un-blinded
			Age, years	7.7	8.2						
			% male	66	57						
			Baseline ACQ	2.49	2.32						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
controlled trial. [References]. <i>Journal of medical Internet research</i> , 14(4), 41-59.			Inclusion criteria: <ul style="list-style-type: none"> • Children aged 4-12 • Diagnosis of asthma or wheezing • Controller meds and poor adherence Exclusion criteria: <ul style="list-style-type: none"> • Not described 	and intrinsic motivation of parents and children.					<ul style="list-style-type: none"> • Balanced attrition

Table 162: Halterman 2012^{633,633}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Halterman Jill, S. et al (2012). Working toward a sustainable system of asthma care: Development of the School-Based Preventive Asthma Care Technology (SB-PACT) trial. 49, 395-400	RCT	N=100		Tele:	Control:	'SB-PACT' intervention: web-based screening, electronic communication with primary care providers, online prescription of medications, direct nurse observation of adherence in schools, assessment of symptoms online	In addition to usual care, families in both groups were provided with written educational hand-outs on asthma triggers, treatment, and local asthma resources	8 m	Hospital visits	T: 1/48 C: 1/51	Funding: National Heart, Lung, and Blood Institute of the National Institutes of Health Risk of bias: <ul style="list-style-type: none"> • Sequence generation fine and well concealed • Families not blind, but assessors were
		Tele: N=48	Age, years	7.5	7.0				ED visits	T: 4/48 C: 3/51	
		Control: N=51	% male	52	63				GP visits	T: 6/48 C: 8/51	
			Inclusion criteria: <ul style="list-style-type: none"> • Children aged 3-10 years • Persistent asthma (physician diagnosed base on NHLBI) Exclusion criteria: <ul style="list-style-type: none"> • Non English speaking, no access to phone • Other significant conditions 						AQLQ	T: 6.46 (0.7) C: 6.31 (0.9)	
	19 inner-city schools in New York, USA							School absence			

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
									• No dropout

Table 163: Jan 2007^{757,757}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Jan, R. L., et al. (2007). An internet-based interactive telemonitoring system for improving childhood asthma outcomes in Taiwan. <i>Telemedicine Journal and e-Health</i> , 13(3), 257-268.	RCT	N=164		Tele:	Control:	“Blue Angel for Asthma Kids”, an Internet-based paediatric asthma monitoring program children and parents. Included symptom and PEF diaries and Asthma Action Plans based on the GINA. Data could be shared with the physician who gave feedback by phone/email.	Traditional treatment in an outpatient allergy and asthma clinic accompanied by a PEF meter and diary. Also received verbal and printed asthma education and an Action Plan as part of usual care.	3 m	PEF morning	T: 18.7 (49.4) C: 10.9 (40)	Funding: National Science Council and Bureau of Health Promotion Risk of bias: <ul style="list-style-type: none"> • Unclear sequence generation, concealed with envelopes • Un-blinded • Low attrition
	1 university medical center in Taiwan	Tele: N=88	Age, years	10.9	9.9				PEF evening	T: 23.1 (56.5) C: 11.1 (41.6)	
		Control: N=76	% male	39.7	36.8						
			Inclusion criteria: <ul style="list-style-type: none"> • Children aged 6-12 years • Access to internet • Physician-diagnosed asthma Exclusion criteria: <ul style="list-style-type: none"> • Other chronic conditions such as broncho-pulmonary dysplasia 								

Table 164: Khan 2004^{858,858}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Tele:	Control:							
Khan, M. S. R., et al (2004). Randomized controlled trial of asthma education after discharge from an emergency department. Journal of Paediatrics & Child Health, 40(12), 674-677.	RCT 1 centre in Sydney, Australia	N=310				Parents received a telephone call by an asthma nurse educator within 2 weeks of discharge to reiterate advice given at discharge. Calls lasted an average of 13 min (range 5 to 44 minutes).	All parents received written materials with facts about asthma, use of spacers, management of exercise induced asthma and when to contact a doctor.	6 m	Hospital visits	T: 0/136 C: 0/130	Funding: Financial Markets Foundation for Children Risk of bias: <ul style="list-style-type: none"> • Random numbers table • Assessors blind • Possible attrition bias
		Tele: N=155	Age, years	4.9						T: 1/136 C: 0/130	
		Control: N=155	% male	65.5							
		Inclusion criteria:									
<ul style="list-style-type: none"> • Children aged 1-15 years • Recent ED discharge 											
Exclusion criteria:											
<ul style="list-style-type: none"> • Non English speaking 											

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Table 165: Liu 2011^{1031,1032}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			Tele:	Control:							
Liu, W. T., et al (2011). A mobile telephone-based interactive self-care system improves asthma control.	RCT Clinics at a teaching hospital in Taiwan	N=89				Mobile phone-based software: with electronic diary to record symptom score, reliever use, and lung function. Staff reviewed data uploaded to website and gave advice in	Written asthma diary and action plan. All subjects received asthma education, self-management plan, and	6 m	Mortality	T: 0/43 C: 0/46	Funding: Unclear Risk of bias: <ul style="list-style-type: none"> • Allocation not described • Un-blinded • High attrition
		Tele: N=60	Age, years	50.4	54				Hospital visits	T: 0/43 C: 1/46	
		Control: N=60	% male	51.2	47.8				ED visits	T: 2/43 C: 12/46	
		Inclusion criteria:									
<ul style="list-style-type: none"> • Adults 											
						FEV1 % predicted	T: 65.2 (21) C: 56.5 (19)				

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
<i>European respiratory journal, 37(2), 310-317</i>			<ul style="list-style-type: none"> Moderate/severe asthma 	accordance with GINA guidelines. Data were given to the doctors to adjust treatment plans.	standard treatment		PEF L/min	T: 382.7 (56) C: 343.5 (52)	

Table 166: Ostojic 2005^{1291,1291}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments	
Ostojic, V., et al. (2005). Improving asthma control through telemedicine: A study of short-message service. <i>Telemedicine Journal & E-Health, 11(1), 28-35.</i>	RCT 1 clinic in Croatia	N=16		Tele:	Control:	Paper diary for PEF, medication use and symptoms. PEF (3 times a day), sent results to a computer in the asthma centre and received weekly text instructions from an asthma specialist about therapy or the need for extra office visits.	Both groups were treated according to GINA guidelines. Controls also kept a daily diary of PEF and symptoms, but results were only reviewed by the physician at the end of the study period.	4 m	Hospital visits	T: 2/8 C: 7/8	Funding: Unclear Risk of bias: <ul style="list-style-type: none"> Computer randomised Un-blinded No dropouts 	
		Tele: N=8	Age, years	24.8	24.5					FEV1 % predicted		T: 81.3 (17.3) C: 78.3 (21.1)
		Control: N=8	% male	63	50							
			% predicted FEV1	77.6	78.9							
			Inclusion criteria: <ul style="list-style-type: none"> Adults with moderate asthma All using LABA/ICS Exclusion criteria: <ul style="list-style-type: none"> Adults with moderate asthma All using LABA/ICS 									

Table 167: Pinnock 2003^{1362,1362}

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
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Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				Tele:	Control:						
Pinnock, H., et al (2003). Accessibility, acceptability, and effectiveness in primary care of routine telephone review of asthma: pragmatic, randomised controlled trial. <i>BMJ</i> , 326(7387), 477-479.	RCT 4 UK GPs	N=278 Tele: N=137 Control: N=141				Telephone review with the asthma nurse. The nurse tried up to 4 times to contact the patients.	Face-to-face reviews in the surgery also with the asthma nurse, one invitation was sent in the usual manner. Content of the review was as the nurse deemed appropriate.	Variable follow-up, pragmatic design	Hospital visits	T: 0/137 C: 0/141	Funding: Educational grant from AstraZeneca Risk of bias: <ul style="list-style-type: none"> Centrally randomised Un-blinded
			Age, years	54.6	56.4				ED visits	T: 0/137 C: 0/141	
			% male	41	42				Oral steroid use	T: 5/137 C: 3/141	
			Baseline AQLQ	5.17	5.16				GP visits	T: 27/137 C: 34/141	
			Inclusion criteria:								
<ul style="list-style-type: none"> Adults aged 18+ Asthma for 1 year + Bronchodilator prescription in previous 6 months 			Exclusion criteria:								
<ul style="list-style-type: none"> COPD Communication difficulties 											

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Table 168: Pinnock 2007^{1361,1362}

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
				Tele	Cont 1	Cont 2						
Pinnock H., et al (2007). Accessibility, clinical effectiveness and practice costs of providing a telephone	RCT 1 UK GP over 3 sites	N=1728 Tele: N=554 Control1: N=515					Sent 3 invitations over the study period to book either a phone or face-to-face review both at a pre-arranged	1) Usual care maintained their well-established asthma clinic but no re call was undertaken. 2) Patients were recalled to face-	12 m	AQLQ	T: 5.29 (1.2) C1: 5.27 (1.2) C2: 5.31 (1.2)	Funding: Scientific Foundation Board of the RCGP Risk of bias: <ul style="list-style-type: none"> Randomised
			Age, yrs	43	45.4	42.3				ACQ	T: 1.20 (1) C1: 1.24 (1) C2: 1.33 (1.1)	
			% male	44.2	44.7	44.9				Cost total	T: £3982 C1: £3340	

Reference	Study type	Number of patients	Patient characteristics				Intervention	Comparisons	Length of follow-up	Outcome measures	Effect sizes	Comments
option for routine asthma reviews: phase IV controlled implementation study. <i>British Journal of General Practice</i> , 57(542): 714–722		Control2: N=659					time. Patients who did not respond to the 3 invitations were phoned and reviewed opportunistically	to-face reviews using invitations by post or with repeat prescriptions. There was no option for a phone review and no attempt to contact non-attenders.		C2: £4485	with coin toss • Un-blinded	
			% with COPD	6.5	7.2	8.5						
			Inclusion criteria: <ul style="list-style-type: none"> Adults aged 12+ years Prescription in previous year Exclusion criteria: <ul style="list-style-type: none"> Diagnosis of COPD 									

Table 169: Prabhakaran 2009^{1392,1392}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Prabhakaran, L., et al (2010). The use of text messaging to improve asthma control: A pilot study using the mobile phone short messaging service (SMS). <i>Journal of telemedicine and telecare</i> , 16(5), 286-290	RCT Hospital in Singapore and location	N=120 Tele: N=60 Control: N=60		Tele:	Control:	SMS monitoring to assist with the management of their asthma control for three months.	All patients were seen by a trained asthma nurse educator who assessed their asthma control, compliance and inhaler technique prior to asthma education. The 60 patients in the control group were left to self-manage their asthma for	3 m	Mortality	T: 0/60 C: 0/60	Funding: Unclear
			Age, years	37	40						
			% male	35	47						
			Inclusion criteria: <ul style="list-style-type: none"> Adults aged 21+ years Previous asthma admission English speaking and able to use a mobile phone Exclusion criteria: <ul style="list-style-type: none"> Significant co-morbidity 								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
			• Mild asthma		three months				

Table 170: Rasmussen 2005^{1435,1436}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments			
Rasmussen, L. et al. (2005). Internet-based monitoring of asthma: A long-term, randomized clinical study of 300 asthmatic subjects. <i>Journal of Allergy & Clinical Immunology</i> , 115(6), 1137-1142.	RCT Copenhagen Denmark	N=300		Tele	Cont 1	Cont 2	Electronic diary, an asthma action plan and a decision support system for the physician. Patients were given a PEF Meter and taught how to fill in a daily diary and respond to the computer's advice. Physicians gave instructions via e-mail or telephone.	1) Specialists taught patients how to adjust medication on the basis of a PEF meter and written action plan 2) Patients were asked to contact their GP and pass on a letter describing the study and giving the test results. GPs in Copenhagen had been sent a circular about asthma and GINA guidelines.	12 m	Hospital visits	T: 0/85 C1: 1/88 C2: 0/80	Funding: Grants from H:S Corporation of University Hospital of Copenhagen, AstraZeneca, and private funds Risk of bias: • Randomised consecutively with sealed envelopes • Un-blinded • Unbalanced dropout • Some selective reporting		
		Tele: N=100	Age, yrs	28	30	30					ED visits		T: 2/85 C1: 0/88 C2: 1/80	
		Control1: N=100	% male	31.8	34.1	37.5					GP visits		T: 3/85 C1: 2/88 C2: 1/810	
		Control2: N=100	% pred FEV1	91	93	92							FEV1 change (mL)	T: 187 (369) C1: 35 (281) C2: 4 (268)
			Baseline AQLQ	6.2	6.2	6.1								
		Inclusion criteria:												
<ul style="list-style-type: none"> Adults aged 18-45 years Asthma according to ATS 														
Exclusion criteria:														
<ul style="list-style-type: none"> Not described 														

Table 171: Ryan 2012^{1493,1493}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				Tele:	Control:						
Ryan, D., et al (2012). Clinical and cost-effectiveness of mobile phone supported self-monitoring of asthma: multicentre randomised controlled trial. <i>BMJ (Online)</i> , 344(7854), e1756.	RCT 32 GPs in England	N=288 Tele: N=145 Control: N=143				Twice daily recording and mobile phone based transmission of symptoms, drug use, and peak flow with immediate feedback prompting action according to an agreed plan	Paper-based monitoring with the same clinical care as the intervention group (BTS/SIGN based). Both groups also received a 30 minute education session from the practice nurse before randomisation	6 m	Hospital visits	T: 3/140 C: 1/141	Funding: Asthma UK Risk of bias: • Centrally randomised • Blinded outcome assessment
			Age, years	46.6	51.5				ED visits	T: 3/140 C: 0/141	
			% male	33.8	41.3				GP visits	T: 51/140 C: 41/141	
			Baseline ACQ	2.32	2.29				Oral steroid use	T: 28/140 C: 30/141	
			Inclusion criteria: • Adults aged 12+ • Poorly controlled asthma						Exclusion criteria: • Other lung disease or other clinical/social problems		
						ACQ	T: 1.57 (0.99) C: 1.56 (1.09)				

2

Table 172: Seid 2012^{1557,1557}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				Tele:	Control:						
Seid, M., et al (2012). The In Vivo adherence intervention for at risk adolescents with asthma: Report of a randomized	RCT 1 site in Cincinnati, USA	N=26 Tele: N=14 Control: N=14				Asthma education, in-person motivational interviewing and problem solving skills training, cell phone with	Asthma education and cell phone without tailored text messaging	1 and 3 m	None of interest	N/A	Funding: National Institutes of Health Risk of bias: • Random number tables
			% male	41.7	21.4						

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
pilot study. <i>Journal of pediatric psychology</i> , 37(4), 390-403			(NHLBI) <ul style="list-style-type: none"> Symptoms in past 2 weeks <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Co-morbid conditions Non English speaking 	tailored text messages					<ul style="list-style-type: none"> Blinded outcome assessment Pilot study

Table 173: van der Meer 2009¹⁸²⁴

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Van Der Meer, V., et al (2010). Self-management for asthma on the Internet: A randomized study. <i>Nederlands tijdschrift voor geneeskunde</i> , 154(9), 403-409.	RCT 37 GPs in Holland	N=200		Tele:	Control:	Website to record FEV1 (daily), ACQ (weekly), and symptoms via internet or text. Also included asthma treatment plan and online education. Patients could contact an asthma nurse when needed. The ACQ score fed into an algorithm and patients received one of 4 treatment messages.	Control patients had access to the part of the website on which a diary of symptoms and exacerbations was kept.	12 m	AQLQ change with 95% CI	T: 0.56 (0.43 to 0.68) C: 0.18 (0.05 to 0.31)	<p>Funding: Unclear</p> <p>Risk of bias:</p> <ul style="list-style-type: none"> Computer randomisation Un-blinded Completer analysis
			Age, years	36	37						
			% male	32	29						
			% predicted FEV1	88	90						
			Baseline ACQ	1.12	1.11						
			% taking LABA/ICS	59	60						
				<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Adults aged 18-50 years ICS for > 3 months in the past year <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Currently on oral steroids 							

Table 174: Vollmer 2006^{1873,1873}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				Tele:	Control:						
Vollmer, W. M., et al (2006). Use and impact of an automated telephone outreach system for asthma in a managed care setting. <i>American Journal of Managed Care</i> , 12(12), 725-733.	RCT Large group health organisation in Oregon, USA	N=6948				Three phone calls 5 months apart with tailored advice to address recent ED care, asthma control and medication use. Optional tailored feedback. The call generated alerts for the provider as to which patients were at high risk of exacerbations.	Routine care with no telephone calls	10 m	AQLQ (in a subset of patients)	T: 5.2 (1.2) C: 5.1 (1.2)	Funding: Centres for Disease Control and Prevention and the Kaiser Permanente Care management Institute Risk of bias: • No details about randomisation or blinding • Some data only collected from a subset of patients
		Tele: N=3389	Age, years	51.8	51.4					T: 132/3220 C: 121/3033	
		Control: N=3367	% male	35	35						
			Baseline AQLQ	5.0	5.2						
			Inclusion criteria: • Adults aged 18+ years • At least 180 days of asthma medication dispensed Exclusion criteria: • COPD								

2

Table 175: Willems 2007^{1917,1918}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
				Tele:	Control:						
Willems, D. C., et al (2007). Process evaluation of a nurse-led telemonitoring	RCT Single centre in the Netherl	N=109 Tele: N=55 (26 adults, 29				Asthma tele-monitoring via home modem. Patients were asked to perform daily	Regular outpatient care: 3 to 6-monthly medical check-ups by	12 m	AQLQ	T: 5.73 (1.09) C: 5.48 (1.18)	Funding: Unclear Baseline characteristics reported for
			Age, years	27.2	28.4				ED visits	T: 0/55 C: 4/54	

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
programme for patients with asthma. <i>Journal of Telemedicine & Telecare</i> , 13(6), 310-317.	ands	children) Control: N=54 (27 adults, 27 children)	% male	58.2	44.4	PEFR and more often in exacerbations. The nurse could increase and decrease asthma medication and involve a doctor if necessary.	their lung specialist or paediatrician				children and adults separately, but not outcome data Risk of bias: <ul style="list-style-type: none"> • Random number list, stratified by age • Un-blinded • Compliance for AQLQ and PEF was low
			% predicted FEV1	94.9	96.0						
			Inclusion criteria: <ul style="list-style-type: none"> • Adults and children aged 7+ • Stage I to III GINA Exclusion criteria: <ul style="list-style-type: none"> • Severe co-morbidity 								

Table 176: Xu 2011^{1948,1949}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Xu, C., et al (2010). A randomized controlled trial of an interactive voice response telephone system and specialist nurse support for childhood	RCT Child hospitals in Australia	N=121 (82 in relevant groups) Tele: N=41 Control: N=41		Tele:	Control:	1) Interactive Voice Response	Patients' primary care physicians were notified and continued to provide primary asthma care. All families had the same initial asthma education with	6 m	Hospital visits	T1: 4/39 T2: 4/38 C: 4/40	Funding: Unclear Risk of bias: <ul style="list-style-type: none"> • Randomisation unclear • Un-blinded • Low dropout
			Age, years	T1: 7.0 T2: 6.5	7.4	2) The nurse support group received follow-up calls from one Nurse Specialist every 2 weeks. Where families			ED visits	T1: 6/39 T2: 8/39 C: 5/40	
			% male	T1: 56.4 T2: 51.2	51.2				Oral steroid use	T1: 16/39 T2: 22/41 C: 21/40	

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
asthma management. <i>Journal of asthma</i> , 47(7), 768-773			Inclusion criteria: <ul style="list-style-type: none"> Children/teens aged 3-16 Recent exacerbation Exclusion criteria: <ul style="list-style-type: none"> Not described 	preferred email contact, the nurse used email to collect the same data and offer education and advice on asthma. 2)	the same Specialist Nurse.		School days lost (yes/no)	T1: 20/38 C: 22/39	
							Parent work days lost (yes/no)	T1: 13/39 C: 13/39	
							AQLQ (child), mean (SD)	T1: 1.1 (1.1) C: 0.5 (0.9)	
							AQLQ (carer), mean (SD)	T1: 1.2 (1.6) C: 1.0 (1.5)	

1

Table 177: Young 2012^{1964,1964}

Reference	Study type	Number of patients	Patient characteristics			Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
Young, H. N., et al (2012). Patient and phaRmacist telephonic encounters (PARTE) in an underserved rural patient population with	RCT Wisconsin, USA	N=98 Tele: N=49 Control: N=49		Tele:	Control:	Telephone consultation from pharmacists regarding their asthma self-management and medication use. Five pharmacists	Usual care, which included mail receipt of a prescription refill with written medication use instructions.	Unknown follow-up	None of interest	N/A	Funding: National Centre for Research Resources, National Institutes of Health Risk of bias:
			Age, years	45.4	43.7						
			% male	26.5	20.4						
			Inclusion criteria:								

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Comments
asthma: results of a pilot study. <i>Telemedicine journal and e-health</i> , 18(6), 427-433			<p>program (uninsured or underinsured people)</p> <ul style="list-style-type: none"> • Diagnosis of asthma and 1+ asthma medications within 6 months <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Enrolment in the FHC pharmacy program 	incorporated the intervention into their usual practice.					<ul style="list-style-type: none"> • No randomisation details • Blinded assessment • Balanced dropout • No relevant outcomes

Appendix H: Economic evidence tables

H.1 Monitoring: Tele-healthcare

Table 178: Gruffydd-Jones 2005⁶⁰³

Gruffydd-Jones K, Hollinghurst S, Ward S, Taylor G. Targeted routine asthma care in general practice using telephone triage. <i>British Journal of General Practice</i> . 2005; 55:918-923.				
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CCA (health outcome: Mini-AQLQ scores)</p> <p>Study design: Within-trial analysis (RCT)</p> <p>Approach to analysis: Analysis of individual level data for asthma control and resource use with unit costs applied.</p> <p>Perspective: UK NHS Time horizon: 12 months Treatment effect duration: 12 months Discounting: Not Applicable</p>	<p>Population: Adult Asthma Patients</p> <p>Patient characteristics: N (control): 62 N (intervention): 84</p> <p>Mean age (control): 49.6 (SD: 16.1) Mean age (intervention): 50.8 (SD: 15.4)</p> <p>Male (control): 39% Male (intervention): 51%</p> <p>Intervention 1: Clinic Group: Patients received 'usual' care by 6 monthly check-up via dedicated asthma nurse.</p> <p>Intervention 2:</p>	<p>Total costs (mean per patient): Intervention 1: £333.85 (SD: 410.64) Intervention 2: £209.85 (SD: 220.94) Incremental (2-1): Bootstrapped cost difference: £122.35 (p-value: 0.071)</p> <p>Currency & cost year: 2004 UK pounds</p> <p>Cost components incorporated: Total routine care (minutes) Number of inhalers Number of tablets Non-routine consultations Length of inpatient stays</p>	<p>Mini-AQLQ score (median per patient at 12 months): Intervention 1: 5.93 (IQR: 2.07) Intervention 2: 6.47 (IQR: 1.22) Incremental (2-1): NR, though the difference in health was not clinically significant</p>	<p>ICER (Intervention 2 versus Intervention 1): Telephone reviews dominated clinical reviews (lower costs and higher health outcomes)</p> <p>Analysis of uncertainty: NR</p>

	<p>Telephone group: patients contacted by telephone at 6 monthly intervals by one or two trained asthma nurses. Patient was asked RCP Morbidity Index and if 'yes' was answered to any of the three questions a clinical asthma review was arranged. If asthma was deemed stable for 3 months telephone interviews were resumed.</p>			
Data sources				
Health outcomes: Mini AQLQ score.				
Quality-of-life weights: NR				
Cost sources: Resource use from within RCT; resources use priced using: BNF; NHS Reference costs; PSSRU 2003				
Comments				
Source of funding: Research grant from Asthma UK. Limitations: Short time horizon of 12 months may not be long enough to capture adverse health impacts and therefore not give an accurate representation of long term health and cost outcomes. Health was also not measured using QALYs, only quality of life not length was considered. Lack of any sensitivity analysis reduces robustness of results.				
Overall applicability^(a): Partially applicable Overall quality^(b): Potentially serious limitations				
1	<i>Abbreviations: CCA: cost–consequence analysis; CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; NR: not reported; QALYs: quality-adjusted life years, SD: Standard</i>			
2	<i>Deviation</i>			
3	<i>(a) Directly applicable / Partially applicable / Not applicable</i>			
4	<i>(b) Minor limitations / Potentially serious limitations / Very serious limitations</i>			
5				
6	Table 179: Ryan 2012^{1493,1493}			
<p>Ryan D, Price D, Musgrave SD, Malhotra S, Lee AJ, Ayansina D et al. Clinical and cost-effectiveness of mobile phone supported self monitoring of asthma: multicentre randomised controlled trial. <i>BMJ</i>. 2012; 344:e1756.</p>				

Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CCA (health outcome: changes in scores on asthma control questionnaire and self-efficacy)</p> <p>Study design: One year multicentre randomised controlled trial conducted in a UK primary care setting - Within trial analysis</p> <p>Approach to analysis: Economic evaluation based on the results of the randomised controlled trial</p> <p>Perspective: UK NHS</p> <p>Time horizon: 12 months</p> <p>Treatment effect duration: 12 months</p> <p>Discounting: NA</p>	<p>Population: 288 adolescents and adults with poorly controlled asthma (ACQ score ≥ 1.5)</p> <p>Patient characteristics: N (control) =142 N (intervention) =145</p> <p>Mean age (control): 51.5 (SD: 17.7) Mean age (intervention): 46.6 (SD: 18)</p> <p>Male (control): 34% Male (intervention): 41%</p> <p>Intervention 1: Mobile phone monitoring: Twice daily recording and mobile phone based transmission of symptoms, drug use, and peak flow with immediate feedback (through t+ Asthma mobile application) prompting action to agreed plan.</p> <p>Intervention 2: Patients asked to keep a paper diary, recording the same information gathered from intervention 1</p>	<p>Total costs (mean per patient): Intervention 1: £315 (SD: 226) Intervention 2: £245 (SD: 201)</p> <p>Incremental (2-1): £70 (CI: £20 to £121; p = 0.006)</p> <p>Currency & cost year: 2008-2009 UK pounds</p> <p>Cost components incorporated: Cost of delivering intervention Nursing costs Tele-monitoring service costs Cost of healthcare provision GP respiratory consultations Practice nurse respiratory consultations Secondary care costs (outpatient and admissions) Emergency services Total cost of prescriptions from respiratory drugs</p>	<p>QALYs (mean per patient): There was no significant change in asthma control or self-efficacy between the two interventions</p>	<p>ICER (Intervention 2 versus Intervention 1): NR</p> <p>Analysis of uncertainty: No sensitivity analysis was conducted</p>

(symptoms, drug use, and peak flow readings twice daily).

Data sources
Health outcomes: Self-reported from patients who participated in the trial.
Cost sources: Unit costs for all resources used by patients in the randomized controlled trial were obtained from the data sources in the UK including the NHS Reference costs (2007-2008), the Personal Social Services Research Unit (2008) and the British National Formulary (BNF 2008).
Comments
Source of funding: Asthma UK. Limitations: Short time horizon of 12 months may not be long enough to capture adverse health impacts and therefore not give an accurate representation of long term health and cost outcomes. Health was also not measured using QALYs, only quality of life not length was considered. Lack of any sensitivity analysis reduces robustness of results.
Overall applicability ^(a) : partially applicable Overall quality ^(b) : potentially serious limitations

Abbreviations: CCA: cost–consequence analysis; 95% CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

Table 180: Willems 2007^{1918,1919}

Willems DC, Joore MA, Hendriks JJ, Wouters EF, Severens JL. Cost-effectiveness of a nurse-led telemonitoring intervention based on peak expiratory flow measurements in asthmatics: results of a randomised controlled trial. Cost-effectiveness and Resource Allocation. Netherlands 2007; 5:10.				
Study details	Population & interventions	Costs	Health outcomes	Cost-effectiveness
<p>Economic analysis: CUA (health outcome: QALYs)</p> <p>Study design: One year single centre randomised controlled trial – Within trial analysis</p> <p>Approach to analysis:</p>	<p>Population: Outpatients with asthma</p> <p>Patient characteristics: N (Control) = 53 N (Intervention) = 56</p> <p>Mean age (control over 18 years old): 45.9 (SD: 15.9)</p> <p>Mean age (intervention over</p>	<p>Total costs (mean per patient):</p> <p>Intervention 1 (over 18 years old): £1,197 (SD: £1212)</p> <p>Intervention 1 (between 7 and 18 years old): £409 (SD: £591)</p> <p>Intervention 2 (over 18 years old): £1,550 (SD: £1,101)</p>	<p>QALYs (mean per patient):</p> <p>Intervention 1 (between 7 and 18 years old): 0.0 (95% CI: 0.00 to 0.02)</p> <p>Incremental (2–1) (Over 18 years old): 0.03 (95% CI: 0.00 to 0.07)</p>	<p>ICER (Intervention 2 versus Intervention 1) (over 18 years old): £10693 per QALY gained (pa) 95% CI: NR</p> <p>Probability Intervention 2 (adults) cost-effective (£20K/30K threshold): NR</p> <p>ICER (Intervention 2 versus Intervention 1) (between 7 and 18 years old): £40865 per QALY gained (pa)</p>

<p>Comparison of health outcomes and costs between tele-monitoring and usual care.</p> <p>Perspective: Dutch societal or healthcare perspective (only healthcare perspective results shown)</p> <p>Time horizon: 12 months</p> <p>Treatment effect duration: 12 months</p> <p>Discounting: NR</p>	<p>18 years old): 45.65 (SD: 11.3)</p> <p>Mean age (control between 7 and 18 years old): 10.85 (SD: 2.3)</p> <p>Mean age (intervention between 7 and 18 years old): 10.57 (SD: 2.1)</p> <p>Male (control over 18 years old): 33.3%</p> <p>Male (intervention over 18 years old): 42.3%</p> <p>Male (control between 7 and 18 years old): 55.6%</p> <p>Male (intervention between 7 and 18 years old): 72.4%</p> <p>Intervention 1: Regular outpatient care. Three to six monthly medical check-ups by their lung specialist or paediatrician. For exacerbations patients received additional care by GP and/or outpatient care.</p> <p>Intervention 2: Patients received an asthma monitor and had a hospital based nurse practitioner as the main caregiver. Patients were instructed to perform daily lung function tests in</p>	<p>Intervention 2 (between 7 and 18 years old): £830 (SD: £405)</p> <p>Incremental (2–1) (over 18 years old): £353 (95% CI: -£114 to £1118; p=NR)</p> <p>Incremental (2–1) (between 7 and 18 years old): £421 (95% CI: £319 to £862; p=NR)</p> <p>Currency & cost year: 2002 Euros (presented here as 2002 UK pounds^(a))</p> <p>Cost components incorporated: General practitioner practice: (GP visit, GP telephone visit, assistant visit, assistant telephone visit, nurse practitioner visit)</p> <p>Hospital care: (day admission, emergency room visit, surgical procedures, diagnostic procedures, laboratory research, lung specialist outpatient visit, paediatric lung specialist</p>	<p>Incremental (2–1) (between 7 and 18 years old): 0.01 (95% CI: 0.00 to 0.02)</p> <p>Incremental (2–1) (Over 18 years old): 0.03 (95% CI: 0.00 to 0.07)</p>	<p>95% CI: NR</p> <p>Probability Intervention 2 (children) cost-effective (£20K/30K threshold): NR</p> <p>Analysis of uncertainty: Using SF-36 instead of EQ-5D leads to drastically different results making the intervention dominated for adults; SF-6D was not assessed in children.</p> <p>Sensitivity analysis was conducted by excluding monitor device costs from the intervention (monitor, modem, batteries and insurance) which equated to £313. This reduced the ICER for adults to £1224 and for children to £10502. This shows that initial capital costs significantly drive the cost-effectiveness result. Therefore in the long run assuming recurrent capital costs will fall the ICER will fall over time, all other things remaining equal.</p>
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	the morning and evening and more often when they were having symptoms. Patients asked to transfer data once a month or more with symptoms. Based on data nurse was able to decrease asthma medication (after three months of stable asthma) or increase (if asthma was unstable) by one step.	outpatient visit, asthma nurse practitioner outpatient visit, other medical specialists outpatient visit) Other healthcare professional costs: (speech therapist, homoeopath, company medical officer) Prescribed medication: (medication, pharmacist fee) Professional home care Intervention costs		
Data sources				
Health outcomes: Taken from the results from the in-trial randomized controlled trial. Quality-of-life weights: EQ-5D, UK tariff. Cost sources: Volumes of hospital care were obtained from the hospital billing system of the university hospital Maastricht. All other resource costs use obtained from cost diaries. Dutch manual for cost research used for unit prices.				
Comments				
Source of funding: NR. Limitations: The costs are not from a UK perspective and therefore may not be generalizable. The time horizon is also very short at 12 months; this may not be enough time to capture rare adverse events that would have a differential probability of occurring across the two groups. The results are extremely sensitive to the choice of HRQoL measure used.				
Overall applicability^(a): Partially applicable Overall quality^(b): Potentially serious limitations				

- 1 Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death);
- 2 HRQoL: Health related quality of life; ICER: incremental cost-effectiveness ratio; NR: not reported; QALYs: quality-adjusted life years; SF-6D: Short form 6 dimensions (scale: 0.0 [death] to 1.0
- 3 [full health], negative values mean worse than death)
- 4 (a) Converted using 2002 purchasing power parities¹²⁸⁴
- 5 (b) Directly applicable / Partially applicable / Not applicable
- 6 (c) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I: GRADE tables

I.1 Monitoring: Questionnaires

Table 181: Clinical evidence profile: Children (5-16 years) with uncontrolled asthma: Monitoring questionnaires + treatment vs UC + treatment.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Children with uncontrolled asthma: Monitoring control + treatment	UC + treatment	Relative (95% CI)	Absolute		
QOL (< 6months) (follow-up 3 months; measured with: PAQLQ; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	46	44	-	MD 0.4 higher (0.17 to 0.63 higher)	⊕○○○ VERY LOW	CRITICAL
QOL (≥ 6months) (follow-up 12 months; measured with: PAQLQ; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	44	-	MD 0.05 lower (0.5 lower to 0.4 higher)	⊕⊕○○ LOW	CRITICAL
Exacerbations (≥ 6months) (follow-up 12 months; assessed with: Course of OCS)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	6/35 (17.1%)	15%	RR 1.14 (0.41 to 3.22)	21 more per 1000 (from 89 fewer to 333 more)	⊕○○○ VERY LOW	CRITICAL
Asthma control (< 6months) (follow-up 3 months; measured with: ACQ; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	very	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	44	-	MD 0.32 lower (0.56 to 0.08)	⊕⊕○○	CRITICAL

	trials	serious ¹	inconsistency	indirectness	imprecision					lower)	LOW	
Asthma control (≥ 6months) (follow-up 12 months; measured with: ACQ; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	46	44	-	MD 0.05 lower (0.35 lower to 0.25 higher)	⊕⊕⊕⊕ LOW	CRITICAL
Lung function (< 6months) (follow-up 3 months; measured with: FEV1 L; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	46	44	-	MD 0.23 higher (0.08 to 0.38 higher)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Lung function (≥ 6months) (follow-up 12 months; measured with: FEV1 L ; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	46	44	-	MD 0.1 higher (0.11 lower to 0.31 higher)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Symptom free days (< 6months) (follow-up 3 months; measured with: % over 2 weeks ; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	46	44	-	MD 1.5 lower (14.5 lower to 11.5 higher)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Symptom free days (≥ 6months) (follow-up 12 months; measured with: % over 2 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	46	44	-	MD 4 higher (9.7 lower to 17.7 higher)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
ICS use (< 6months) (follow-up 3 months; measured with: mean daily dose ug; Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	46	44	-	MD 14 higher (79 lower to 107 higher)	⊕⊕⊕⊕ VERY LOW	IMPORTANT

ICS use (≥ 6months) (follow-up 12 months; measured with: mean daily dose ug; Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	46	44	-	MD 14 higher (75 lower to 103 higher)	⊕○○○ VERY LOW	IMPORTANT

1 The majority of the evidence was from studies at very high risk of bias

2 95% CI crosses one MID

3 95% CI for the absolute effect crosses one MID

4 95% CI crosses both MIDs

Table 182: Clinical evidence profile: Adults and young people (>16 years) overall: Monitoring questionnaires + treatment vs UC + treatment.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adults overall: Monitoring control + treatment	UC + treatment	Relative (95% CI)	Absolute		
QOL (≥ 6months) (follow-up 6-12 months; measured with: AQLQ; range of scores: 1-7; Better indicated by higher values)												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	171	162	-	MD 0.32 higher (0.17 to 0.47 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Exacerbations (≥ 6months) (follow-up 12 months; assessed with: course of OCS)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	11/91 (12.1%)	10.9%	HR 1.18 (0.51 to 2.73)	18 more per 1000 (from 52 fewer to 161 more)	⊕○○○ VERY LOW	CRITICAL
Exacerbations (≥ 6months) (follow-up 6-12 months; assessed with: ER, hospitalisation or OCS)												
2	randomised trials	serious ¹	no serious inconsistency	serious ³	serious ⁴	none	21/171 (12.3%)	11.2%	RR 1.1 (0.61 to 1.99)	11 more per 1000 (from 44 fewer to 111 more)	⊕○○○ VERY LOW	CRITICAL
UHU (≥ 6months) (follow-up 6 months; assessed with: ER or hospitalisation)												
1	randomised	very	no serious	no serious	serious ⁴	none	1/80	7.1%	RR 0.17	59 fewer per 1000	⊕○○○	CRITICAL

	trials	serious ⁵	inconsistency	indirectness			(1.3%)		(0.02 to 1.46)	(from 70 fewer to 33 more)	VERY LOW	
Asthma control (< 6 months) (follow-up 3 months; measured with: ACT; range of scores: 5-25; Better indicated by higher values)												
1	randomised trials	very serious ⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	99	84	-	MD 0.3 higher (0.73 lower to 1.33 higher)	⊕⊕⊕⊕ LOW	CRITICAL
Asthma control (≥ 6 months) (follow-up 12 months; measured with: ACQ ; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	none	91	92	-	MD 0.47 lower (0.64 to 0.3 lower)	⊕⊕⊕⊕ LOW	CRITICAL
Asthma control (≥ 6 months) (follow-up 6 months; measured with: ACT; range of scores: 5-25; Better indicated by higher values)												
1	randomised trials	very serious ⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	70	-	MD 0.5 higher (0.86 lower to 1.86 higher)	⊕⊕⊕⊕ LOW	CRITICAL
Lung function (≥ 6 months) (follow-up 12 months; measured with: FEV1 L; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	none	91	92	-	MD 0.25 higher (0.03 to 0.47 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
Symptom free days (≥ 6 months) (follow-up 12 months; measured with: % over 2 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	none	91	92	-	MD 10.9 higher (0.05 to 21.75 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
ICS use (≥ 6 months) (follow-up 12 months; measured with: mean daily dose ug; Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	91	92	-	MD 57 higher (38 lower to 152 higher)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
Rescue medication (< 6 months) (follow-up 3 months; measured with: puffs/day; Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	none	99	84	-	MD 0.62 lower (1.21 to 0.03 lower)	⊕⊕⊕⊕ LOW	IMPORTANT
Rescue medication (> 6 months) (follow-up 6 months; measured with: puffs/day; Better indicated by lower values)												

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	70	-	MD 0.23 lower (0.66 lower to 0.2 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
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1 The majority of the evidence was from studies at high risk of bias

2 95% CI crosses both the MIDs

3 Evidence from one study with an indirect outcome (ER, hospitalisation or OCS)

4 95% CI for the absolute effect crosses one MID

5 The majority of the evidence was from studies at very high risk of bias

6 95% CI crosses one MID

I.2 Monitoring: Lung function tests

Table 183: Clinical evidence profile: Adults: Monitoring PEF versus symptom monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEF versus symptoms monitoring: adults	Control	Relative (95% CI)	Absolute		
QOL ≥6 months (follow-up 2 years; assessed with: AQLQ increase >0.5 points)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	52/134 (38.8%)	39.1%	RR 0.99 (0.73 to 1.35)	4 fewer per 1000 (from 106 fewer to 137 more)	⊕○○○ VERY LOW	CRITICAL
QOL ≥6 months (follow-up 2 years; assessed with: AQLQ decrease >0.5 points)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ^{2,3}	none	16/134 (11.9%)	8.6%	RR 1.39 (0.67 to 2.88)	34 more per 1000 (from 28 fewer to 162 more)	⊕○○○ VERY LOW	CRITICAL
Exacerbation ≥6 months (follow-up 6-12 months; assessed with: need for OCS)												
2	randomised	very	serious ⁴	no serious	very serious ³	none	17/71	16.9%	RR 1.28 (0.29 to	47 more per 1000 (from 120 fewer to	⊕○○○	CRITICAL

	trials	serious ¹		indirectness			(23.9%)		5.57)	772 more)	VERY LOW	
Exacerbations ≥6 months (follow-up 12 months; measured with: number of OCS courses; Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	50	45	-	MD 0.20 lower (0.74 lower to 0.34 higher)	⊕⊕⊕⊕ LOW	CRITICAL
UHU ≥6 months (follow-up 2 years; measured with: Total asthma-related health care utilisation; Better indicated by lower values)												
1	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	148	146	-	MD 0.11 lower (0.59 lower to 0.37 higher)	⊕⊕⊕⊕ MODERATE	CRITICAL
UHU ≥6 months (follow-up 6-12 months; assessed with: Hospitalisation)												
3	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	very serious ³	none	4/146 (2.7%)	2.2%	RR 1.17 (0.31 to 4.43)	4 more per 1000 (from 15 fewer to 75 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
UHU ≥6 months (follow-up 12 months; measured with: Number of hospital admissions; Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	50	45	-	MD 0.05 lower (0.16 lower to 0.06 higher)	⊕⊕⊕⊕ VERY LOW	CRITICAL
UHU ≥6 months (follow-up 12 months; measured with: days hospitalisation; Better indicated by lower values)												
1	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	40	-	MD 0.03 lower (0.21 lower to 0.15 higher)	⊕⊕⊕⊕ MODERATE	CRITICAL
UHU ≥6 months (follow-up 6-12 months; assessed with: ED visits)												
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	9/100 (9%)	2/92 (2.2%)	RR 3.78 (0.96 to 14.93)	60 more per 1000 (from 1 fewer to 303 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
UHU ≥6 months (follow-up 12 months; measured with: Mean number of ED visits ; Better indicated by lower values)												
2	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	98	85	-	MD 0.04 lower (0.2 lower to 0.12 higher)	⊕⊕⊕⊕ MODERATE	CRITICAL

UHU ≥6 months (follow-up 6 months; assessed with: Unscheduled doctors visit)												
2	randomised trials	serious ⁵	very serious ⁶	no serious indirectness	very serious ³	none	22/90 (24.4%)	28.1%	RR 0.77 (0.18 to 3.34)	65 fewer per 1000 (from 230 fewer to 658 more)	⊕○○○ VERY LOW	CRITICAL
Rescue medication ≥6months (follow-up 12 months; assessed with: requiring nebulised salbutamol)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	3/28 (10.7%)	5.4%	RR 1.98 (0.35 to 11.08)	53 more per 1000 (from 35 fewer to 544 more)	⊕○○○ VERY LOW	IMPORTANT
FEV1 L ≥6 months (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	48	40	-	MD 0.26 lower (0.61 lower to 0.09 higher)	⊕○○○ VERY LOW	IMPORTANT
FEV1 % ≥6 months (follow-up 6-12 months; range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	87	76	-	MD 0.10 higher (0.92 lower to 1.12 higher)	⊕⊕○○ LOW	IMPORTANT
PEF % best ≥6 months (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	31	32	-	MD 5.31 higher (1.91 lower to 12.53 higher)	⊕○○○ VERY LOW	IMPORTANT
Time off school/work ≥6 months (follow-up 6-12 months)												
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	11/100 (11%)	8.3%	RR 1.41 (0.62 to 3.21)	34 more per 1000 (from 32 fewer to 183 more)	⊕○○○ VERY LOW	IMPORTANT
Mean days off work ≥6 months (follow-up 12 months; Better indicated by lower values)												
2	randomised	very	no serious	no serious	serious ²	none	98	85	-	MD 2.5 higher (1.27	⊕○○○	IMPORTANT

	trials	serious ¹	inconsistency	indirectness							to 3.74 higher)	VERY LOW	
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¹ The majority of the evidence was from studies at very high risk of bias

² 95% CI crosses one MID

³ 95% CI crosses two MIDs

⁴ Heterogeneity in the point estimates, I²=52%

⁵ The majority of the evidence was from studies at high risk of bias

⁶ Heterogeneity in the point estimates, I²=86%

Table 184: Clinical evidence profile: Children: Monitoring PEF versus symptom monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PEF versus symptoms monitoring: children	Control	Relative (95% CI)	Absolute		
Exacerbations <6months (follow-up 3 months; assessed with: OCS)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	1/12 (8.3%)	8.3%	RR 1.00 (0.07 to 14.21)	0 fewer per 1000 (from 77 fewer to 1000 more) ³	⊕○○○ VERY LOW	CRITICAL
Exacerbations ≥6months (follow-up 12 months; assessed with: OCS)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/19 (36.8%)	0%	OR 16.34 (3.25 to 82.24)	370 more per 1000 (from 150 more to 590 more) ³	⊕⊕○○ LOW	CRITICAL
UHU <6 months (follow-up 12 weeks; assessed with: Hospitalisation)												
1	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	very serious ²	none	1/44 (2.3%)	0%	OR 7.56 (0.15 to 381.04)	20 more per 1000 (from 40 fewer to 80 more) ³	⊕○○○ VERY LOW	CRITICAL
UHU <6 months (follow-up 12 weeks; assessed with: Attendance at A&E)												
1	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	very serious ²	none	1/44 (2.3%)	0%	OR 7.56 (0.15 to 381.04)	20 more per 1000 (from 40 fewer to 80 more) ³	⊕○○○ VERY LOW	CRITICAL

UHU(<6 months) (follow-up 12 weeks; assessed with: Emergency GP visits)												
1	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	very serious ²	none	10/44 (22.7%)	24.4%	RR 0.93 (0.44 to 1.97)	17 fewer per 1000 (from 137 fewer to 237 more)	⊖○○○ VERY LOW	CRITICAL
Rescue meds ≥6 months (follow-up 12 months; assessed with: requiring nebulised salbutamol)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	2/17 (11.8%)	0%	OR 14.15 (0.79 to 252.1)	120 more per 1000 (from 50 fewer to 280 more) ³	⊖○○○ VERY LOW	IMPORTANT
FEV1 % best (<6 months) (follow-up 12 weeks; Better indicated by higher values)												
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	101	101	-	MD 0.39 higher (0.21 lower to 0.98 higher)	⊕⊕○○ LOW	IMPORTANT
PEF % best (<6 months) (follow-up 12 weeks; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	44	45	-	MD 2.8 higher (2.15 to 3.45 higher)	⊖○○○ VERY LOW	IMPORTANT
Time off school (<6 months) (follow-up 12 weeks)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	15/44 (34.1%)	28.9%	RR 1.18 (0.64 to 2.18)	52 more per 1000 (from 104 fewer to 341 more)	⊖○○○ VERY LOW	IMPORTANT

¹ The majority of the evidence was from studies at very high risk of bias

² 95% CI crosses 2 MIDs

³ Manual risk difference calculation due to no events in one group

⁴ The majority of the evidence was from studies at high risk of bias

⁵ 95% CI crosses one MID

I.3 Monitoring: FeNO

Table 185: Clinical evidence profile: FeNO versus Conventional Monitoring Adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO versus conventional monitoring ADULTS	Control	Relative (95% CI)	Absolute		
UHU (ED visit) ≥6 months (follow-up mean 12 months)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	2/205 (0.98%)	1.4%	OR 0.68 (0.12 to 3.98)	4 fewer per 1000 (from 12 fewer to 39 more)	⊕○○○ VERY LOW	CRITICAL
UHU (hospitalisation) ≥6 months (follow-up mean 12 months)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	1/205 (0.49%)	1%	OR 0.52 (0.05 to 5.07)	5 fewer per 1000 (from 9 fewer to 39 more)	⊕○○○ VERY LOW	CRITICAL
Exacerbation (OCS) ≥6 months (follow-up mean 52 weeks)												
3	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	33/197 (16.8%)	31.3%	RR 0.84 (0.56 to 1.26)	50 fewer per 1000 (from 138 fewer to 81 more)	⊕○○○ VERY LOW	CRITICAL
Exacerbation (OCS) ≥6 months (follow-up mean 9 months)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	-	-	HR 0.91 (0.39 to 2.11)	- ³	⊕○○○ VERY LOW	CRITICAL
Exacerbation (OCS) ≥6 months (follow-up mean 12 months)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	-	-	OR 0.64 (0.27 to 1.56)	- ³	⊕○○○ VERY LOW	CRITICAL

AQLQ (≥ 6 months) (follow-up mean 6 weeks; measured with: Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	115	112	-	MD 0 higher (0.22 lower to 22 higher) ⁵	⊕⊕⊕⊕ LOW	CRITICAL
ACQ ≥6 months (follow-up 9-12 months; measured with: Asthma Control Questionnaire; range of scores: 0-6; Better indicated by lower values)												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	320	324	-	MD 0.05 lower (0.13 lower to 0.04 higher)	⊕⊕⊕⊕ MODERATE	CRITICAL
ACQ (clinically important improvement, ≥0.5) ≥6 months (follow-up mean 12 months; assessed with: Asthma Control Questionnaire)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	29/81 (35.8%)	25.7%	RR 1.39 (0.86 to 2.26)	100 more per 1000 (from 36 fewer to 324 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
FEV1 %pred (follow-up 9-12 months; range of scores: 0-100; Better indicated by higher values)												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	366	370	-	MD 0.45 higher (0.69 lower to 1.59 higher)	⊕⊕⊕⊕ VERY LOW	IMPORTANT
FEV1, litres ≥6 months (follow-up mean 12 months; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	88	78	-	MD 0.03 lower (0.11 lower to 0.06 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
PEF am (L/min) ≥6 months (follow-up 9-12 months; Better indicated by higher values)												
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	161	160	-	MD 2 higher (10.39 lower to 14.39 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
PEF pm (L/min) ≥6 months (follow-up mean 9 months; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	115	112	-	MD 3.8 higher (10 lower to 17.6 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
ICS use ≥6 months (follow-up mean 12 months; measured with: fluticasone or BDP equivalent; Better indicated by lower values)												

2	randomised trials	serious ¹	no serious inconsistency	serious ⁶	serious ²	none	104	108	-	SMD 0.53 lower (0.8 to 0.25 lower)	⊕○○○ VERY LOW	IMPORTANT
Rescue medication (puffs/day) ≥6 months (follow-up 9-12 months; Better indicated by lower values)												
2	randomised trials	very serious ¹	no serious inconsistency	serious ⁶	no serious imprecision	none	161	160	-	MD 0.06 lower (0.12 lower to 0 higher)	⊕○○○ VERY LOW	IMPORTANT
% symptom free days ≥6 months (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	46	48	-	MD 5.6 higher (8.51 lower to 19.71 higher)	⊕○○○ VERY LOW	IMPORTANT
Time of work (number of people) ≥6 months (follow-up 9 months)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	-	-	OR 2 (1.17 to 3.41)	- ³	⊕○○○ VERY LOW	IMPORTANT

¹ Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias

² Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs

³ Control group event rate not reported

⁵ 97.5% CI reported and extracted

⁶ Downgraded by one/two increments because: the majority of the evidence had indirect outcomes

Table 186: Clinical evidence profile: FeNO versus Conventional Monitoring Children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeNO versus conventional monitoring CHILD	Control	Relative (95% CI)	Absolute		
UHU (unscheduled visits) ≥6 months (follow-up 46-52 weeks)												
2	randomised trials	no serious risk of bias	serious ¹	no serious indirectness	very serious ²	none	65/294 (22.1%)	29.9%	RR 0.67 (0.29 to	99 fewer per 1000 (from 212 fewer to	⊕○○○ VERY LOW	CRITICAL

									1.55)	164 more)		
UHU (hospitalisation) ≥6 months (follow-up 46-52 weeks)												
4	randomised trials	serious ³	no serious inconsistency	no serious indirectness	very serious ²	none	15/366 (4.1%)	3.4%	RR 0.97 (0.48 to 1.95)	1 fewer per 1000 (from 18 fewer to 32 more)	⊕○○○ VERY LOW	CRITICAL
UHU (number of children ≥1 emergency room admin) ≥6 months (follow-up mean 52 weeks)												
1	randomised trials	very serious ³	no serious inconsistency	no serious indirectness	very serious ²	none	2/45 (4.4%)	8.7%	RR 0.51 (0.1 to 2.65)	43 fewer per 1000 (from 78 fewer to 144 more)	⊕○○○ VERY LOW	CRITICAL
Exacerbation (OCS) ≥6 months (follow-up mean 43 weeks)												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	115/462 (24.9%)	19.2%	RR 0.74 (0.61 to 0.9)	50 fewer per 1000 (from 19 fewer to 75 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Asthma control (ACT score) ≥6 months (follow-up mean 46 weeks; measured with: ACT; range of scores: 5-25; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	250	244	-	MD 0.06 higher (0.27 lower to 0.39 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
PACQLQ (Pediatric Asthma Caregiver) ≥6 months (follow-up mean 30 weeks; measured with: Pediatric Asthma Care Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	very serious ³	no serious inconsistency	no serious indirectness	no serious imprecision	none	75	72	-	MD 0 higher (0.24 lower to 0.24 higher)	⊕⊕○○ LOW	CRITICAL
FEV1 % pred ≥6 months (follow-up 46-52 weeks; range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ²	none	289	290	-	MD 0.94 higher (0.31 lower to 2.19 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
ICS dose ≥6 months (follow-up 46 weeks; measured with: fluticasone; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious ⁴	no serious imprecision	none	250	244	-	MD 118.9 higher (48.5 to 189.3 higher)	⊕⊕⊕○ MODERATE	IMPORTANT

% symptom free days ≥6 months (follow-up 30 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious ³	no serious inconsistency	no serious indirectness	very serious ²	none	75	72	-	MD 0.3 higher (10 lower to 10.6 higher)	⊕○○○ VERY LOW	IMPORTANT
Number of symptom days in last 2 weeks; ≥6 months (follow-up mean 46 weeks; Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	250	244	-	MD 0.04 higher (0.21 lower to 0.29 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Number of patients not using inhaled corticosteroids or anti-leukotrienes ≥6 months (follow-up mean 12 months)												
1	randomised trials	serious ³	no serious inconsistency	no serious indirectness	very serious ²	none	2/32 (6.3%)	18.8%	RR 0.33 (0.07 to 1.53)	126 fewer per 1000 (from 175 fewer to 100 more)	⊕○○○ VERY LOW	IMPORTANT
Rescue medication (no. of patients needed beta-agonist due to symptoms) ≥6 months (follow-up mean 12 months)												
1	randomised trials	very serious ³	no serious inconsistency	no serious indirectness	serious ²	none	16/32 (50%)	81.3%	RR 0.62 (0.42 to 0.9)	309 fewer per 1000 (from 81 fewer to 472 fewer)	⊕○○○ VERY LOW	IMPORTANT
Number of school days missed in last 2 weeks; ≥6 months (follow-up mean 46 weeks; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	250	244	-	MD 0.04 lower (0.12 lower to 0.04 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Time off (school/work - number of children missed school) ≥6 months (follow-up mean 12 months)												
1	randomised trials	very serious ³	no serious inconsistency	no serious indirectness	very serious ²	none	10/46 (21.7%)	26.1%	RR 0.83 (0.4 to 1.73)	44 fewer per 1000 (from 157 fewer to 191 more)	⊕○○○ VERY LOW	IMPORTANT

1 Downgraded by one/two increments because: heterogeneity, I²=50%, p=0.04

2 Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs

3 Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias

4 Downgraded by one/two increments because: the majority of the evidence had indirect outcomes

I.4 Monitoring: Challenge tests

Table 187: Clinical evidence summary: ADULTS Methacholine challenge test versus no challenge test for asthma monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ADULTS Methacholine challenge test versus no challenge test	Control	Relative (95% CI)	Absolute		
Mortality (≥6 months) (follow-up 40 weeks)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	1/105 (0.95%)	0%	OR 7.53 (0.15 to 379.61)	10 more per 1000 (from 20 fewer to 40 more) ³	⊕○○○ VERY LOW	CRITICAL
Asthma exacerbations (≥6 months) (follow-up 40 weeks)												
1	randomised trials	very serious ¹	no serious inconsistency	serious ⁴	very serious ²	none	22/105 (21%)	24.3%	RR 0.86 (0.52 to 1.42)	34 fewer per 1000 (from 117 fewer to 102 more)	⊕○○○ VERY LOW	CRITICAL
Rescue medications (≥6 months) (follow-up 40 weeks; measured with: Albuterol puffs/day; Better indicated by lower values)												
1	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	107	-	MD 0.1 lower (0.58 lower to 0.38 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
ICS use >6months (follow-up 40 weeks; measured with: mean daily dose (mcg; fluticasone propionate); Better indicated by higher values)												
1	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	107	-	MD 131.2 higher (83.57 to 178.83 higher)	⊕⊕⊕○ MODERATE	IMPORTANT
FEV1 (≥6 months) (follow-up 40-104 weeks; measured with: L; Better indicated by higher values)												

2	randomised trials	serious ⁵	serious ⁶	no serious indirectness	no serious imprecision	none	137	142	-	MD 0.04 lower (0.09 lower to 0.16 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
% symptom free days (≥6 months) (follow-up 40 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	107	-	MD 5.1 lower (20.06 lower to 9.86 higher)	⊕⊕⊕⊕ MODERATE	IMPORTANT
PEF am (≥6 months) (follow-up 40 weeks; measured with: L/min; Better indicated by higher values)												
1	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	107	-	MD 8.6 lower (17.20 lower to 0 higher)	⊕⊕⊕⊕ MODERATE	IMPORTANT
PEF pm (≥6 months) (follow-up 40 weeks; measured with: L/min; Better indicated by higher values)												
1	randomised trials	serious ⁵	no serious inconsistency	no serious indirectness	serious ⁷	none	105	107	-	MD 6 lower (29.96 lower to 17.96 higher)	⊕⊕⊕⊕ LOW	IMPORTANT

¹ The majority of the evidence was from studies at very high risk of bias due to allocation concealment and missing data

² 95% CI crosses 2 MIDs

³ Manual calculation of absolute effect as zero events in the control group

⁴ Evidence from one study - exacerbations not defined

⁵ The majority of the evidence was from studies at high risk of bias due to allocation concealment

⁶ Point estimates show statistical heterogeneity I²=72% P<0.06. Only 2 studies so random effects model used.

⁷ 95% CI crosses one MID

8 **Table 188: Clinical evidence summary: ADULTS Mannitol challenge test versus no challenge test for asthma monitoring**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ADULTS Mannitol challenge test versus no challenge test	Control	Relative (95% CI)	Absolute		

AQLQ (≥6 months) (follow-up 52 weeks; measured with: mini AQLQ; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	no serious imprecision	none	61	58	-	MD 0.06 higher (0.3 lower to 0.42 higher)	⊕⊕⊕ LOW	CRITICAL
Asthma exacerbations (≥6 months) (follow-up 52 weeks)												
1	randomised trials	serious ³	no serious inconsistency	serious ²	very serious ⁴	none	12/61 (19.7%)	22.4%	RR 0.88 (0.44 to 1.76)	27 fewer per 1000 (from 125 fewer to 170 more)	⊕⊕⊕ VERY LOW	CRITICAL
Rescue medications (≥6 months) (follow-up 52 weeks; measured with: Albuterol puffs/day; Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ⁵	none	61	58	-	MD 0.31 lower (0.73 lower to 0.11 higher)	⊕⊕⊕ VERY LOW	IMPORTANT
ICS use >6months (follow-up 52 weeks; measured with: mean daily dose (mcg; ciclesonide); Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	no serious imprecision	none	61	58	-	MD 306 higher (241.71 to 370.29 higher)	⊕⊕⊕ LOW	IMPORTANT
FEV1% (≥6 months) (follow-up 52 weeks; Better indicated by higher values)												
1	randomised trials	serious ^{1,6}	no serious inconsistency	serious ²	no serious imprecision	none	61	58	-	MD 0.3 higher (8.21 lower to 8.81 higher)	⊕⊕⊕ LOW	IMPORTANT
PEF% (≥6 months) (follow-up 52 weeks; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	no serious imprecision	none	61	58	-	MD 2.7 lower (13.17 lower to 7.77 higher)	⊕⊕⊕ LOW	IMPORTANT
PEF am (≥6 months) (follow-up 52 weeks; measured with: L/min; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	very serious ⁴	none	61	58	-	MD 1.5 higher (34.7 lower to 37.7 higher)	⊕⊕⊕ VERY LOW	IMPORTANT

- ¹ The majority of the evidence was from studies at high risk of bias due to blinding
- ² Patients initially underwent step-down of their existing treatment. Patients on combination inhalers were switched to an equivalent dose of the same ICS only (unclear whether LABA was continued).
- ³ The majority of the evidence was from studies at high risk of bias due to missing data
- ⁴ 95% CI crosses 2 MIDs
- ⁵ 95% CI crosses one MID
- ⁶ The majority of the evidence was from studies at high risk of bias due to baseline differences

Table 189: Clinical evidence profile: CHILDREN Challenge test versus no challenge test for asthma monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CHILDREN Challenge test versus no challenge test	Control	Relative (95% CI)	Absolute		
Asthma exacerbations (≥6 months) (follow-up 2 years; assessed with: OCS course)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	very serious ³	none	16/102 (15.7%)	16.4%	RR 0.96 (0.51 to 1.79)	7 fewer per 1000 (from 80 fewer to 130 more)	⊕○○○ VERY LOW	CRITICAL
ICS dose (follow-up 2 years; measured with: Mean daily dose for treatment period; Better indicated by higher values)												
1	randomised trials	serious ⁴	no serious inconsistency	serious ²	serious ⁵	none	85	90	-	MD 84 higher (10.66 to 157.34 higher)	⊕○○○ VERY LOW	IMPORTANT
FEV1% (≥6 months) (follow-up 2 years; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious ⁴	no serious inconsistency	serious ²	no serious imprecision	none	93	92	-	MD 6 higher (1.2 lower to 10.8 higher)	⊕○○○ LOW	IMPORTANT
% symptom free days (≥6 months) (follow-up 2 years; measured with: in last 3 months of treatment; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious ⁴	no serious inconsistency	serious ²	very serious ³	none	85	90	-	MD 1.1 lower (10.1 lower to 7.9 higher)	⊕○○○ VERY LOW	IMPORTANT

- ¹ No explanation was provided
- ² Patients initially underwent step-down of their existing treatment.
- ³ 95% CI crosses both MIDs
- ⁴ The majority of the evidence was at high risk of bias due to allocation concealment and baseline differences
- ⁵ 95% CI crosses one MID

I.5 Monitoring adherence to treatment

Table 190: Clinical evidence profile: Children with uncontrolled asthma: Monitoring adherence + treatment vs UC + treatment for asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Children with uncontrolled asthma: Monitoring adherence + treatment	UC + treatment	Relative (95% CI)	Absolute		
Adherence <6months (follow-up 4 months; measured with: % of prescribed doses measured by the electronic inhaler; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	14	12	-	MD 28.9 higher (8.62 to 49.18 higher)	⊕○○○ VERY LOW	CRITICAL
Adherence ≥6months (follow-up 18 months; measured with: Number of canister refills (100% adherence = 3.0); range of scores: 0-3; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	76	81	-	MD 0.02 lower (0.29 lower to 0.25 higher)	⊕⊕○○ LOW	CRITICAL
Adherence (self-reported) ≥6months (follow-up 18 months; measured with: % self-reported adherence in previous 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	76	81	-	MD 1.95 higher (5.87 lower to 9.77 higher)	⊕⊕○○ LOW	CRITICAL
Exacerbation < 6months (follow-up 4 months; assessed with: need for OCS)												

1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	3/14 (21.4%)	8.3%	RR 2.57 (0.31 to 21.59)	130 more per 1000 (from 57 fewer to 1000 more)	⊕○○○ VERY LOW	CRITICAL
Exacerbation ≥6 months (follow-up 18 months; measured with: no. of OCS courses in 6 months; Better indicated by lower values)												
1	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	no serious imprecision	none	76	81	-	MD 0.22 higher (0.19 lower to 0.63 higher)	⊕⊕⊕○ MODERATE	CRITICAL
UHU ≥6 months (follow-up 18 months; measured with: Hospitalisations in previous 6 months ; Better indicated by lower values)												
1	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	no serious imprecision	none	76	81	-	MD 0 higher (4.8 lower to 4.8 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Rescue medication < 6months (follow-up 4 months; assessed with: Reliever medication 3 or more times a week)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	2/14 (14.3%)	0%	OR 6.92 (0.41 to 118.14)	140 more per 1000 (from 7 more to 360 more) ⁵	⊕○○○ VERY LOW	IMPORTANT

1 The majority of the evidence was from studies at very high risk of bias

2 95% CI crosses one MID

3 95% CI crosses both MIDs

4 The majority of the evidence was from studies at high risk of bias

5 Manual calculation of absolute risk difference as no events in the control group

6 **Table 191: Clinical evidence profile: Adults overall: Monitoring adherence + treatment vs UC + treatment for asthma**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adults overall: Monitoring adherence +	UC + treatment	Relative (95% CI)	Absolute		

							treatment						
Adherence ≥6months (follow-up 12 months; measured with: % adherence to prescription refills in previous 3 months; range of scores: 0-100; Better indicated by higher values)													
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	0	-	-	MD 2 lower (8.61 lower to 4.61 higher)	⊕○○○ VERY LOW	CRITICAL	
QOL <6months (follow-up 10 weeks; measured with: AQLQ; range of scores: 1-7; Better indicated by higher values)													
1	randomised trials	very serious ³	no serious inconsistency	serious ⁴	serious ⁵	none	10	9	-	MD 0.37 higher (0.08 to 0.66 higher)	⊕○○○ VERY LOW	CRITICAL	
Exacerbation ≥6months (follow-up 12 months; assessed with: course of OCS)													
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	307/1335 (23%)	22%	HR 1.07 (0.89 to 1.29)	13 more per 1000 (from 22 fewer to 54 more)	⊕⊕○○ LOW	CRITICAL	
UHU (hospitalisation) ≥6months (follow-up 12 months)													
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁶	none	10/1335 (0.75%)	0.81%	HR 0.86 (0.32 to 2.31)	1 fewer per 1000 (from 6 fewer to 11 more)	⊕○○○ VERY LOW	CRITICAL	
UHU (ED visit) ≥6months (follow-up 12 months)													
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ⁵	none	127/1335 (9.5%)	8.1%	HR 1.22 (0.83 to 1.79)	17 more per 1000 (from 13 fewer to 59 more)	⊕○○○ VERY LOW	CRITICAL	
Lung function <6months (follow-up 10 weeks; measured with: FEV1 L; Better indicated by higher values)													
1	randomised trials	very serious ³	no serious inconsistency	serious ⁴	very serious ²	none	10	9	-	MD 0.12 lower (7.31 lower to 7.07 higher)	⊕○○○ VERY LOW	IMPORTANT	

1 The majority of the evidence was from studies at very high risk of bias

- 2 95% CI crosses both MIDs
- 3 The majority of the evidence is from studies at very high risk of bias
- 4 Population indirectness: includes severe asthma
- 5 95% CI crosses one MID
- 6 95% CI crosses both the MIDs but only downgraded by one as the 95% CI for the absolute effect is small

I.6 Monitoring inhaler technique

Table 192: ADULTS: Monitoring inhaler technique vs no monitoring for asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ADULTS: Monitoring inhaler technique	No monitoring	Relative (95% CI)	Absolute		
Lung function <6 months (follow-up 3 months; measured with: PEF Min%Max (higher is less variability); range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	53	44	-	MD 6.2 higher (2.68 to 9.72 higher)	⊕○○○ VERY LOW	IMPORTANT
Lung function ≥6 months (follow-up 6 months; measured with: PEF Min%Max (higher is less variability); range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	53	44	-	MD 4.5 higher (0.79 to 8.21 higher)	⊕○○○ VERY LOW	IMPORTANT
QOL <6 months (follow-up 3 months; measured with: Marks AQLQ; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	44	-	MD 0.55 lower (0.77 to 0.33 lower)	⊕⊕○○ LOW	CRITICAL
QOL ≥6 months (follow-up 6 months; measured with: Marks AQLQ; range of scores: 0-10; Better indicated by lower values)												

1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	53	44	-	MD 0.5 lower (0.74 to 0.26 lower)	⊕○○○ VERY LOW	CRITICAL
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¹ The evidence was from one study at very high risk of bias for this outcome

² 95% CI crosses one MID

Table 193: ADULTS: Monitoring (verbal and electronic) vs verbal monitoring only for asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ADULTS: Monitoring (verbal and electronic)	Verbal monitoring only	Relative (95% CI)	Absolute		
QOL <6 months (follow-up 6 weeks; measured with: mini AQLQ; range of scores: 1-7; Better indicated by higher values)												
2	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	53	52	-	MD 0.38 higher (0.02 lower to 0.79 higher)	⊕○○○ VERY LOW	CRITICAL
Lung function <6 months (follow-up 6 weeks; measured with: FEV1 L; Better indicated by higher values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	36	35	-	MD 0.23 lower (0.55 lower to 0.09 higher)	⊕○○○ VERY LOW	IMPORTANT
Lung function <6 months (follow-up 6 weeks; measured with: FEV1 % pred; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious ³	no serious inconsistency	no serious indirectness	serious ²	none	17	17	-	MD 9.1 higher (3.71 lower to 21.91 higher)	⊕○○○ LOW	IMPORTANT

¹ The majority of the evidence was from studies at very high risk of bias for this outcome

² 95% CI crosses one MID

³ The majority of the evidence was from studies at high risk of bias for this outcome

Table 194: CHILDREN: Monitoring (verbal and electronic) vs verbal monitoring only for asthma

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CHILDREN: Monitoring (verbal and electronic)	Verbal monitoring only	Relative (95% CI)	Absolute		
Lung function <6 months (follow-up 6 weeks; measured with: FEV1 % pred; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	6	6	-	MD 3.2 lower (15.27 lower to 8.87 higher)	⊕○○○ VERY LOW	IMPORTANT
QOL <6 months (follow-up 6 weeks; measured with: PAQLQ; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	very serious ³	no serious inconsistency	no serious indirectness	very serious ²	none	6	6	-	MD 0.03 higher (0.66 lower to 0.72 higher)	⊕○○○ VERY LOW	CRITICAL

¹ The evidence was from one study at high risk of bias for this outcome² 95% CI crosses both MIDs³ No explanation was provided**5 I.7 Monitoring: Tele-healthcare****6 Table 195: Adult comparison 1: tele-health services vs face-to-face equivalents**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tele-health services	face-to-face equivalents	Relative (95% CI)	Absolute		
Quality of life (follow-up mean 12 months; measured with: Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												

3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	491	469	-	MD 0.01 lower (0.17 lower to 0.14 higher)	⊕⊕⊕○ MODERATE	CRITICAL
UHU hospitalisation (follow-up mean 6 months²)												
2	randomised trials	very serious ^{1,3}	no serious inconsistency	no serious indirectness	very serious ⁴	none	0/222 (0%)	0.6%	OR 0.14 (0 to 7.06) ⁵	5 fewer per 1000 (from 6 fewer to 35 more)	⊕○○○ VERY LOW	CRITICAL
UHU ED visit (follow-up mean 6 months²)												
2	randomised trials	very serious ^{1,3}	no serious inconsistency	no serious indirectness	very serious ⁴	none	2/222 (0.9%)	0%	OR 7.75 (0.48 to 124.9) ⁵	-	⊕○○○ VERY LOW	CRITICAL
Exacerbations requiring oral steroids												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁴	none	5/137 (3.6%)	2.1%	RR 1.72 (0.42 to 7.04)	15 more per 1000 (from 12 fewer to 127 more)	⊕○○○ VERY LOW	CRITICAL
Asthma control (follow-up mean 12 months; measured with: Asthma Control Questionnaire; range of scores: 0-6; Better indicated by lower values)												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	354	328	-	MD 0.11 lower (0.27 lower to 0.04 higher)	⊕⊕⊕○ MODERATE	CRITICAL
UHU GP visits (follow-up mean 6 months²)												
2	randomised trials	serious ^{1,6}	no serious inconsistency	no serious indirectness	serious ⁴	none	30/222 (13.5%)	13.2%	RR 0.86 (0.56 to 1.32)	18 fewer per 1000 (from 58 fewer to 42 more)	⊕⊕○○ LOW	CRITICAL
Change in FEV1 (mL) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	very serious ^{1,3}	no serious inconsistency	no serious indirectness	serious ⁷	none	85	88	-	MD 152 higher (54 to 250 higher)	⊕○○○ VERY LOW	IMPORTANT
Withdrawal (follow-up 6-12 months)												
3	randomised trials	no serious risk of bias	serious ⁸	no serious indirectness	very serious ⁴	none	35/334 (10.5%)	12%	RR 0.78 (0.32 to 1.9)	26 fewer per 1000 (from 82 fewer to 108 more)	⊕○○○ VERY LOW	IMPORTANT

- ¹ Studies could not use blinding to control for performance or detection bias
- ² Pinnock 2003 was a pragmatic trial of variable intervention duration, but did not contribute any events to the analysis
- ³ Evidence of sub-optimal randomisation procedures and imputation of missing values, and selective reporting
- ⁴ 95% CI crosses both the MIDs
- ⁵ Very rare events - Peto odds ratio used
- ⁶ While there were several issues with one of the studies in the analysis, it only accounted for 6.6% of the analysis weight.
- ⁷ 95% CI crossed an MID
- ⁸ Heterogeneity was high (I squared = 79%)

Table 196: Adult comparison 2: tele-monitoring vs paper-based monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tele-monitoring	Paper-based monitoring	Relative (95% CI)	Absolute		
Quality of life (follow-up 6-12 months; measured with: Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
2	randomised trials	serious ¹	serious ²	no serious indirectness	serious ³	none	188	196	-	MD 0.21 higher (0.09 lower to 0.5 higher)	⊕○○○ VERY LOW	CRITICAL
UHU hospitalisation (follow-up 4-6 months)												
3	randomised trials	serious ⁴	serious ⁵	no serious indirectness	very serious ⁶	none	5/191 (2.6%)	2.2%	RR 0.60 (0.13 to 2.86)	9 fewer per 1000 (from 19 fewer to 41 more)	⊕○○○ VERY LOW	CRITICAL
UHU ED visit (follow-up mean 6 months)												
2	randomised trials	serious ⁷	serious ⁸	no serious indirectness	very serious ⁶	none	5/183 (2.7%)	13%	RR 0.89 (0.02 to 33.53)	14 fewer per 1000 (from 127 fewer to 1000 more)	⊕○○○ VERY LOW	CRITICAL
Exacerbations requiring oral steroids (follow-up mean 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁶	none	28/140 (20%)	21.3%	RR 0.94 (0.59 to 1.49)	13 fewer per 1000 (from 87 fewer to 104 more)	⊕⊕○○ LOW	CRITICAL

Asthma control (follow-up 6-12 months; measured with: Asthma Control Questionnaire; range of scores: 0-6; Better indicated by lower values)												
2	randomised trials	serious ¹	very serious ⁹	no serious indirectness	serious ³	none	240	238	-	MD 0.24 lower (0.72 lower to 0.24 higher)	⊕○○○ VERY LOW	CRITICAL
UHU GP visits (follow-up mean 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ³	none	51/140 (36.4%)	29.1%	RR 1.25 (0.89 to 1.76)	73 more per 1000 (from 32 fewer to 221 more)	⊕⊕⊕○ MODERATE	CRITICAL
Change in FEV1 (mL) (follow-up mean 12 months; Better indicated by higher values)												
1	randomised trials	serious ¹⁰	no serious inconsistency	no serious indirectness	serious ³	none	101	99	-	MD 250 higher (33.36 to 466.64 higher)	⊕⊕○○ LOW	IMPORTANT
PEF (L/min) (follow-up mean 6 months; Better indicated by higher values)												
1	randomised trials	serious ⁷	no serious inconsistency	no serious indirectness	serious ³	none	43	46	-	MD 39.2 higher (16.58 to 61.82 higher)	⊕⊕○○ LOW	IMPORTANT
Withdrawal (follow-up 4-12 months)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁶	none	58/312 (18.6%)	15.2%	RR 1.01 (0.73 to 1.39)	2 more per 1000 (from 41 fewer to 59 more)	⊕⊕○○ LOW	IMPORTANT

¹ One study analysed complete cases and did not blind participants, investigators or outcome assessors, which carried the majority of the analysis weight.

² Heterogeneity was high (I squared = 53%)

³ 95% CI crosses one of the MIDs

⁴ Only one study used any blinding procedures (outcome assessors), and there were uncertainties regarding allocation concealment

⁵ Heterogeneity was not statistically significant (I squared = 42%), but point estimates are very different

⁶ 95% CIs cross both MIDs

⁷ Study carrying the most weight did not blind outcome assessors (and could not blind participants and investigators), and dropout was high in both groups

⁸ Heterogeneity was high (I squared = 80%)

⁹ Heterogeneity was very high (I squared = 91%)

¹⁰ No blinding of outcome assessors (and unable to blind participants and investigators). Only complete cases were analysed.

Table 197: Adult comparison 3: tele-healthcare package vs nothing (usual care)

Quality assessment	No of patients	Effect	Quality	Importance
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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tele-health packages	Nothing (usual care)	Relative (95% CI)	Absolute		
Quality of life (follow-up 10-12 months; measured with: Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
3	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	806	827	-	MD 0.08 higher (0.03 lower to 0.20 higher)	⊕⊕⊕○ MODERATE	CRITICAL
UHU hospitalisation (follow-up 6-12 months)												
4	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision ²	none	1/205 (0.49%)	5.6%	OR 0.16 (0.05 to 0.56) ⁴	47 fewer per 1000 (from 24 fewer to 53 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
UHU ED visit (follow-up 6-12 months)												
4	randomised trials	serious ¹	no serious inconsistency ⁴	no serious indirectness	very serious ⁵	none	10/210 (4.8%)	6.5%	RR 0.82 (0.38 to 1.8)	12 fewer per 1000 (from 40 fewer to 52 more)	⊕○○○ VERY LOW	CRITICAL
Exacerbations requiring oral steroids (follow-up mean 12 months)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ⁵	none	21/31 (67.7%)	72.4%	RR 0.94 (0.67 to 1.3)	43 fewer per 1000 (from 239 fewer to 217 more)	⊕○○○ VERY LOW	CRITICAL
Asthma control (follow-up mean 12 months; measured with: Asthma Control Questionnaire; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	270	286	-	MD 0.04 lower (0.2 lower to 0.12 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
UHU GP visits (follow-up 6-12 months)												
3	randomised trials	serious ¹	Serious ⁶	no serious indirectness ⁷	very serious ⁵	none	31/150 (20.7%)	38.9%	RR 0.96 (0.39 to 2.37)	16 fewer per 1000 (from 237 fewer to 533 more)	⊕○○○ VERY LOW	CRITICAL
Change in FEV1 (mL) (follow-up mean 6 months; Better indicated by higher values)												

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ⁸	none	85	80	-	MD 183 higher (85 to 281 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
Symptom days per month (range of scores: 0-30; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁸	none	311	297	-	MD 0.6 higher (0.82 lower to 2.02 higher)	⊕⊕⊕⊕ MODERATE	IMPORTANT
Symptom nights per month (range of scores: 0-30; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁸	none	311	297	-	MD 0.1 lower (1.21 lower to 1.01 higher)	⊕⊕⊕⊕ MODERATE	IMPORTANT
Withdrawal (follow-up 6-12 months)												
5	randomised trials	serious ¹	no serious inconsistency ⁽⁴⁾	no serious indirectness	serious ⁵	none	28/255 (11%)	11.1%	RR 0.81 (0.51 to 1.29)	21 fewer per 1000 (from 54 fewer to 32 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT

¹ Issues across studies with blinding, completeness of outcome data, and allocation concealment

² Confidence intervals were wide but did not cross an MID

³ Very rare events - Peto odds ratio used

⁴ Point estimates were varied but statistical heterogeneity was low - random effects sensitivity did not change imprecision

⁵ 95% CI crossed both MIDs

⁶ Heterogeneity was high (I squared = 66%)

⁷ One study was only recruited older adults (53% of analysis weight)

⁸ 95% CIs crossed an MID

Table 198: Child comparison 1: tele-health services vs face-to-face equivalents

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tele-health services	face-to-face equivalents	Relative (95% CI)	Absolute		
Quality of life - child (follow-up mean 12 months; measured with: Paediatric Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	60	60	-	MD 0.3 higher (0.11 lower to 0.71 higher)	⊕⊕⊕⊕ LOW	CRITICAL

Quality of life - caregiver (follow-up mean 12 months; measured with: Paediatric Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	60	60	-	MD 0.2 higher (0.12 lower to 0.52 higher)	⊕⊕⊕⊕ LOW	CRITICAL
UHU hospitalisation (follow-up mean 12 months)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	1/60 (1.7%)	1.7%	RR 1 (0.06 to 15.62)	0 fewer per 1000 (from 16 fewer to 249 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
UHU ED visit (follow-up mean 12 months)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	4/60 (6.7%)	3.3%	RR 2 (0.38 to 10.51)	33 more per 1000 (from 20 fewer to 314 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
FEV1 % predicted (follow-up mean 12 months; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	60	60	-	MD 5.2 higher (1.48 lower to 11.88 higher)	⊕⊕⊕⊕ LOW	IMPORTANT

¹ No blinding and unbalanced attrition

² 95% CI crosses an MID

³ 95% CI crosses both MIDs

Table 199: Child comparison 2: tele-monitoring vs paper-based monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tele-monitoring	Paper-based monitoring	Relative (95% CI)	Absolute		
Change in morning PEF (L/min) (follow-up mean 3 months; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	82	71	-	MD 7.80 higher (6.37 lower to 21.97 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
Change in evening PEF (L/min) (follow-up mean 3 months; Better indicated by higher values)												

1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	82	71	-	MD 12 higher (3.59 lower to 27.59 higher)	⊕⊕⊕⊕ LOW	IMPORTANT
Withdrawal (follow-up mean 3 months)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	6/88 (6.8%)	6.6%	RR 1.04 (0.33 to 3.26)	3 more per 1000 (from 44 fewer to 149 more)	⊕⊕⊕⊕ VERY LOW	IMPORTANT

¹ Participants and investigators could not be blind (outcome assessors were blinded)

² 95% CI crosses an MID

³ 95% CI crosses both MIDs

Table 200: Child comparison 3: tele-healthcare package vs nothing (usual care)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tele-health packages	Nothing (usual care)	Relative (95% CI)	Absolute		
Quality of life - child (follow-up 6-12 months; measured with: Paediatric Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
1	randomised trials	serious ¹	No serious inconsistency	no serious indirectness	serious ³	none	41	41	-	MD 0.70 higher (0.29 to 1.11 higher)	⊕⊕⊕⊕ LOW	CRITICAL
Quality of life - caregiver (follow-up 6-12 months; measured with: Paediatric Asthma Quality of Life Questionnaire; range of scores: 1-7; Better indicated by higher values)												
2	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision ²	none	89	92	-	MD 0.18 higher (0.10 lower to 0.46 higher)	⊕⊕⊕⊕ MODERATE	CRITICAL
UHU hospitalisation (follow-up 3-12 months)												
5	randomised trials	serious ⁴	no serious inconsistency ⁵	no serious indirectness	very serious ⁶	none	11/305 (3.6%)	2%	RR 1.43 (0.59 to 3.46)	9 more per 1000 (from 8 fewer to 49 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
UHU ED visit (follow-up 3-12 months)												

4	randomised trials	serious ⁴	no serious inconsistency ⁵	no serious indirectness	very serious ⁶	none	19/285 (6.7%)	9.2%	RR 1 (0.56 to 1.8)	0 fewer per 1000 (from 40 fewer to 74 more)	⊕○○○ VERY LOW	CRITICAL
Exacerbations requiring oral steroids (follow-up 6-12 months)												
2	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	very serious ⁶	none	41/62 (66.1%)	71.9%	RR 1.01 (0.8 to 1.27)	7 more per 1000 (from 144 fewer to 194 more)	⊕○○○ VERY LOW	CRITICAL
Asthma control (follow-up mean 12 months; measured with: Asthma Control Questionnaire; range of scores: 0-6; Better indicated by lower values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ³	none	148	153	-	MD 0.31 lower (0.56 to 0.06 lower)	⊕⊕○○ LOW	CRITICAL
UHU GP visits (follow-up mean 8 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁶	none	6/48 (12.5%)	15.7%	RR 0.80 (0.30 to 2.13)	31 fewer per 1000 (from 110 fewer to 177 more)	⊕⊕○○ LOW	CRITICAL
Withdrawal (follow-up 3-12 months)												
5	randomised trials	serious ⁴	serious ⁷	no serious indirectness	serious ⁶	none	51/408 (12.5%)	16.1%	RR 0.86 (0.53 to 1.41)	23 fewer per 1000 (from 76 fewer to 66 more)	⊕○○○ VERY LOW	IMPORTANT

¹ One or more study did not blind outcome assessors

² MID is close to, but does not cross, the 0.5 MID

³ 95% CI crosses one MID

⁴ Issues across studies with blinding, completeness of outcome data, and allocation concealment

⁵ Point estimates were varied but statistical heterogeneity was low - random effects sensitivity did not change imprecision

⁶ 95% CI crosses both MIDs

⁷ Some inconsistency (I squared = 38%), random effects used

Table 201: Adult comparison 4: Telehealthcare without healthcare professional involvement vs usual care

Quality assessment	No of patients	Effect	Quality	Importance
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No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interactive voice response telephone calls	no calls	Relative (95% CI)	Absolute		
QOL <6 months (follow-up 10 weeks; measured with: AQLQ; range of scores: 0-7; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	serious ²	none	25	25	-	MD 0.23 higher (0.32 lower to 0.78 higher)	⊕⊕○○ LOW	CRITICAL
Asthma Control Questionnaire <6 months (follow-up 10 weeks; measured with: ACT; range of scores: 5-25; Better indicated by higher values)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	25	25	-	MD 0.72 higher (1.51 lower to 2.95 higher)	⊕○○○ VERY LOW	CRITICAL

¹ Method of randomisation and allocation concealment unclear

² Crosses one MID

³ Crosses two MIDs

4

Table 202: Child comparison 4: Telehealthcare without healthcare professional involvement vs usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Telephone calls	No calls	Relative (95% CI)	Absolute		
Exacerbations ≥6 months (follow-up 6 months; assessed with: Self report OCS (assumed to be for exacerbation))												
1	randomised trials	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	serious ⁴	none	16/39 (41%)	52.5%	RR 0.78 (0.48 to 1.26)	116 fewer per 1000 (from 273 fewer to 136 more)	⊕○○○ VERY LOW	CRITICAL
QOL ≥6 months (follow-up 6 months; measured with: Pediatric Asthma Quality of Life Questionnaire (carer); range of scores: 0-7; Better indicated by higher values)												
1	randomised trials	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	serious ⁴	none	39	41	-	MD 0.2 higher (0.48 lower to 0.88 higher)	⊕○○○ VERY LOW	CRITICAL
QOL ≥6 months (follow-up 6 months; measured with: Pediatric Asthma Quality of Life Questionnaire (child); range of scores: 0-7; Better indicated by higher values)												
1	randomised	very	no serious	no serious	no serious	none	39	41	-	MD 0.6 higher (0.16 to	⊕⊕○○	CRITICAL

	trials	serious ^{1,2,3}	inconsistency	indirectness	imprecision					1.04 higher)	LOW	
UHU ED visit ≥6 months (follow-up 6 months; assessed with: ED visit self report)												
1	randomised trials	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	very serious ⁵	none	6/39 (15.4%)	12.5%	RR 1.23 (0.41 to 3.7)	29 more per 1000 (from 74 fewer to 338 more)	⊕○○○ VERY LOW	CRITICAL
UHU hospitalisation ≥6 months (follow-up 6 months; assessed with: Hospital admission self report)												
1	randomised trials	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	very serious ⁵	none	4/39 (10.3%)	10%	RR 1.03 (0.28 to 3.82)	3 more per 1000 (from 72 fewer to 282 more)	⊕○○○ VERY LOW	CRITICAL
School days lost ≥6 months (follow-up 6 months; assessed with: Self report (yes/no to any time off school))												
1	randomised trials	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	very serious ⁵	none	20/38 (52.6%)	56.4%	RR 0.93 (0.62 to 1.4)	39 fewer per 1000 (from 214 fewer to 226 more)	⊕○○○ VERY LOW	IMPORTANT
Parents' work days lost ≥6 months (follow-up 6 months; assessed with: Self report (yes/no to any work days lost))												
1	randomised trials	very serious ^{1,2,3}	no serious inconsistency	no serious indirectness	very serious ⁵	none	13/39 (33.3%)	33.3%	RR 1 (0.53 to 1.87)	0 fewer per 1000 (from 157 fewer to 290 more)	⊕○○○ VERY LOW	IMPORTANT
Controller medication use in patients who should have been on controller medications at baseline ≥6 months (follow-up 12 months; assessed with: i.e. persistent asthma)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	none	7/19 (36.8%)	16.7%	RR 2.21 (0.82 to 5.97)	202 more per 1000 (from 30 fewer to 830 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Persistent asthma on controllers at baseline but discontinued at 6 months (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁵	none	6/42 (14.3%)	5.2%	RR 2.76 (0.73 to 10.42)	92 more per 1000 (from 14 fewer to 490 more)	⊕⊕○○ LOW	IMPORTANT
Of those who met severity criteria for controllers at baseline, number on them at 12 months (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious ⁴	none	34/53 (64.2%)	61%	RR 1.05 (0.81 to 1.37)	30 more per 1000 (from 116 fewer to 226 more)	⊕⊕⊕○ MODERATE	IMPORTANT

1 Method of randomisation and allocation concealment unclear

2 Groups not comparable at baseline

- ³ Underpowered
- ⁴ Crosses one MID
- ⁵ Crosses two MIDs

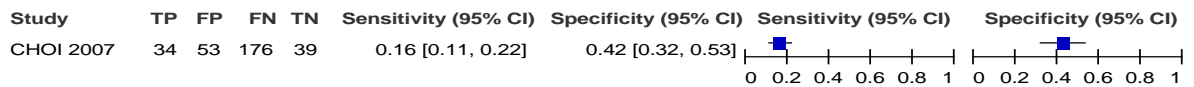
1 Appendix J: Forest plots

2 J.1 Diagnosis: Signs and symptoms

3 J.1.1 Coupled sensitivity / specificity forest plots and ROC curves

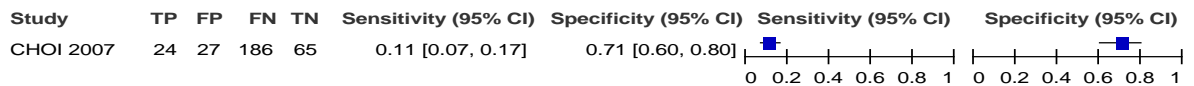
4 J.1.1.1 Adults: symptoms vs. physician Dx and an objective test

5 **Figure 47: Paroxysmal coughing**



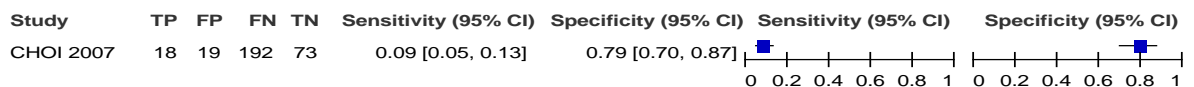
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7 **Figure 48: Dyspnoea without wheeze**



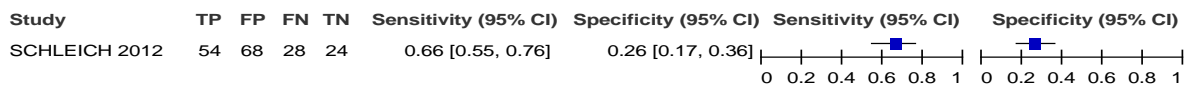
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9 **Figure 49: Wheeze without dyspnoea**



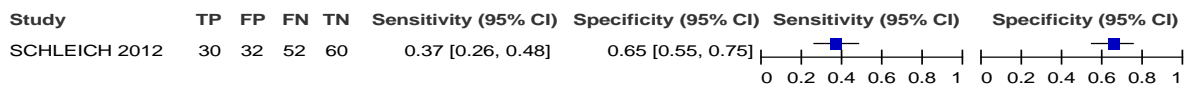
10

11 **Figure 50: Diurnal cough**



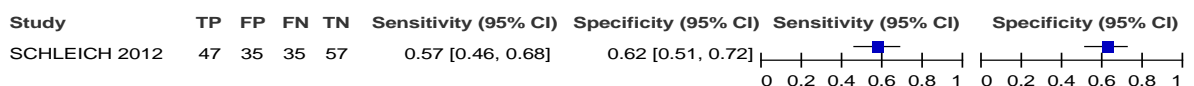
12

13 **Figure 51: Nocturnal cough**



14

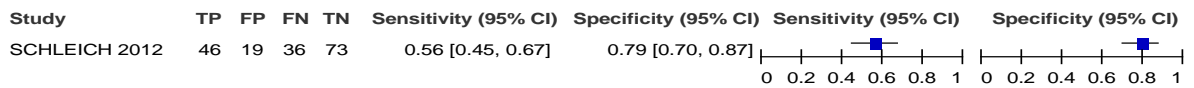
15 **Figure 52: Diurnal wheeze**



16

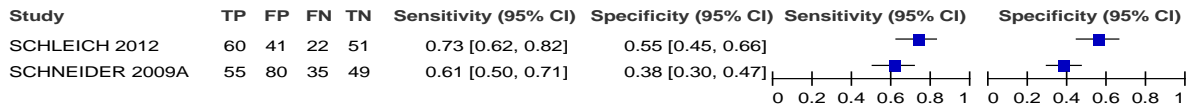
17

1 **Figure 53: Nocturnal wheeze**



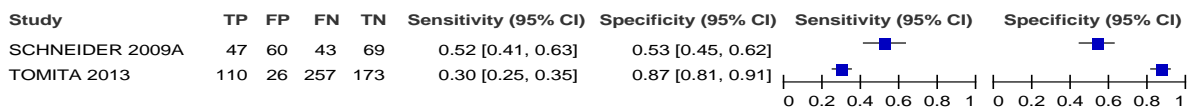
2

3 **Figure 54: Dyspnoea**



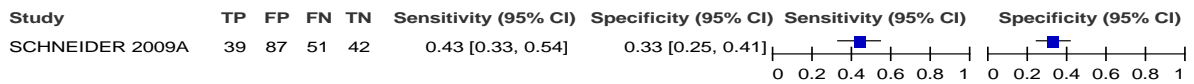
4

5 **Figure 55: Wheeze**



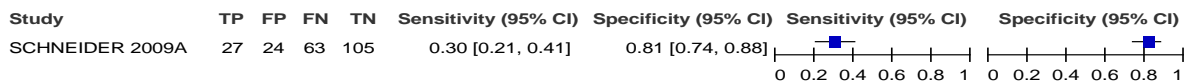
6

7 **Figure 56: Cough**



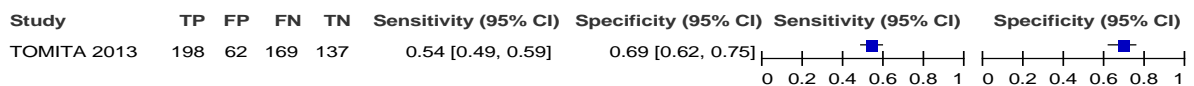
8

9 **Figure 57: Nocturnal dyspnoea**



10

11 **Figure 58: Diurnal symptoms**



12

13 **Figure 59: Total symptom score ≥5**

14 CHOI 2007: numbers for 2x2 table not reported. Sensitivity 74.3%, Specificity 47.8%

15 **Figure 60: Dyspnoea attacks**

16 SCHNEIDER 2012: numbers for 2x2 table not reported. Sensitivity 40%, Specificity 78.4%

17 **Figure 61: Dyspnoea going upstairs**

18 SCHNEIDER 2012: numbers for 2x2 table not reported. Sensitivity 47.1%, Specificity 49.6%

19 **Figure 62: Dyspnoea when walking**

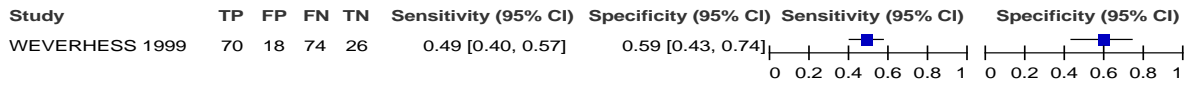
20 SCHNEIDER 2012: numbers for 2x2 table not reported. Sensitivity 4.8%, Specificity 93.2%

1 **Figure 63: Dyspnoea on minimal exercise**

2 SCHNEIDER 2012: numbers for 2x2 table not reported. Sensitivity 2.5%, Specificity 94.1%

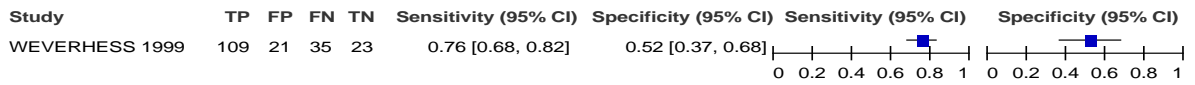
3 **Children <5 years: symptoms vs. physician Dx**

4 **Figure 64: Cough and wheeze**



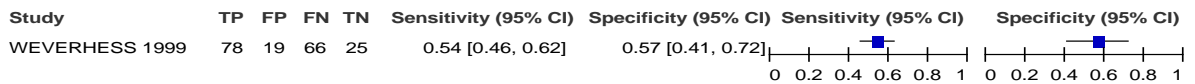
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6 **Figure 65: Dyspnoea**



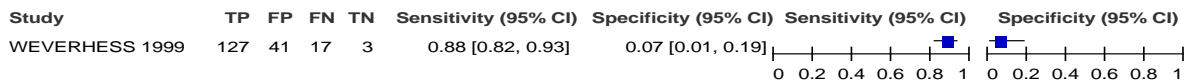
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8 **Figure 66: Wheeze**



9

10 **Figure 67: Cough**



11

12

1 J.2 Diagnosis: History of atopic disorders

2 J.2.1 Coupled sensitivity / specificity forest plots and ROC curves

Figure 68: Adults: Personal history of atopic disorders

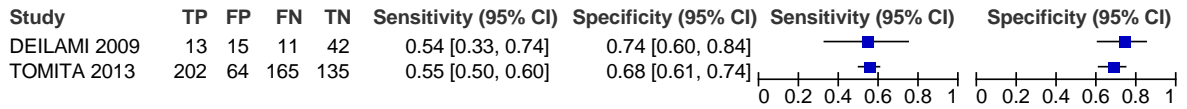


Figure 69: Adults: Family history of atopic disorders

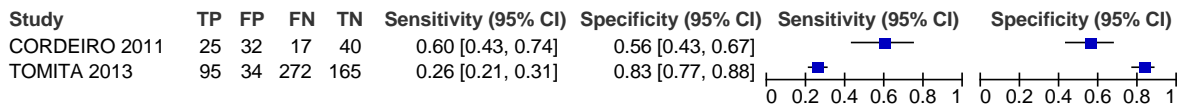


Figure 70: Children 5-16 years: Family history of asthma

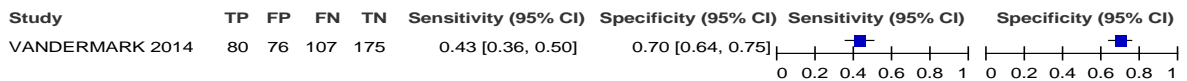


Figure 71: Children <5 years: Family history of atopic disorders

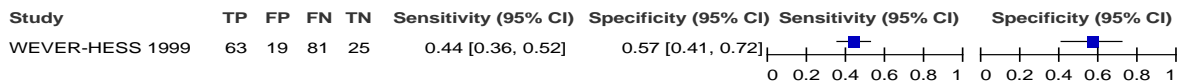


Figure 72: Children <5 years: Personal history of rhinitis

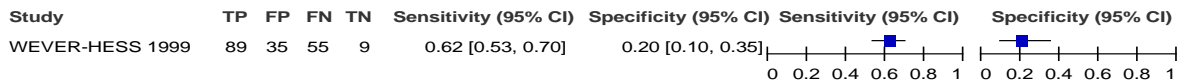
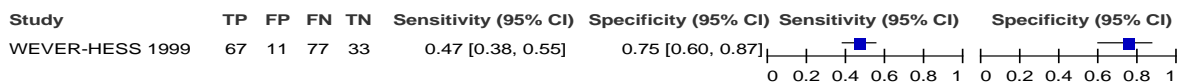


Figure 73: Children <5 years: Personal history of eczema



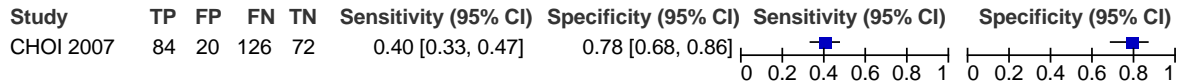
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4

1 **J.3 Diagnosis: Symptoms after exercise**

2 **J.3.1 Coupled sensitivity / specificity forest plots and ROC curves**

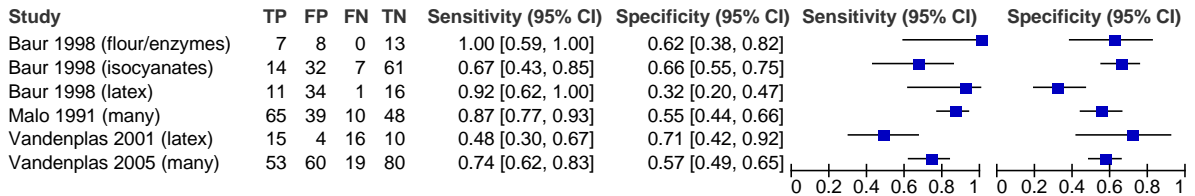
Figure 74: Clinical history of symptoms in response to exercise vs Reference Standard (adults)



3 **J.4 Diagnosis: Occupational asthma**

4 **J.4.1 Question whether symptoms are better away from work vs. reference standard**

5 **Figure 75: Asking whether their symptoms are better away from work (all causative agents)**



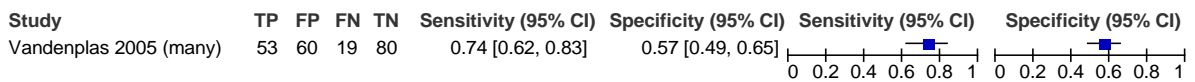
6

7 **Figure 76: Improvement or disappearance of symptoms at weekend.**



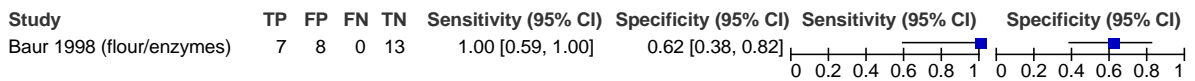
8

9 **Figure 77: Improvement of disappearance of symptoms during vacation.**



10

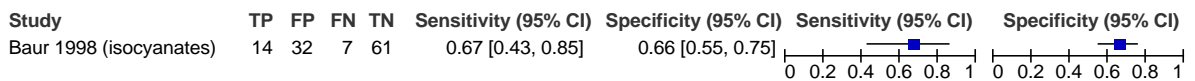
11 **Figure 78: Symptoms better away from work (flour).**



12

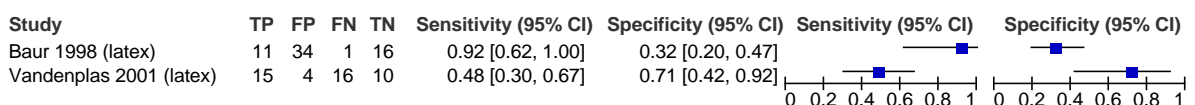
13 **Figure 79: Symptoms better away from work (isocyanate).**

14



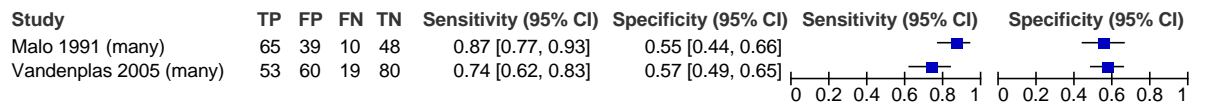
15

16 **Figure 80: Symptoms better away from work (latex).**



17

1 **Figure 81: Symptoms better away from work (many causal agents).**



2

1 J.5 Diagnosis: Spirometry

2 J.5.1.1 Coupled sensitivity / specificity forest plots and ROC curves

3 Adults: FEV1/FVC ratio measures

Figure 82: FEV1/FVC <70%

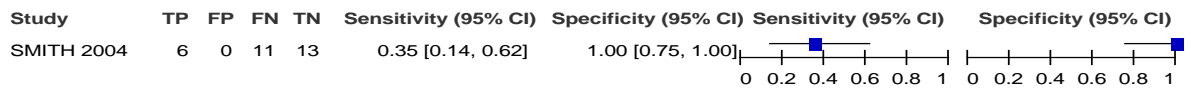
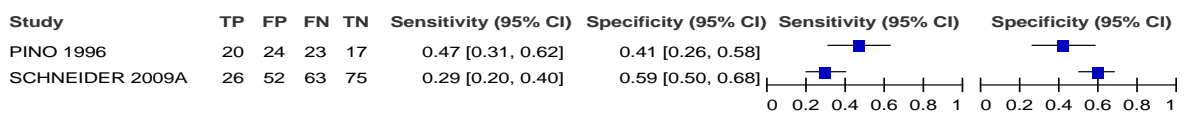
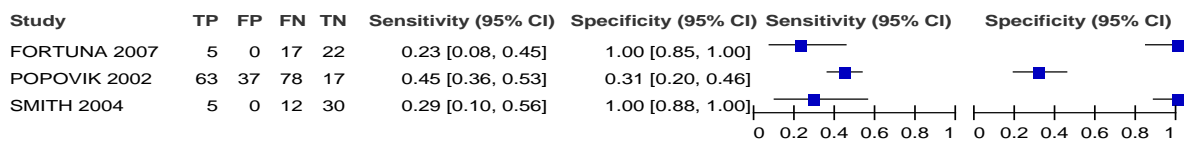


Figure 83: FEV1/FVC <70% and/or FEV1<80%



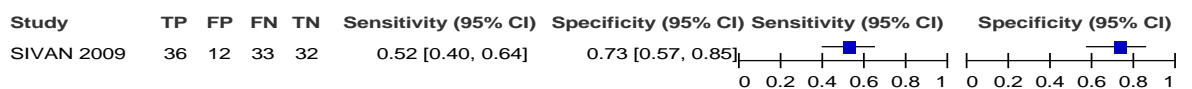
4 Adults: FEV1 only measures

Figure 84: FEV1 <80%



5 Children: FEV1 measures

Figure 85: FEV1 <80%



6
7

1 J.6 Diagnosis: Bronchodilator reversibility

2 J.6.1.1 Adults: Bronchodilator reversibility vs. Physician Dx

Figure 86: $\Delta FEV1\%init \geq 12\%$ and $\Delta FEV1[L] \geq 0.2L$

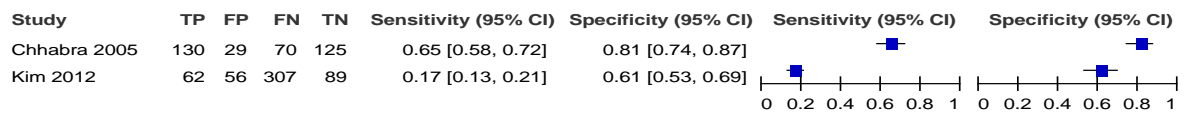
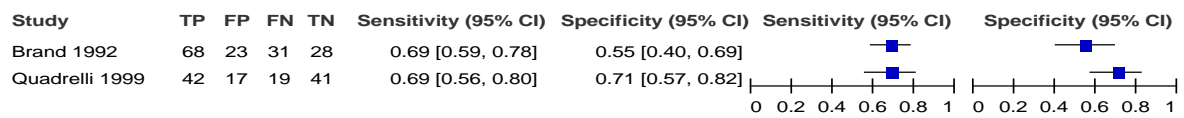


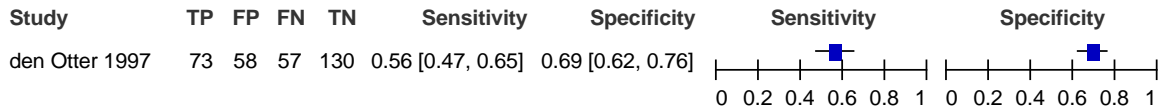
Figure 87: $\Delta FEV1\%init > 15\%$ and $\Delta FEV1[L] > 0.2L$



1 J.7 Diagnosis: PEF variability

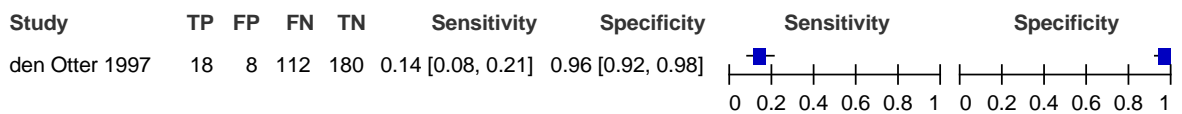
2 J.7.1.1 Adults > 16 years

Figure 88: Amp%mean (mean over 3 weeks >5%)



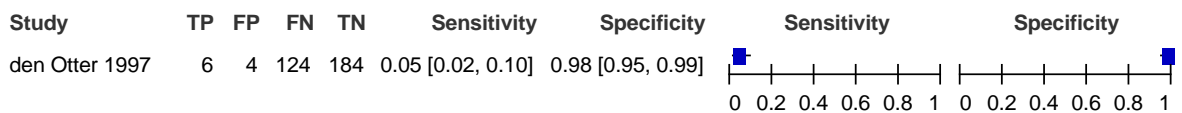
3

Figure 89: Amp%mean (mean over 3 weeks >10%)



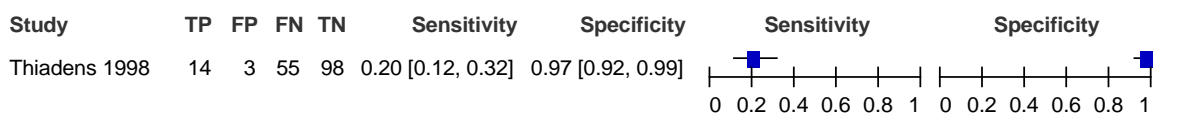
4

Figure 90: Amp%mean (mean over 3 weeks >15%)



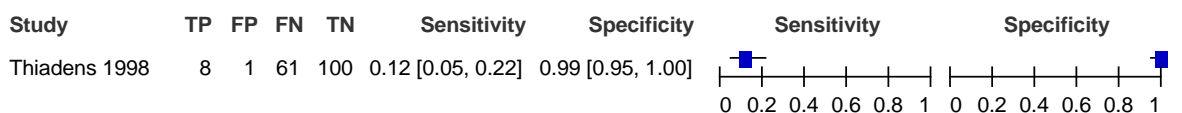
5

Figure 91: Amp%highest (>15% on 4 days or more)



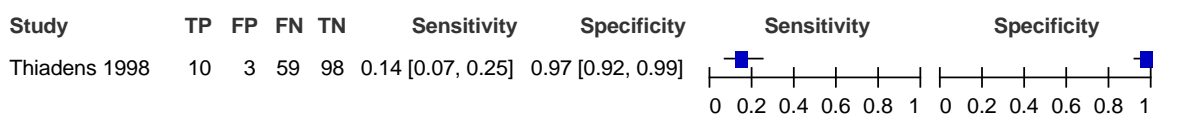
6

Figure 92: Amp%highest (>20% on 3 days or more)



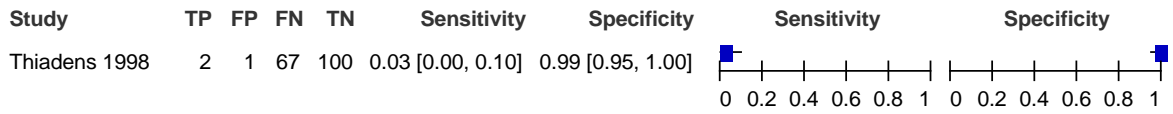
7

Figure 93: Amp%highest (mean over 2 weeks >10%)



8

Figure 94: Amp%highest (mean over 2 weeks >10%)

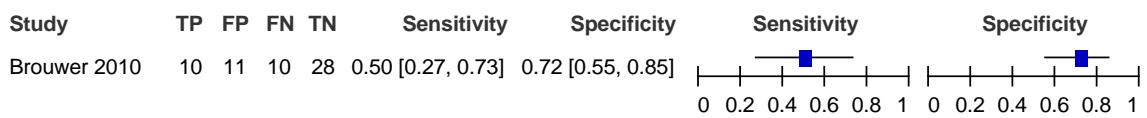


1

2 J.7.1.2 **Children 5-16 years**

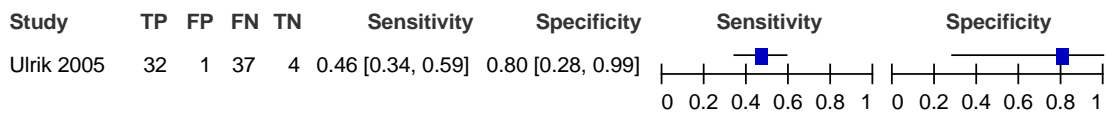
3

Figure 95: Amp%mean >12.3%



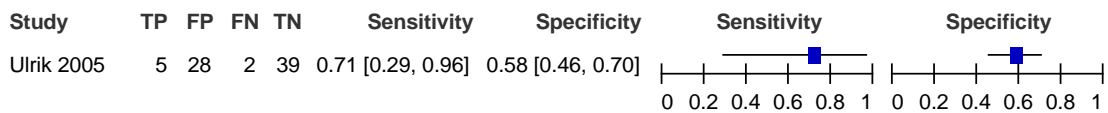
4

Figure 96: Amp%mean >20% versus PC20 histamine >16mg/mL.



5

Figure 97: Amp%mean >20% versus bronchodilator reversibility change in FEV1 >10%.



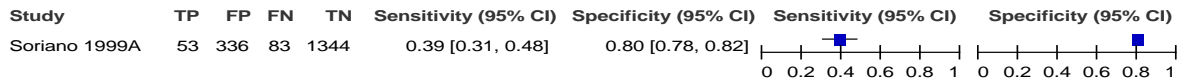
6

7

1 J.8 Diagnosis: Skin prick tests

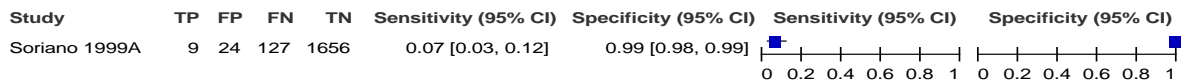
2 J.8.1.1 Skin prick tests vs. Physician Dx with objective test: ADULTS

Figure 98: *D. pteronyssinus* (Der P) +/- *D. farinae* (house dust mite)



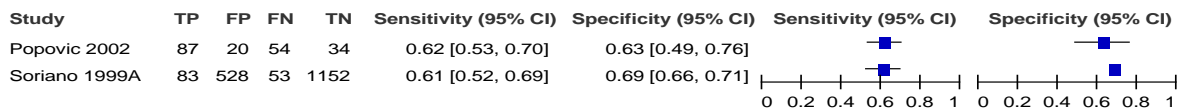
3

Figure 99: *Alternaria temius* (mould)



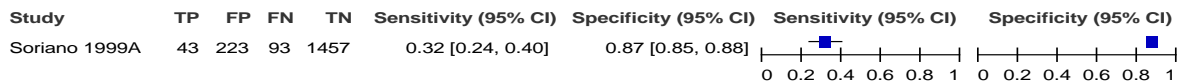
4

Figure 100: ≥ 1 positive from mixed allergens (mite and grass, plus ≥ 1 more of weed, tree, dust, cat, dog, feathers, mould, egg, milk)



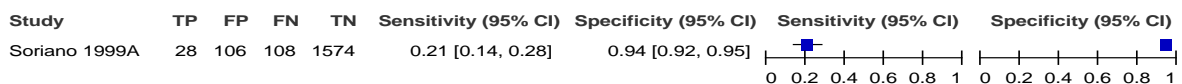
5

Figure 101: Grasses mixed or timothy only



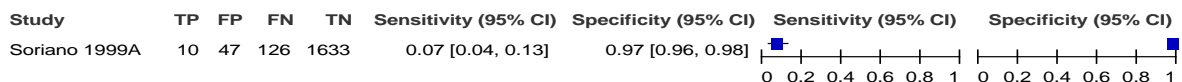
6

Figure 102: Cat



7

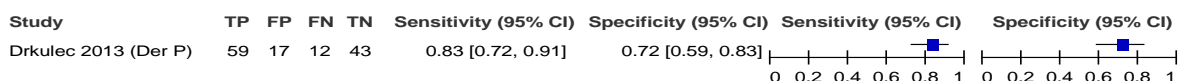
Figure 103: *Cladosporium*



8

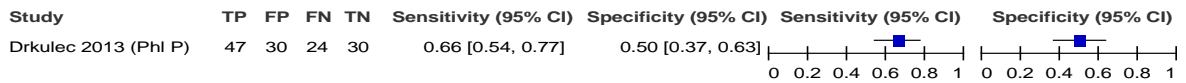
9 J.8.1.2 Skin prick tests vs. Physician Dx with objective test: CHILDREN 5-16 years

Figure 104: *D. pteronyssinus* (Der P) +/- *D. farinae* (house dust mite)



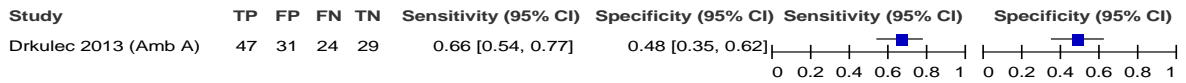
10

Figure 105: Phleum pratense (Phl P) timothy grass from Gramineae family



1

Figure 106: Ambrosia artemisifoliae (Amb A) common ragweed



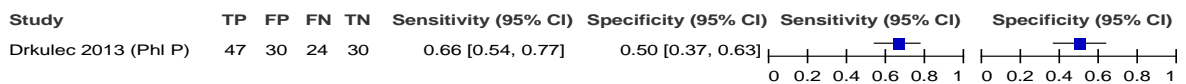
2

Figure 107: ≥1 positive from mixed allergens (mite and grass, plus ≥1 more of weed, tree, dust, cat, dog, feathers, mould, egg, milk)



3

Figure 108: Grasses mixed or timothy only



4

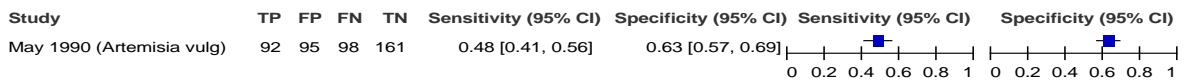
5 J.8.1.3 Skin prick tests vs. Physician Dx *without* objective test: ADULTS

Figure 109: Gramineae (grasses) both wild and cultivated



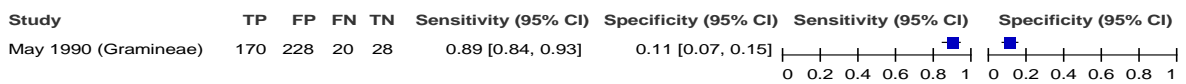
6

Figure 110: Artemisia vulgaris (mugwort)



7

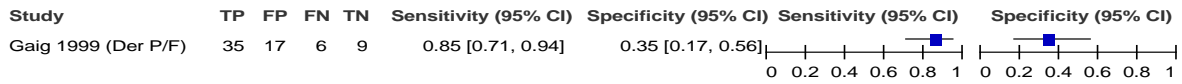
Figure 111: Grasses mixed or timothy only .



8

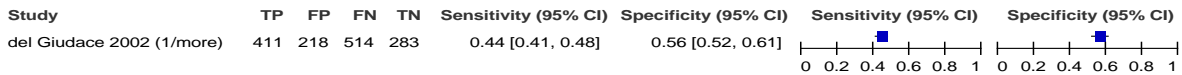
1 J.8.1.4 Skin prick tests vs. Physician Dx *without* objective test: CHILDREN 5-16 years

Figure 112: D. pteronyssinus (Der P) +/- D. farinae (house dust mite)



2

Figure 113: ≥1 positive from mixed allergens (mite and grass, plus ≥1 more of weed, tree, dust, cat, dog, feathers, mould, egg, milk).



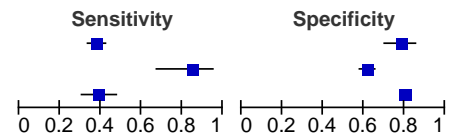
3 J.9 Diagnosis: IgE

4 J.9.1.1 Adults: IgE vs. Physician Dx

Figure 114: DUST MITE specific IgE

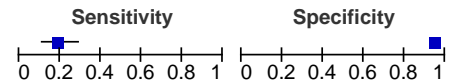
Dust mite IgE vs Physician (≥0.35 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Abraham 2007	187	27	306	97	0.38 [0.34, 0.42]	0.78 [0.70, 0.85]
Linneberg 2006	27	260	5	417	0.84 [0.67, 0.95]	0.62 [0.58, 0.65]
Soriano 1999	53	336	83	1344	0.39 [0.31, 0.48]	0.80 [0.78, 0.82]



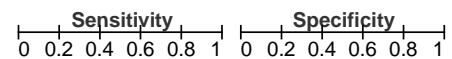
Dust mite vs. Physician Dx (≥0.70 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Plaschke 1999	16	86	68	1402	0.19 [0.11, 0.29]	0.94 [0.93, 0.95]



Dust mite vs. Physician Dx (≥100 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity
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Dust mite IgE vs. Physician Dx (unclear cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity
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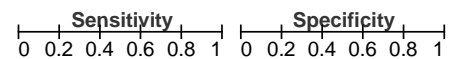
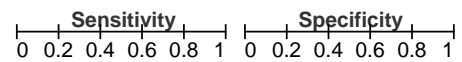


Figure 115: BIRCH specific IgE

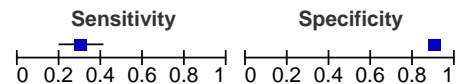
Birch IgE vs. Physician Dx (≥ 0.35 cut-off)

Study TP FP FN TN Sensitivity Specificity



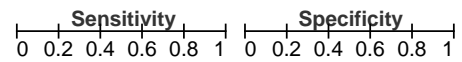
Birch IgE vs. Physician Dx (≥ 0.70 cut-off)

Study TP FP FN TN Sensitivity Specificity
Plaschke 1999 25 155 59 1333 0.30 [0.20, 0.41] 0.90 [0.88, 0.91]



Birch IgE vs. Physician Dx (≥ 100 cut-off)

Study TP FP FN TN Sensitivity Specificity



Birch IgE vs. Physician Dx (unclear cut-off)

Study TP FP FN TN Sensitivity Specificity

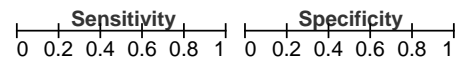
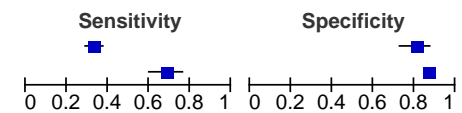


Figure 116: GRASSspecific IgE

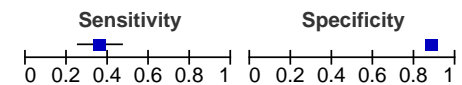
Grass IgE vs. Physician Dx (≥ 0.35 cut-off)

Study TP FP FN TN Sensitivity Specificity
Abraham 2007 164 24 329 100 0.33 [0.29, 0.38] 0.81 [0.73, 0.87]
Soriano 1999 93 223 43 1457 0.68 [0.60, 0.76] 0.87 [0.85, 0.88]



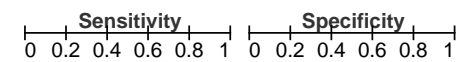
Grass IgE vs. Physician Dx (≥ 0.70 cut-off)

Study TP FP FN TN Sensitivity Specificity
Plaschke 1999 30 187 54 1301 0.36 [0.26, 0.47] 0.87 [0.86, 0.89]



Grass IgE vs. Physician Dx (≥ 100 cut-off)

Study TP FP FN TN Sensitivity Specificity



Grass IgE vs. Physician Dx (unclear cut-off)

Study TP FP FN TN Sensitivity Specificity

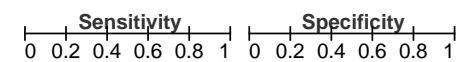
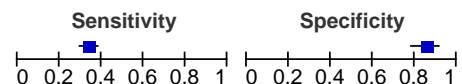


Figure 117: ALTERNARIAspecific IgE

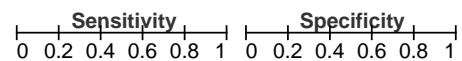
Alternaria IgE vs. Physician Dx (≥ 0.35 cut-off)

Study TP FP FN TN Sensitivity Specificity
Abraham 2007 167 18 326 106 0.34 [0.30, 0.38] 0.85 [0.78, 0.91]



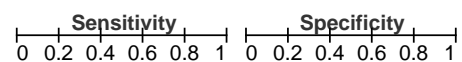
Alternaria IgE vs. Physician Dx (≥ 0.70 cut-off)

Study TP FP FN TN Sensitivity Specificity



Alternaria IgE vs. Physician Dx (≥ 100 cut-off)

Study TP FP FN TN Sensitivity Specificity



Alternaria IgE vs. Physician Dx (unclear cut-off)

Study TP FP FN TN Sensitivity Specificity

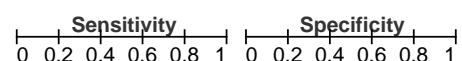
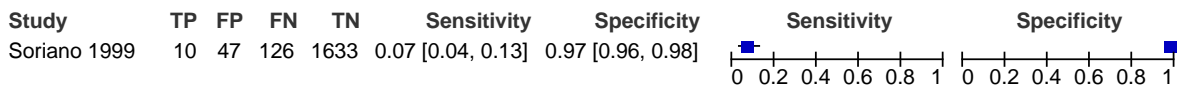
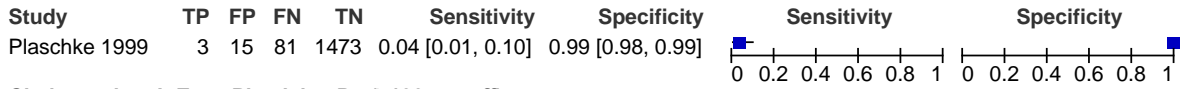


Figure 118: CLADOSPORIUM specific IgE

Cladosporium IgE vs. Physician Dx (≥ 0.35 cut-off)



Cladosporium IgE vs. Physician Dx (≥ 0.70 cut-off)



Cladosporium IgE vs. Physician Dx (≥ 100 cut-off)



Cladosporium IgE vs. Physician Dx (unclear cut-off)

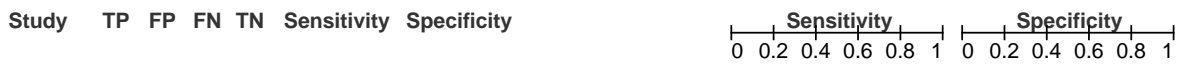
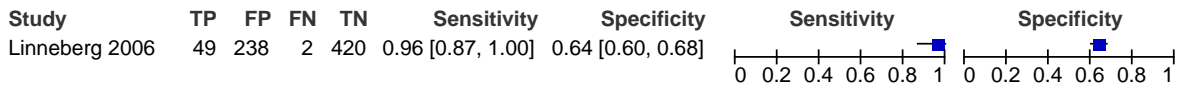


Figure 119: POLLEN specific IgE

Pollen IgE vs. Physician Dx (≥ 0.35 cut-off)



Pollen IgE vs. Physician Dx (≥ 0.70 cut-off)



Pollen IgE vs. Physician Dx (≥ 100 cut-off)



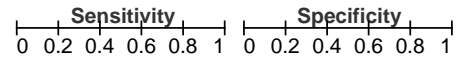
Pollen IgE vs. Physician Dx (unclear cut-off)



Figure 120: TOTAL IgE

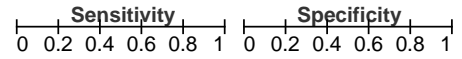
Total IgE vs. Physician Dx (≥ 0.35 cut-off)

Study TP FP FN TN Sensitivity Specificity



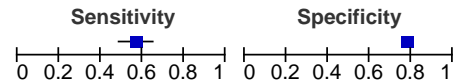
Total IgE vs. Physician Dx (≥ 0.70 cut-off)

Study TP FP FN TN Sensitivity Specificity



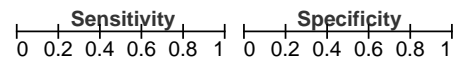
Total IgE vs. Physician Dx (≥ 100 cut-off)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Tschopp 1998	87	1807	66	6309	0.57 [0.49, 0.65]	0.78 [0.77, 0.79]



Total IgE vs. Physician Dx (unclear cut-off)

Study TP FP FN TN Sensitivity Specificity



1 **Figure 121: Cat IgE**

Cat IgE vs. Physiican Dx (≥ 0.35 cut-off)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Abraham 2007	49	60	75	433	0.40 [0.31, 0.49]	0.88 [0.85, 0.91]		
Soriano 1999	27	106	109	1574	0.20 [0.14, 0.28]	0.94 [0.92, 0.95]		

Cat IgE vs. Physician Dx (≥ 0.70 cut-off)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Plaschke 1999	34	140	50	1348	0.40 [0.30, 0.52]	0.91 [0.89, 0.92]		

2
3 **Figure 122: Dog IgE**

Dog IgE vs. Physician Dx (≥ 0.35 cut-off)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Abraham 2007	42	61	82	432	0.34 [0.26, 0.43]	0.88 [0.84, 0.90]		

Dog IgE vs. Physician Dx (≥ 0.70 cut-off)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)

4
5

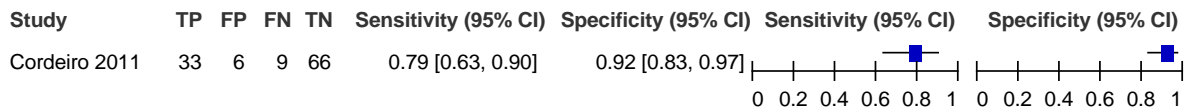
1 J.10 Diagnosis: FeNO

2.10.1.1 Coupled sensitivity / specificity forest plots and ROC curves

3 Forest plots: FeNO vs. Physician Dx with objective test

4 Adults

5 Figure 123: FeNO >27ppb



6

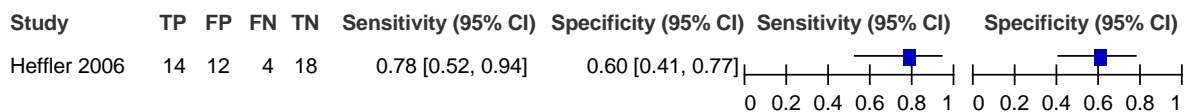
7 ADULTS: FeNO >30ppb

8 Voutilainen 2013. Number of TP, FP, FN and TN not provided.

9 Sensitivity: 43.0%; Specificity: 89.0%

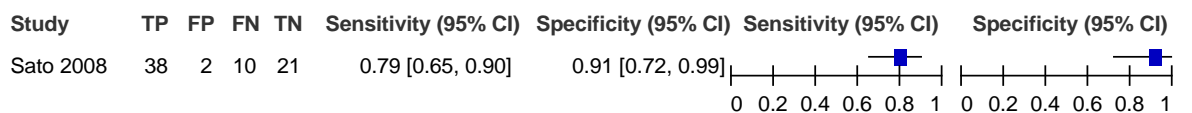
10

11 Figure 124: FeNO >36ppb



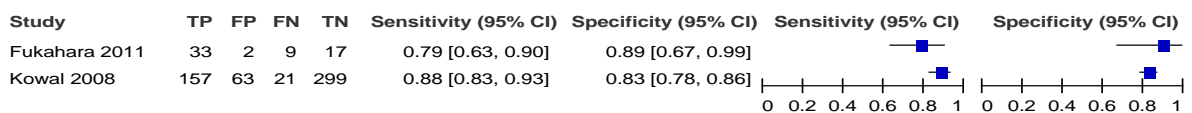
12

13 Figure 125: FeNO >38.8ppb



14

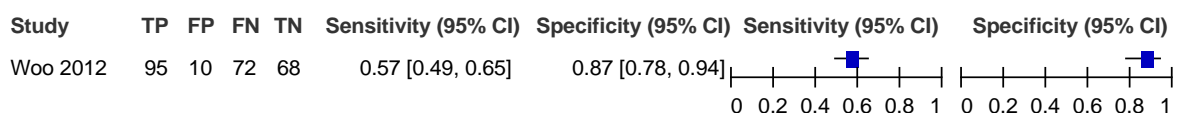
15 Figure 126: ADULTS: FeNO >40ppb



16

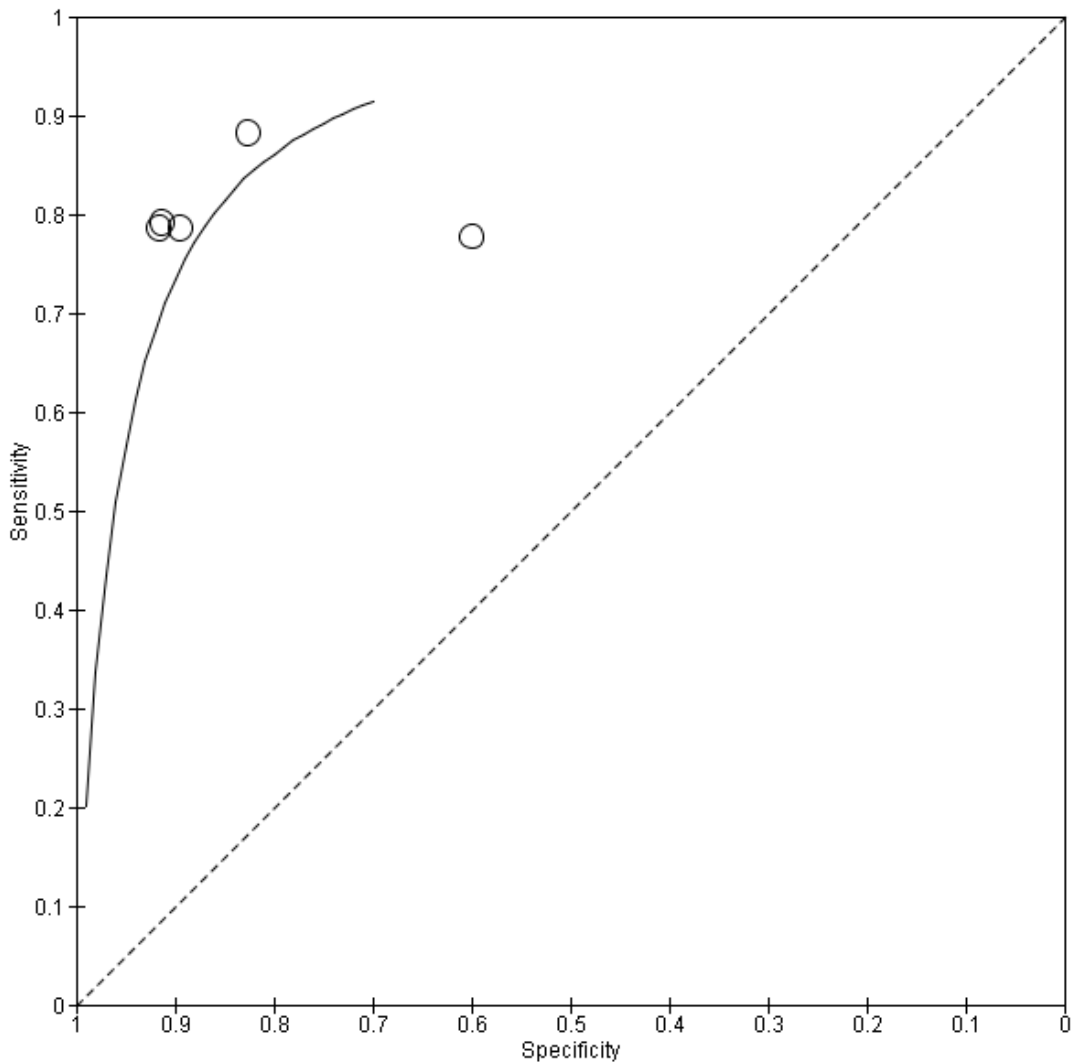
17 Children

18 Figure 127: CHILDREN: FeNO >22ppb



19

1 **Summary ROC Curve (fitted at a variety of test thresholds, selecting one threshold per study):**
 2 **Adults only**



3
4

5 **Forest plots: FeNO vs. other tests**

6 ADULTS:

7 **Figure 128: Adults: FeNO >30ppb versus methacholine ≤8mg/mL**

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chatkin 1999	6	4	2	26	0.75 [0.35, 0.97]	0.87 [0.69, 0.96]		

8

FeNO levels

Table 203: FeNO levels – medians and means presented

Reference	Population and mean or median FeNO levels (ppb)								
	Asthma (bronchial, allergic or non-allergic)	Chronic cough	Bronchitis	Eosinophilic bronchitis	Rhinitis	GERD	Mixed non-asthma Dx	Healthy	Cough variant asthma
BERLYNE 2000	39	-	-	65.0	-	-	-	10	-
CARDINALE 2005	22.7 (children)	-	-	-	15.3 (children)	-	-	5.9 (children)	-
CHATKIN 1999** (also c-c study)	75.0	16.7	-	-	-	-	-	28.3	-
CIPRANDI 2013^	34 (children)	-	-	-	27 children	-	-	-	-
CORDEIRO 2011** [§]	44	-	-	-	21	-	17	-	-
DEYKIN 2002	57.9	-	-	-	-	-	-	26.3	-
FUKHARA 2011**	90.1	-	-	-	-	-	40.1	-	-
HEFFLER 2006** [§] (also c-c study)	59.7	-	-	-	-	-	30.4	12.2	-
KOSTIKAS 2008** [£] (also c-c study)	24.0	-	-	-	17.5	-	11.0	11.0	-
KOWAL 2008** (also c-c study)	86	-	-	-	37	14.8	-	13	-
LOUHELAINEN 2008A	35.5 (children) 81.8 (adult)	- -	- -	-	-	-	-	11.9 (children) 16.6 (adult)	-
SATO 2008**	93.5	-	16.4	-	-	-	21.2	-	-
SHIMODA 2013	92.6	-	-	-	-	-	-	18.0	35.6
SHOME 2006	24.8	-	-	-	-	-	-	5.9	-
WOO 2012**	23.4 (children)	-	-	-	-	-	12.6 (children)	-	-
VOUTILAINEN 2013** [§]	29.7	-	-	-	-	-	14.6	-	-
ZIETKOWSKI 2006A	64.9	-	-	-	-	-	-	12.9	-

Reference	Population and mean or median FeNO levels (ppb)								
	Asthma (bronchial, allergic or non-allergic)	Chronic cough	Bronchitis	Eosinophilic bronchitis	Rhinitis	GERD	Mixed non-asthma Dx	Healthy	Cough variant asthma
MEDIAN (range) ALL	50.95 (22.7-93.5)	16.7	16.4	65.0	21.0 (15.3-37.0)	14.8	17.0 (11.0-40.1)	12.6 (5.9-28.3)	35.6
MEDIAN (range) Adults/mixed	62.3 (24.0-93.5)	16.7	16.4	65.0	27 (17.5-37)	14.8	19.1 (11.0-40.1)	13.0 (5.9-28.3)	35.6
MEDIAN (range) Children only	28.7 (22.7-35.5)	-	-	-	21.2 (15.3-27)	-	12.6	8.9 (5.9-11.9)	-

- (a)** ** is a sens/spec study
- (b)** ^all patients have allergy (positive skin prick test)
- (c)** \$ mixed population of adults and children
- (d)** £ excluding smokers

1 J.11 Diagnosis: Eosinophils

2.11.1.1 ADULTS: PBE vs. Physician Dx

Figure 129: PBE ≥4.15%

TILEMANN 2011: 2x2 table not reported. Sensitivity 36%, specificity 83%

Figure 130: PBE cut-off not reported

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
POPOVIC 2002	21	33	120	21	0.15 [0.09, 0.22]	0.39 [0.26, 0.53]		

3.11.1.2 Children 5-16 years: PBE vs. Physician Dx

Figure 131: PBE >4%

SHIELDS 1999: 2x2 table not reported. Sensitivity 62%, specificity 67%

Figure 132: PBE >8%

SHIELDS 1999: 2x2 table not reported. Sensitivity 38%, specificity 93%

Figure 133: PBE ≥0.45 x 10⁹/l

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
KOTANIEMI 2002	18	8	15	41	0.55 [0.36, 0.72]	0.84 [0.70, 0.93]		

4.11.1.3 PBE counts

5 Table 204: Adults: PBE counts

Study	N	Counts	Units
PBE counts only			
BACKER 2002	624 (N=103 asthma)	Non-asthma: 0.19 Asthma: 0.26	x10 ⁹ /L
HALVANI 2012	98 (N=61 asthma)	Healthy: 0.21 Asthma ICS: 0.40 Asthma no ICS: 0.52	x10 ⁹ /L
HUNTER 2002	110 (N=89 asthma)	Healthy: 1.9 Pseudoasthma: 2.0 Asthma: 4.3	%
KHAKZAD 2009	62 (N=50 asthma)	Healthy: 1.2 All asthma: 1.0 Mild intermittent: 2.0 Mild persistent: 3.6 Moderate persistent: 3.2 Severe: 3.2	%
KROEGEL 1998	56 (N=14 asthma)	Healthy: 0.10 Bronchiectasis: 0.10	x10 ⁹ /L median

Study	N	Counts	Units
		COPD: 0.12 Allergic asthma: 0.31	
METSO 2000	190 (N=160 asthma)	Healthy: 0.13 Pre-Tx 1: 0.11 Pre-Tx 2: 0.14 Pre-Tx 3: 0.12	x10 ⁹ /L
RYTILA 2000	68 (N=25 asthma)	Healthy: 0.11 Symptomatic: 0.17 All asthma: 0.41 Atopic asthma: 0.51 Non-atopic asthma: 0.27	x10 ⁹ /L
TOMASIAKLOZOWS KA 2012	110 (N=91 asthma)	Healthy: 32.0 A stable – no ICS: 29.5 A stable - ICS: 42.4 A unstable – ICS: 49.8	cells/mm ³
ZIETKOWSKI 2006A	140 (N=101 asthma)	Healthy: 119 A allergic: 247 A non-allergic: 211	cells/mm ³
Median (range)	Asthma	0.29 (0.10 - 0.52) 3.2 (2.0 – 4.3)	x10⁹/L %
	Non-asthma**	0.13 (0.10 – 0.21) 1.9 (1.2 – 2.0)	x10⁹/L %
Median (range)	A – allergic	0.41 (0.31 – 0.51)	x10⁹/L
	A – non allergic	0.27 (0.27)	x10⁹/L
Other results:	<ul style="list-style-type: none"> • 1 study showed that >50% of pts had PBE count >0.45 x10⁹/L. • 2 studies showed that patients with asthma had higher PBE counts (cells/mm³) than healthy controls (although stable asthma without ICS Tx was similar to healthy controls in 1 study). • 1 study showed that patients with allergic asthma had higher PBE counts (cells/mm³) than patients with non-allergic asthma. • 1 study showed that patients with asthma treated with ICS had higher PBE counts (cells/mm³) than patients with asthma not treated with ICS (regardless of whether the asthma was stable or unstable). 		

1 ICS = inhaled corticosteroid; A = allergic; Tx = treatment. *where applicable, all units have been converted into x10⁹/L as
2 these are the standard units used in current UK clinical practice. **this includes healthy controls

3

4 **Table 205: Children 5-16 years: PBE counts**

Study	N	Counts	Units*	
PBE counts only				
LABBE 2001	143 (N=88 asthma)	Healthy: 0.25 Chronic cough: 0.21 Asthma: 0.40	x10 ⁹ /L	Children (mean 7 yrs)

Study	N	Counts	Units*	
NORDLUND 2012	39	Asthma (mild/mod): 0.25	$\times 10^9/L$	Children (mean 14 yrs)
SILVESTRI 2001A	112	Allergic: 500, 7.5% Non-allergic: 125, 2.5%	Cells/mm ³ and %	Children (mean 11 yrs)
SILVESTRI 2003	92	All: 5.5% Atopic: 6.7% Non-atopic: 3.0%	%	Children (mean 11 yrs)
TUCHINDA 1987	1000	0 – 500 = 40% 501-1000 = 29% 1001-1500 = 16% 1501-2000 = 9% >2000 = 7%	Cells/mm ³	Children <13 years (mean not reported)
VILA-INDURAIN 1999	57 (N=36 asthma)	• Healthy: 161 • Asthma (norm FEV ₁): 509 • Asthma (< norm FEV ₁ , norm with SABA): 397 • Asthma (< norm FEV ₁ , not norm with SABA): 319	Cells/mm ³	Children (8-18 yrs, mean not reported)
Mean (range)	Asthma	0.33 (0.25 – 0.40)	$\times 10^9/L$	
	Non-asthma**	5.5 (5.5)	%	
		0.23 (0.21 – 0.25)	$\times 10^9/L$	
		-	%	
	A – allergic	-	$\times 10^9/L$	
		7.1 (6.7 – 7.5)	%	
	A - nonallergic	-	$\times 10^9/L$	
		2.8 (2.5 – 3.0)	%	
Other results:	<ul style="list-style-type: none"> • 1 study showed that the % of pts decreased with increasing PBE cell counts (0-500 cells/mm³ had the most pts, with >2000 cells/mm³ having the least). • 1 study showed that patients with asthma had higher PBE counts (cells/mm³) than healthy controls • 1 study showed that patients with allergic asthma had higher PBE counts (cells/mm³) than patients with non-allergic asthma • 1 study showed that patients with asthma with a normal FEV₁ had higher PBE counts (cells/mm³) than patients with asthma with <normal FEV₁ (regardless of whether the FEV₁ normalised with SABA). 			

1 SABA = short-acting beta-agonists; *where applicable, all units have been converted into $\times 10^9/L$ as these are the standard
2 units used in current UK clinical practice. **this includes healthy controls

3

4 **Table 206: Children <5 years: PBE counts**

Study	N	Counts	Units	
PBE counts only				
PIIPPOSAVOLLAINE N 2007	83	Asthma: 0.1	$10^9/L$	Children (<2 yrs, mean not reported)

Study	N	Counts	Units
Median		Asthma 0.1	10 ⁹ /L
Range of means		Asthma 0.1	10 ⁹ /L

1 J.12 Diagnosis: Histamine and methacholine challenge tests

2.12.1.1 Coupled sensitivity / specificity forest plots and ROC curves

3 Adults: Methacholine/Histamine Challenge Tests vs Reference Standard

Figure 134: PC20 ≤8mg/ml

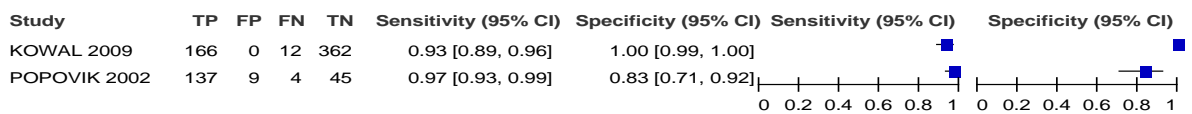


Figure 135: PD20 ≤6900µg

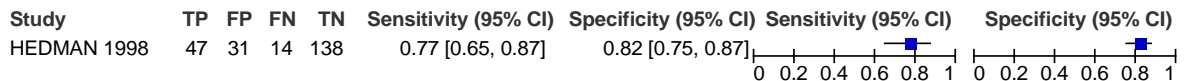
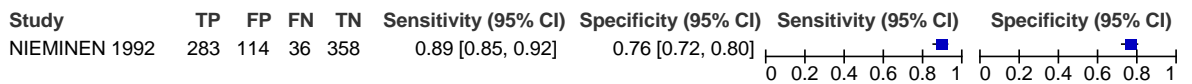


Figure 136: PD20 ≤2600µg



4

Children: Methacholine/Histamine Challenge Tests vs Reference Standard

Figure 137: Age <18 yrs- PC20 ≤16mg/ml

Data unsuitable for RevMan:

ANDERSON 2009 (n=115; MCT cut-off 16mg/ml): Sensitivity 66.2%; Specificity = 62.9%

Methacholine/Histamine Challenge Tests vs Other Tests

Figure 138: Histamine Challenge Test vs Mannitol (adults)- PD15≤1mg

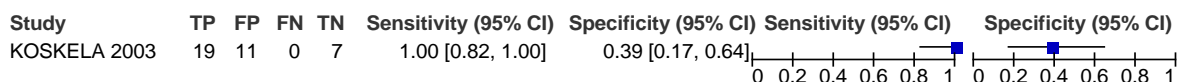


Figure 139: Histamine Challenge Test vs Mannitol (adults) - PD15≤0.4mg

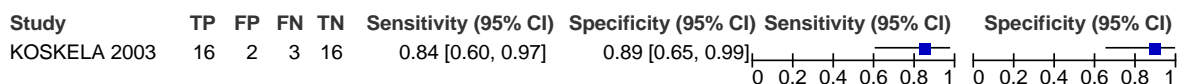


Figure 140: Histamine Challenge Test vs Mannitol (<18 yrs)

1 No data found on sensitivity or specificity

2 J.13 Diagnosis: Mannitol challenge test

3.13.1.1 Coupled sensitivity / specificity forest plots

4 Mannitol Challenge Test vs Reference Standard

Figure 141: Mannitol Challenge Test vs Reference Standard (all age groups) $\geq 15\%$ fall in FEV1 ≤ 635 mg or 10% fall between consecutive doses

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
ANDERSON 2009	134	34	106	101	0.56 [0.49, 0.62]	0.75 [0.67, 0.82]		

Figure 142: Mannitol Challenge Test vs Reference Standard (<18 yrs) $\geq 15\%$ fall in FEV1 ≤ 635 mg or 10% fall between consecutive doses

Data unsuitable for RevMan:

1. ANDERSON 2009: Sensitivity 63.2%; Specificity = 81.4%

5

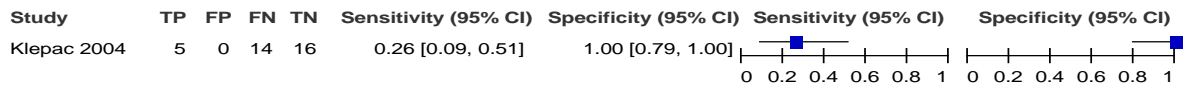
6

1 J.14 Diagnosis: Exercise challenge test

2

3.14.1.1 Exercise test vs. Physician Dx: ADULTS

Figure 143: Exercise test Δ FEV1 \geq 10%

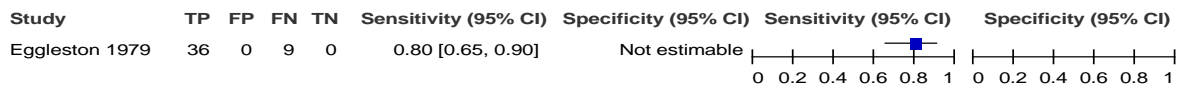


4

5.14.1.2 Exercise test vs. other tests: ADULTS

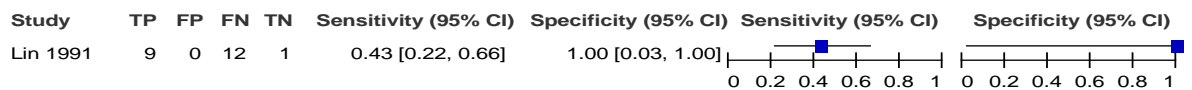
6

Figure 144: Exercise test Δ FEV1 \geq 18% vs. methacholine



7

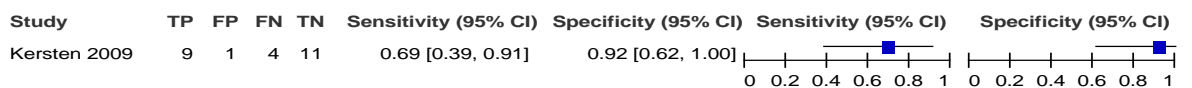
Figure 145: Exercise test Δ FEV1 \geq 20% vs. methacholine



8.14.1.3 Exercise test vs. other tests: CHILDREN 5-16 years

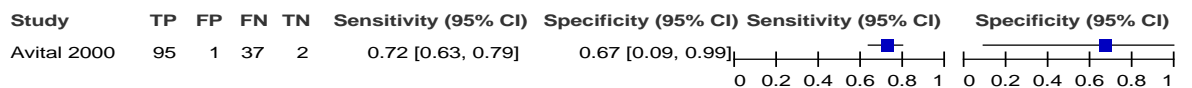
9

Figure 146: Cold air exercise test Δ FEV1 % init $>$ 15% vs. mannitol Δ FEV1 % init $>$ 15%.



10

Figure 147: Exercise Δ FEV1 \geq 8.2% vs. methacholine PC20 \leq 8mg/mL



11

12

1 J.15 Monitoring: Questionnaires

2.15.1.1 Children (5-16 years) with uncontrolled asthma: Monitoring questionnaires + treatment vs UC + treatment.

3

Figure 148: QOL <6 months (PAQLQ; scale 1-7)

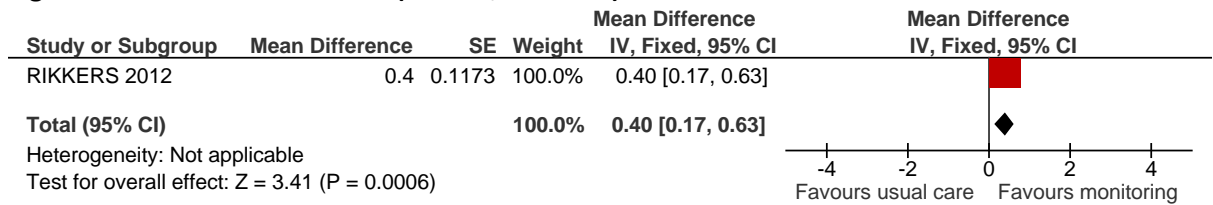


Figure 149: QOL ≥6 months (PAQLQ; range 1-7)

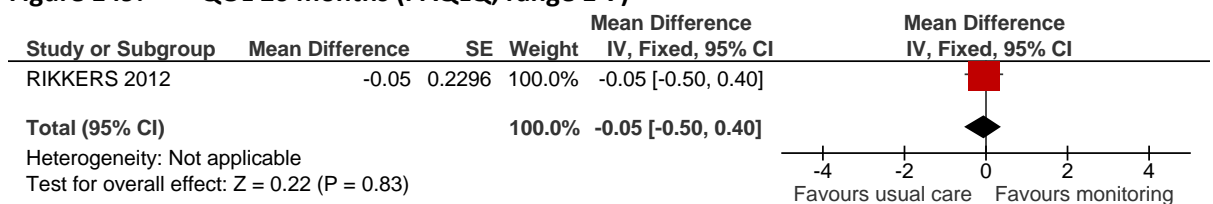


Figure 150: Exacerbations (OCS) ≥6 months

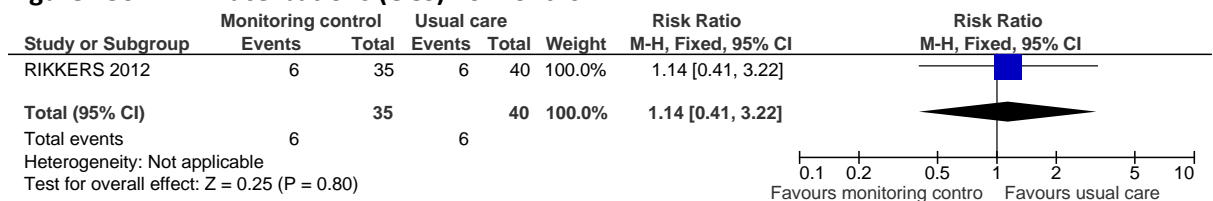


Figure 151: Asthma control <6 months (ACQ, range 0-6)

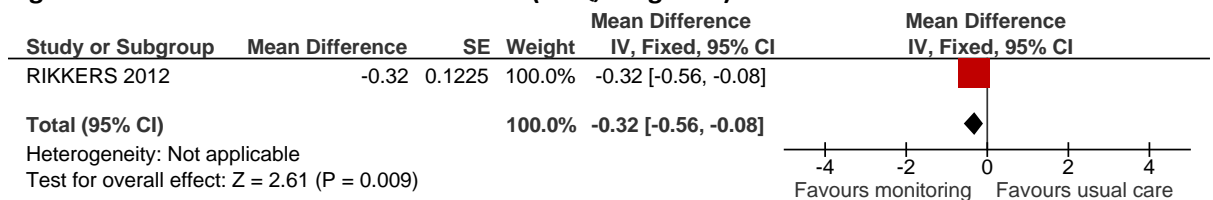


Figure 152: Asthma control ≥6 months (ACQ, range 0-6)

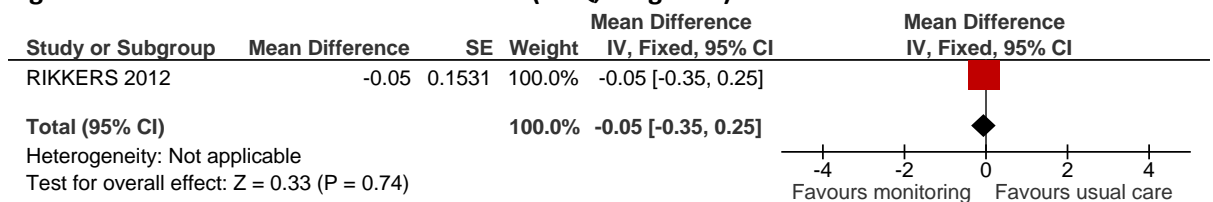


Figure 153: Lung Function <6 months (FEV1 L)

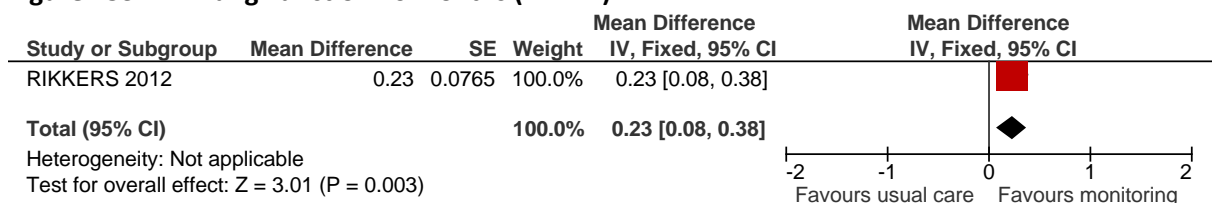


Figure 154: Lung Function ≥ 6 months (FEV1 L)

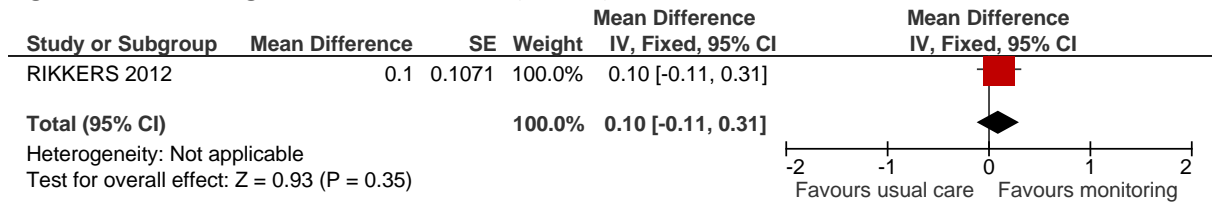


Figure 155: Symptom free days < 6 months (% over 2 weeks)

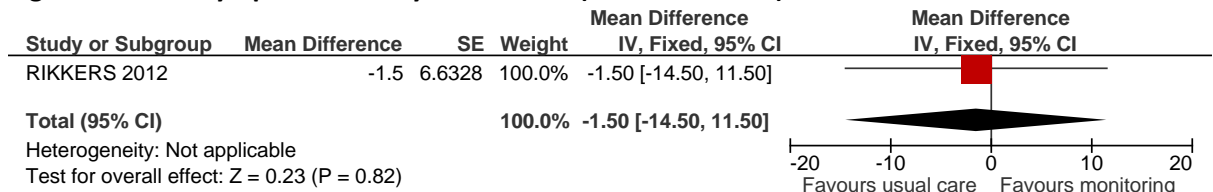


Figure 156: Symptom free days ≥ 6 months (% over 2 weeks)

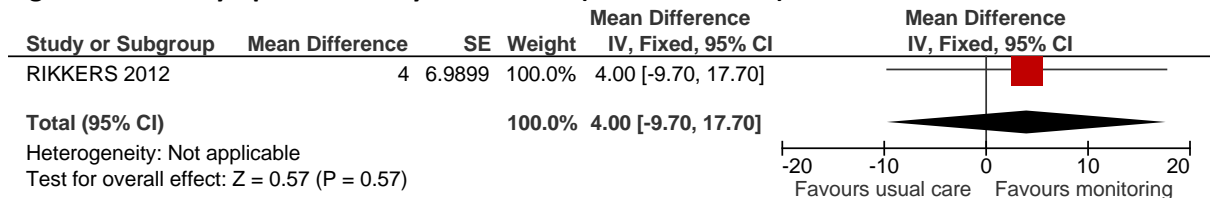


Figure 157: ICS use < 6 months (mean daily dose)

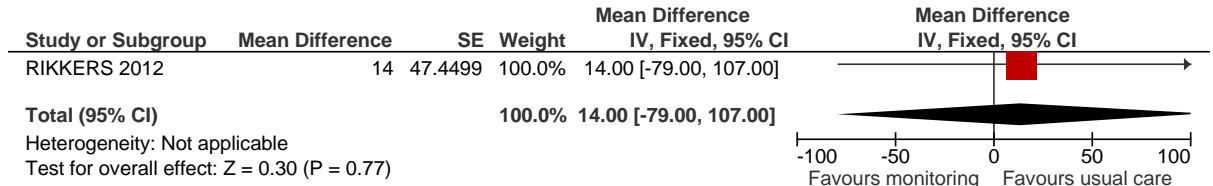
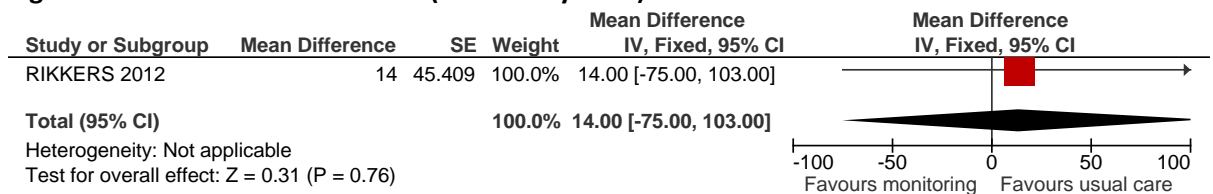


Figure 158: ICS use ≥ 6 months (mean daily dose)



1

2.15.1.2 Adults and young people (> 16 years) overall: Monitoring questionnaires + treatment vs UC + treatment.

3

Figure 159: QOL ≥ 6 months (PAQLQ; range 1-7)

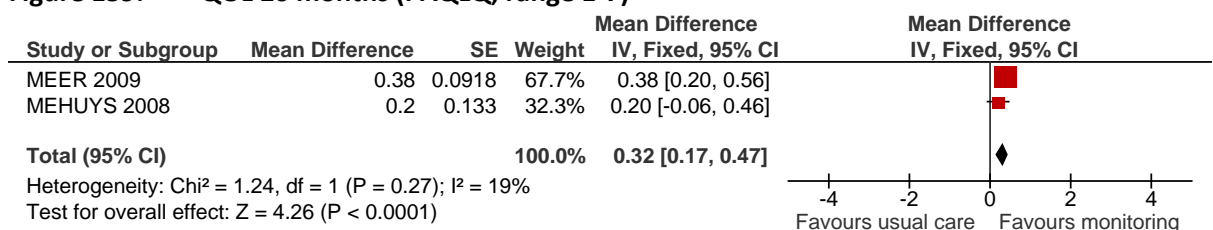


Figure 160: Exacerbations (OCS) ≥6 months

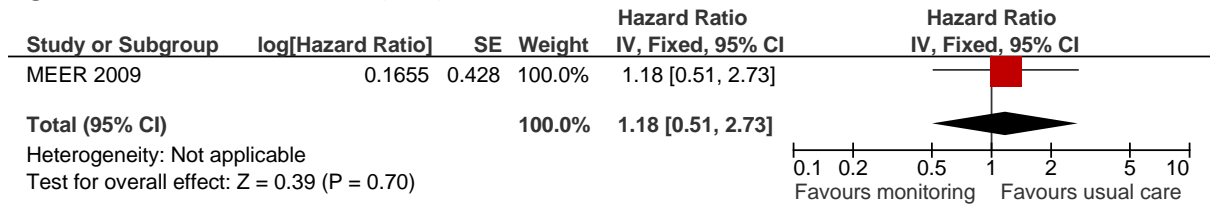


Figure 161: Exacerbations (OCS, ER or hospitalisation) ≥6 months

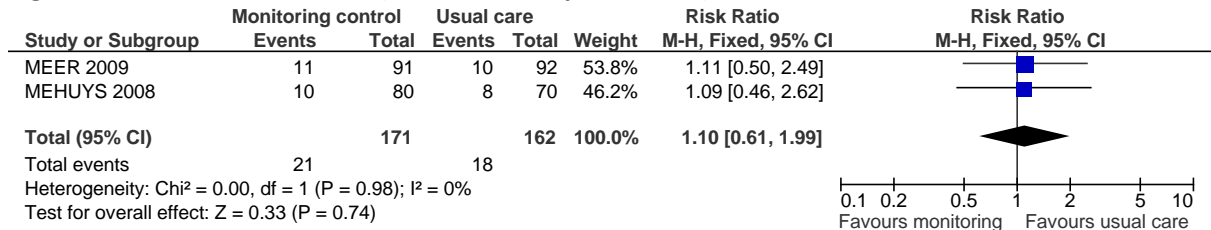


Figure 162: UHU (ER or hospitalisation) ≥6 months

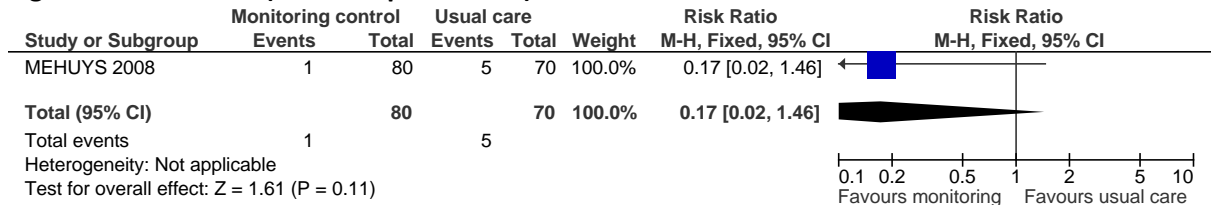


Figure 163: Asthma control <6 months (ACT, range 5-25)

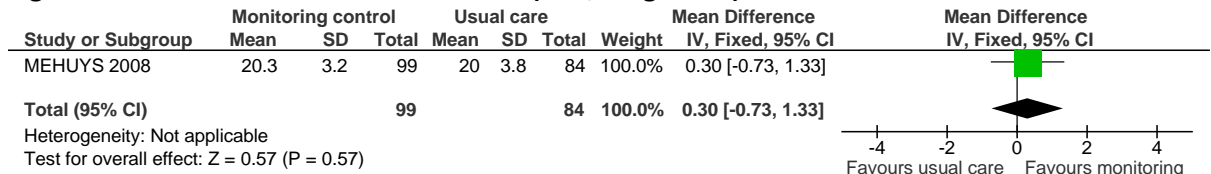


Figure 164: Asthma control ≥6 months (ACT, range 5-25)

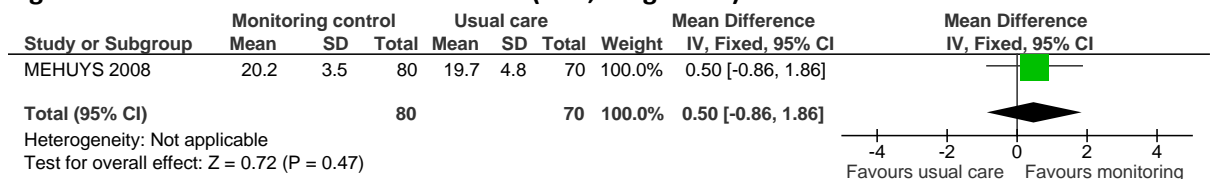


Figure 165: Asthma control ≥6 months (ACQ, range 0-6)

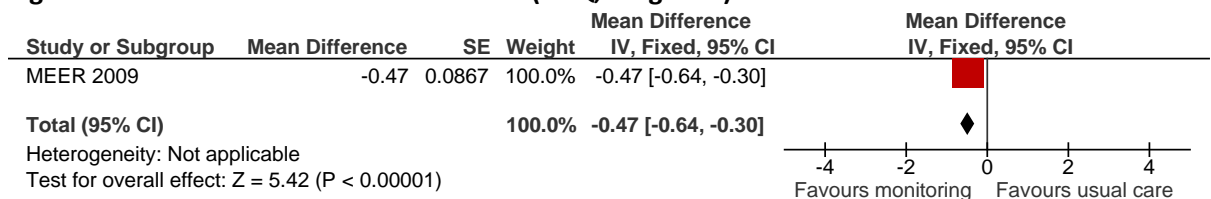


Figure 166: Lung Function ≥6 months (FEV1 L)

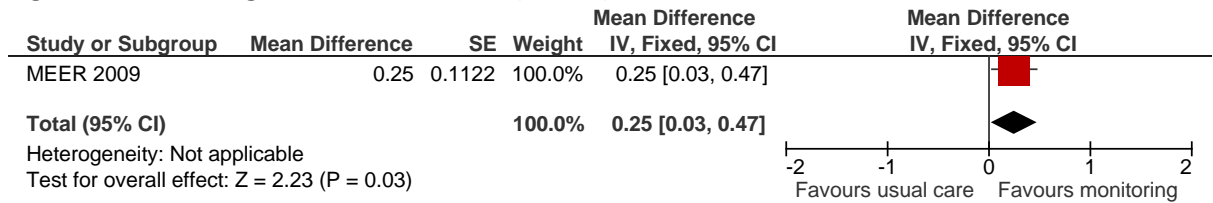
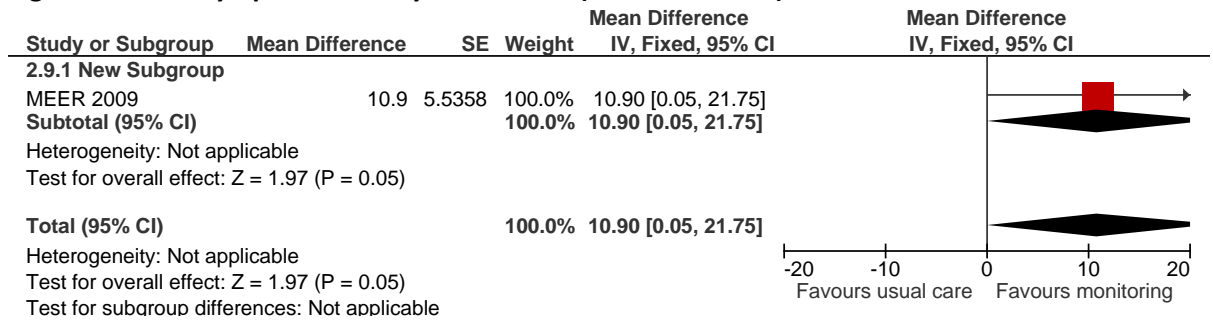


Figure 167: Symptom free days ≥6 months (% over 2 weeks)



1

Figure 168: ICS use ≥6 months (mean daily dose)

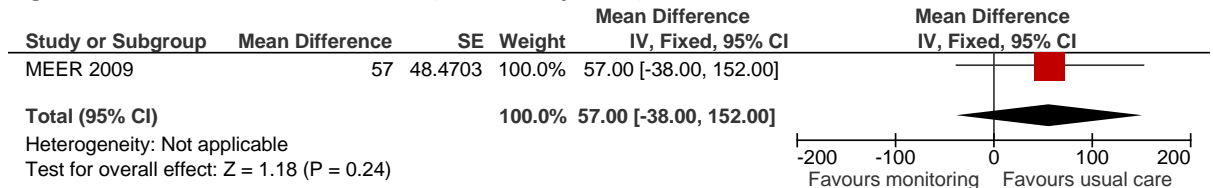


Figure 169: Rescue medication <6 months (mean puffs/day)

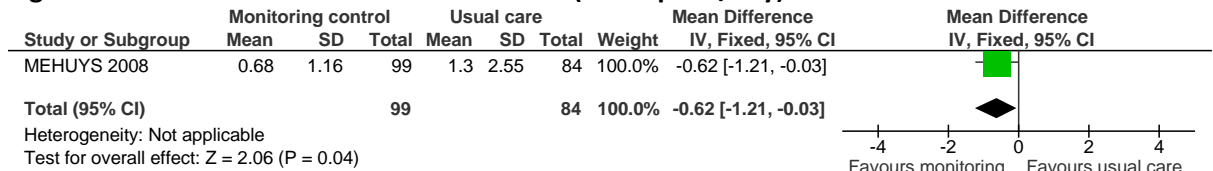
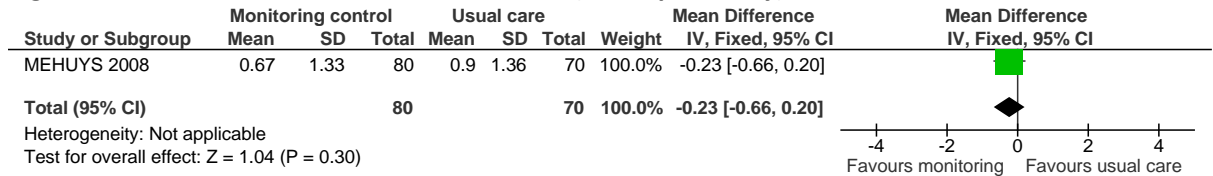


Figure 170: Rescue medication ≥6 months (mean puffs/day)



2

3

1 J.16 Monitoring: Lung function test

2.16.1.1 Adults: Monitoring PEF versus symptom monitoring

Figure 171: QOL ≥6 months (AQLQ increase more than 0.5 points)

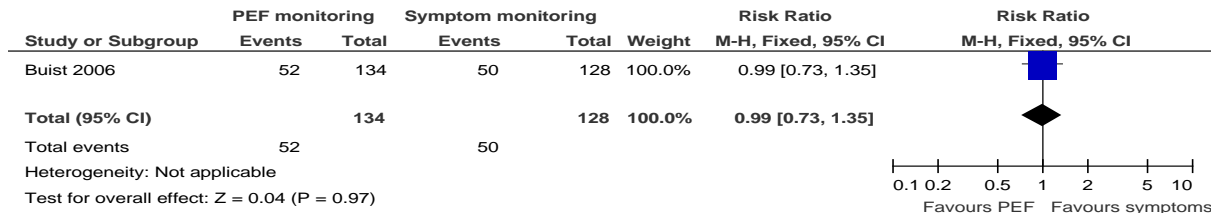


Figure 172: QOL ≥6 months (AQLQ decrease more than 0.5 points)

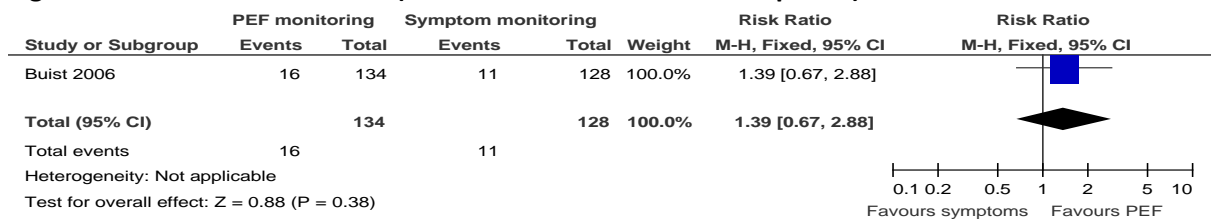


Figure 173: Exacerbations ≥6 months (OCS)

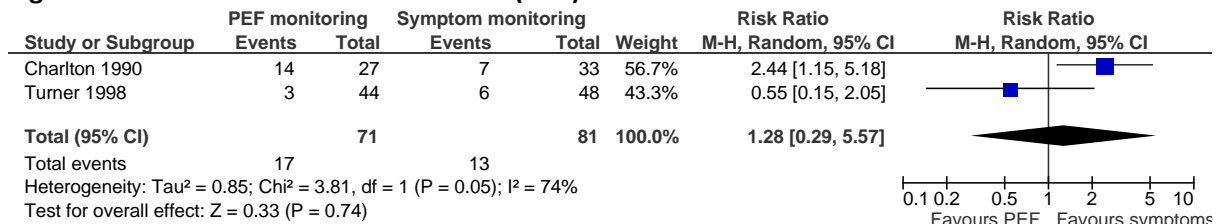


Figure 174: Exacerbations ≥6 months (no. of OCS courses)

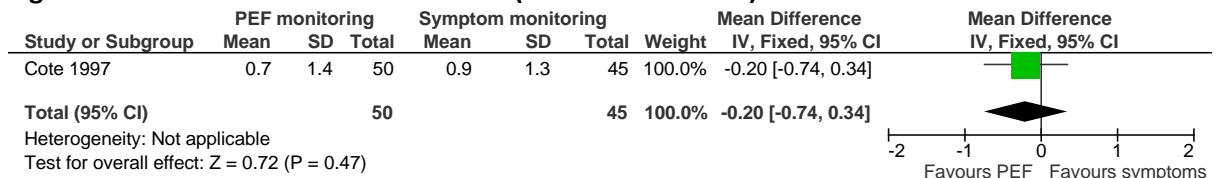


Figure 175: UHU ≥6 months (total asthma-related health care utilisation)

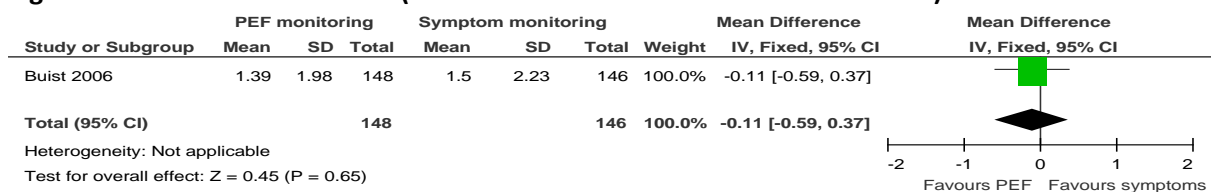


Figure 176: UHU ≥6 months (Hospitalisation)

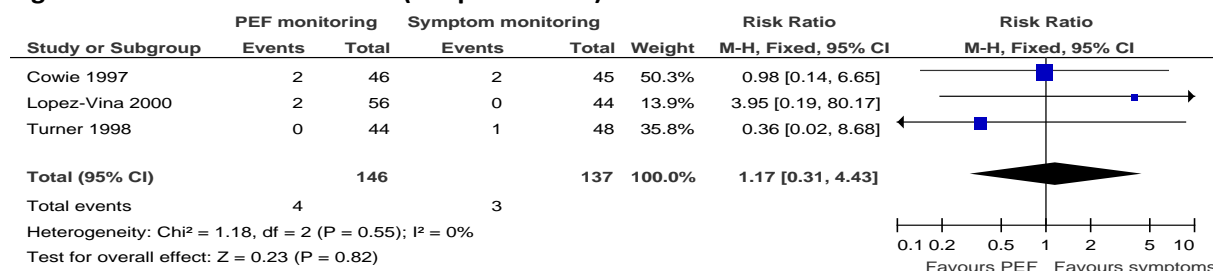


Figure 177: UHU ≥6 months (mean number of hospital admissions)

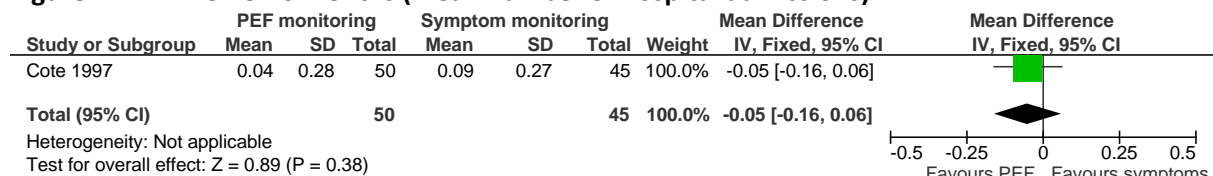


Figure 178: UHU ≥6 months (mean number of days of hospitalisation)

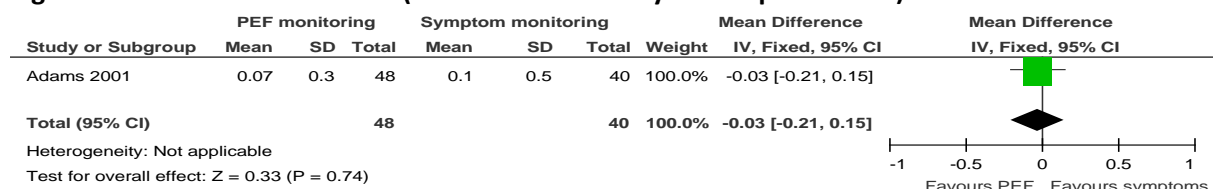


Figure 179: UHU ≥6 months (ED visits)

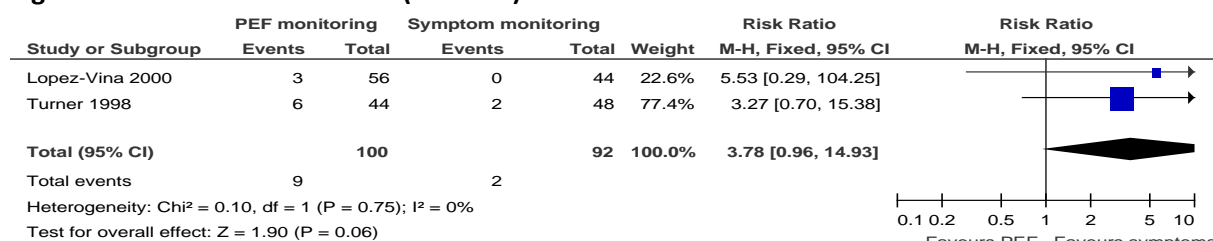


Figure 180: UHU ≥6 months (mean number of ED visits)

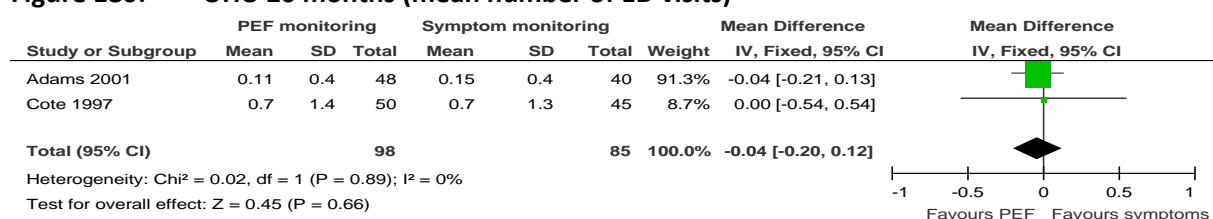


Figure 181: UHU ≥6 months (unscheduled doctors visits)

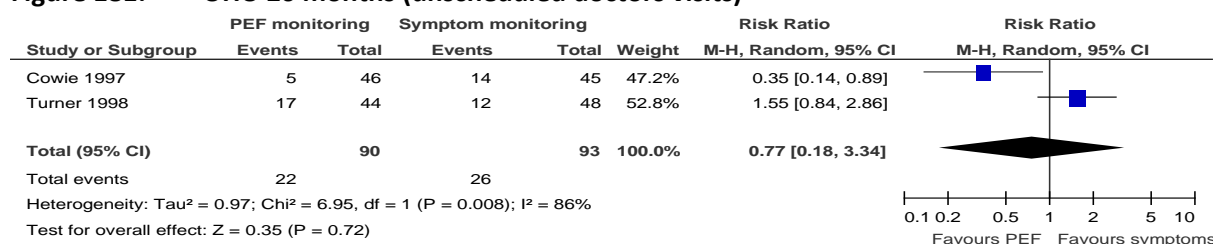


Figure 182: Rescue medications ≥6 months (no. of patients requiring nebulised salbutamol)

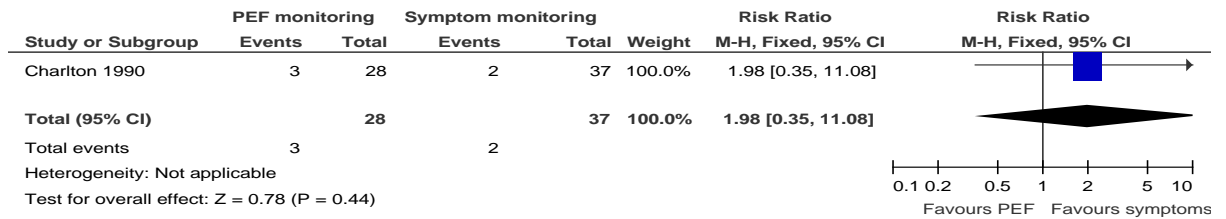


Figure 183: FEV1 L ≥6 months

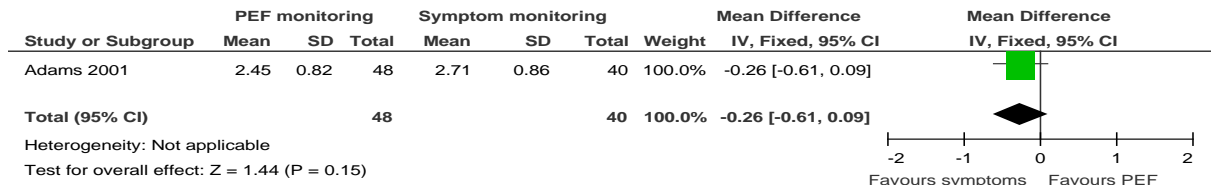


Figure 184: FEV1 % ≥6 months

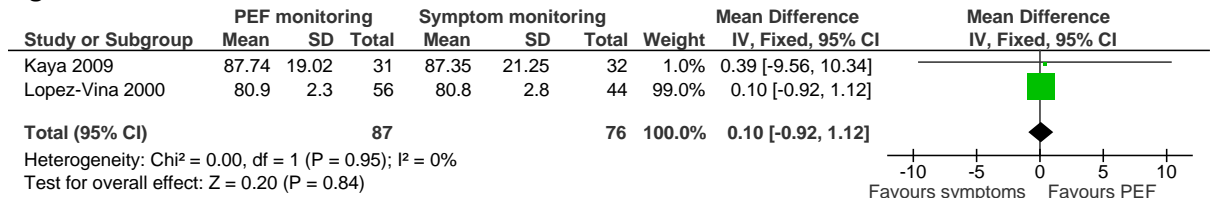


Figure 185: PEF % ≥6 months

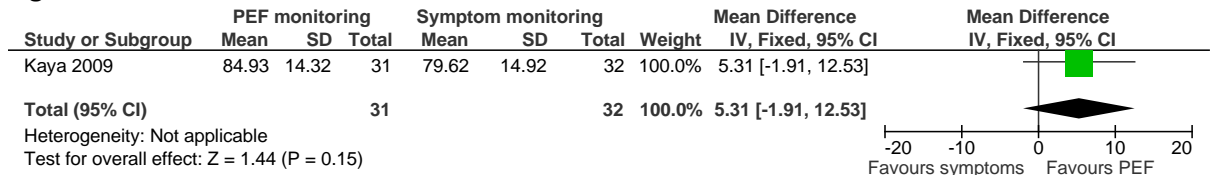


Figure 186: Time off work ≥6 months (number of patients)

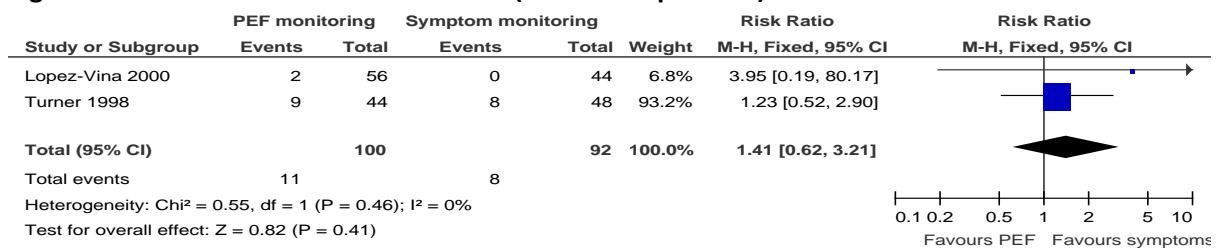
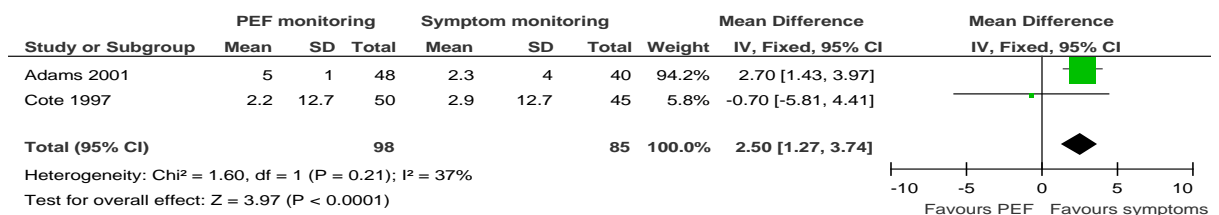


Figure 187: Time off work ≥6 months (mean number of days)



1.16.1.2 Children: Monitoring PEF versus symptom monitoring

Figure 188: Exacerbations <6 months (OCS)

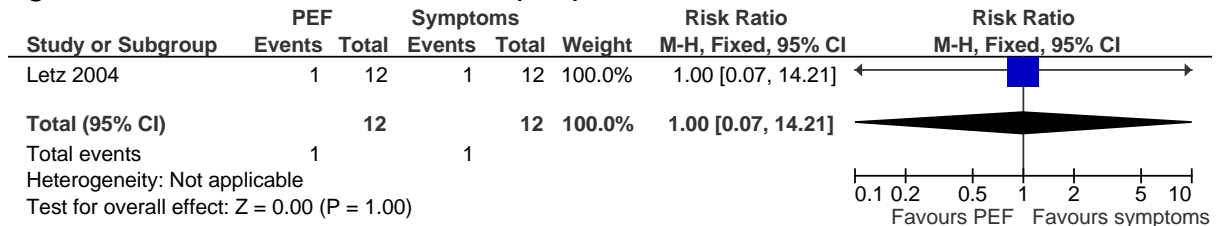


Figure 189: Exacerbations ≥6 months (OCS)

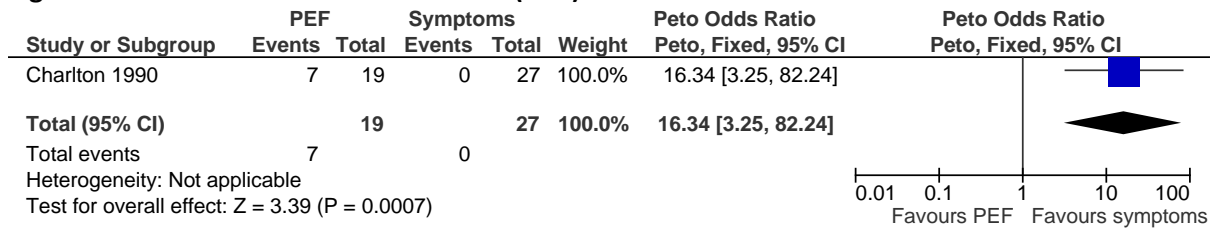


Figure 190: UHU <6 months (hospitalisation)

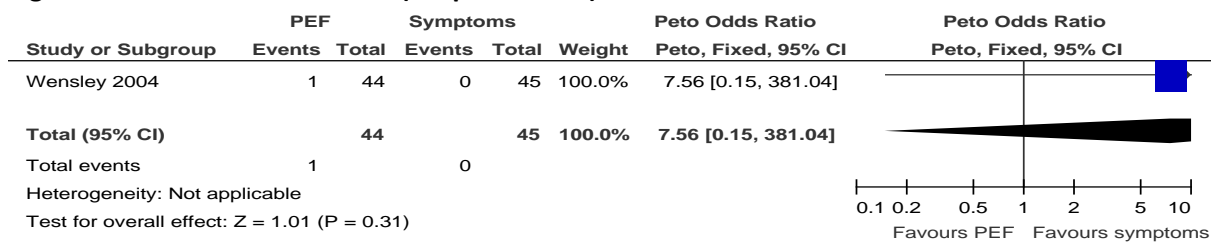


Figure 191: UHU <6 months (attendance at A&E)

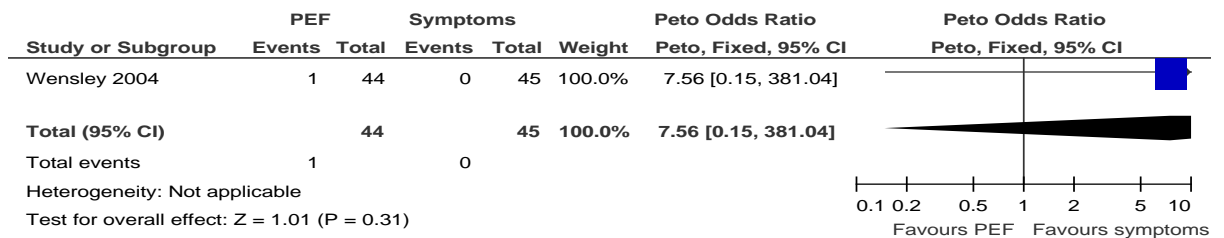


Figure 192: UHU <6 months (emergency GP visits)

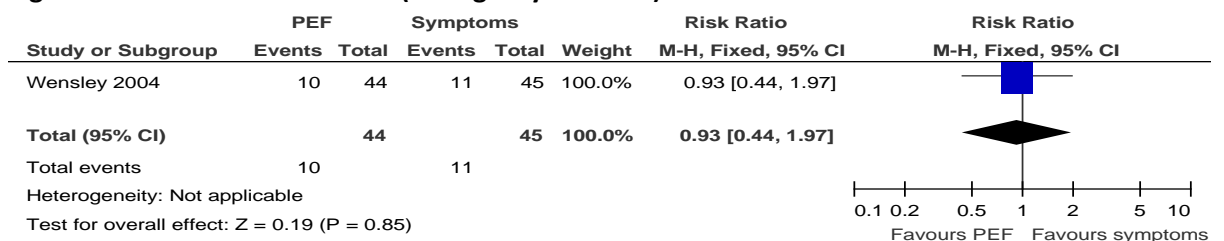


Figure 193: Rescue medications ≥ 6 months (no. of patients requiring nebulised salbutamol)

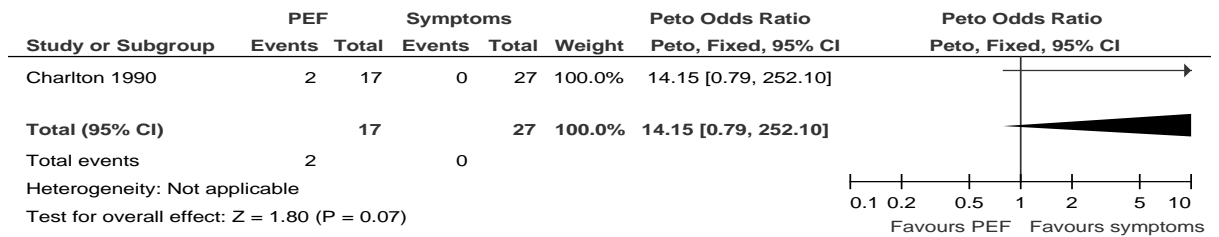


Figure 194: FEV1 % <6 months

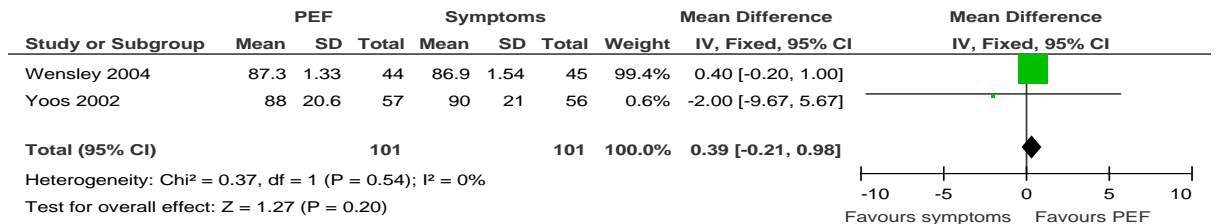


Figure 195: PEF % L/min <6 months

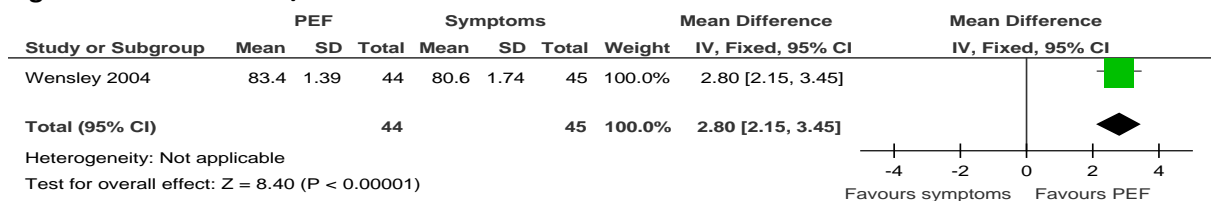
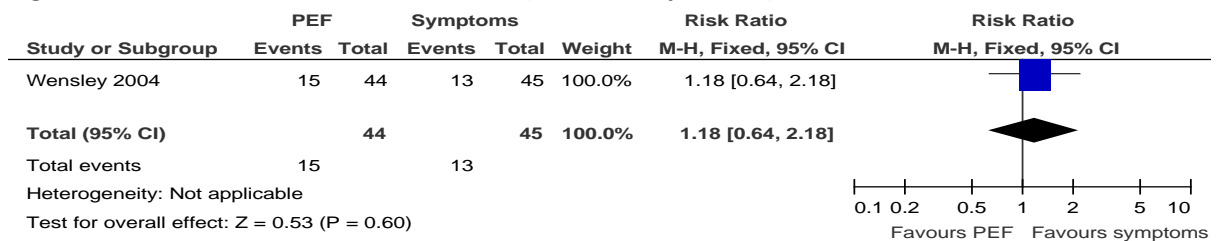


Figure 196: Time off school <6months (number of patients)



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1 J.17 Monitoring: FeNO

2.17.1.1 Adults – Unscheduled healthcare utilisation

Figure 197: FeNO versus Conventional Monitoring in Adults, UHU – ED visit [≥6 months]

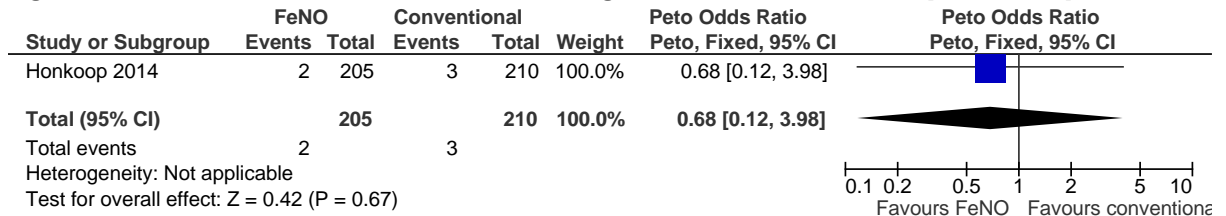
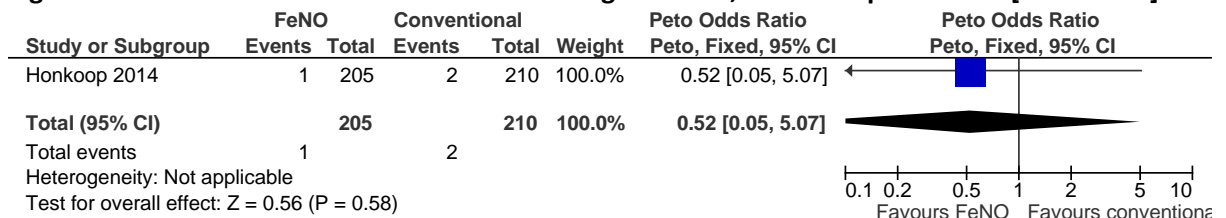


Figure 198: FeNO versus Conventional Monitoring in Adults, UHU - hospitalisation [≥6 months]



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4.17.1.2 Adults - Exacerbation

Figure 199: FeNO versus Conventional Monitoring in Adults, exacerbation [≥6 months]

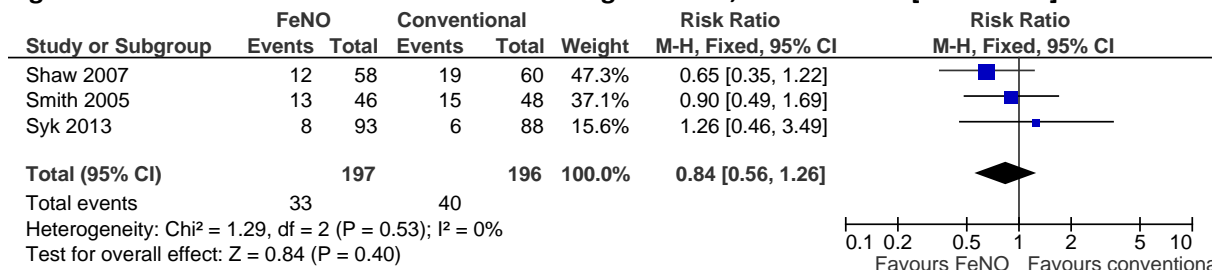
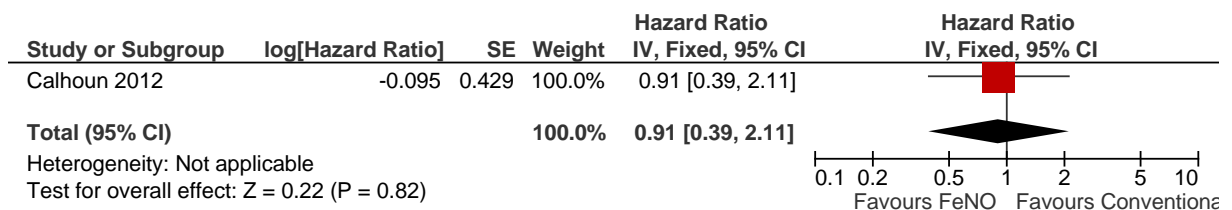
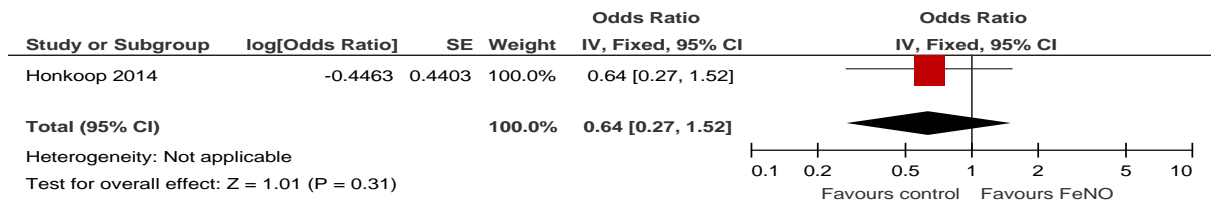


Figure 200: FeNO versus Conventional Monitoring in Adults, exacerbation [≥6 months]



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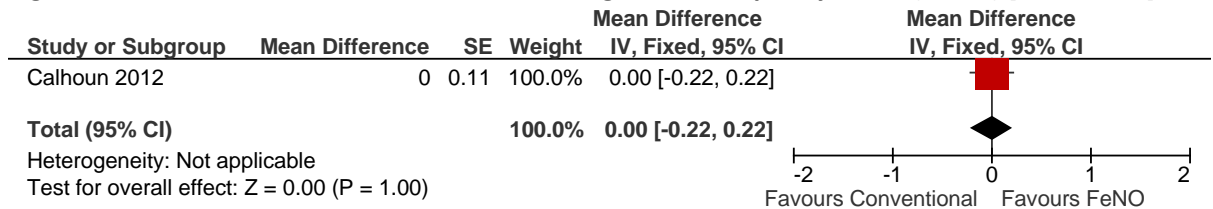
Figure 201: FeNO versus Conventional Monitoring in Adults, exacerbation [≥6 months]



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2.17.1.3 Adults - Quality of Life

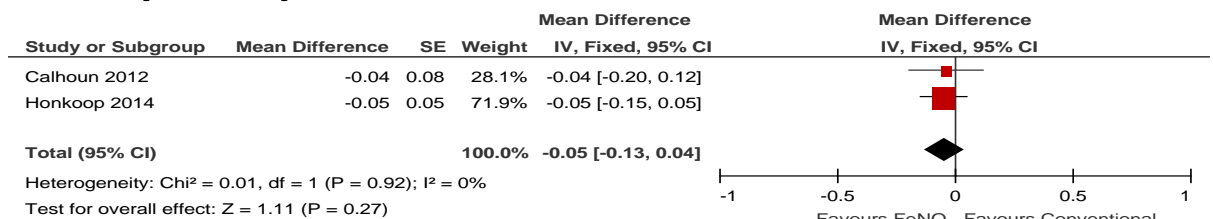
Figure 202: FeNO versus Conventional Monitoring in Adults, quality of life (AQLQ) [≥6 months]



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4.17.1.4 Adults - Asthma Control Questionnaire

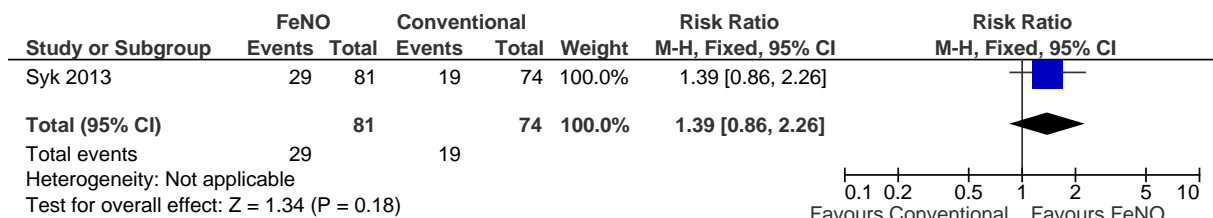
Figure 203: FeNO versus Conventional Monitoring in Adults, asthma control questionnaire (ACQ) [≥6 months]



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Figure 204: FeNO versus Conventional Monitoring in Adults, asthma control questionnaire (ACQ, clinically important improvement, ≥0.5) [≥6 months]



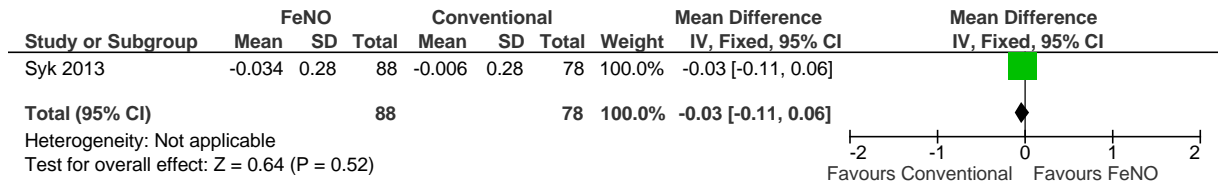
7

8.17.1.5 Adults - Lung Function

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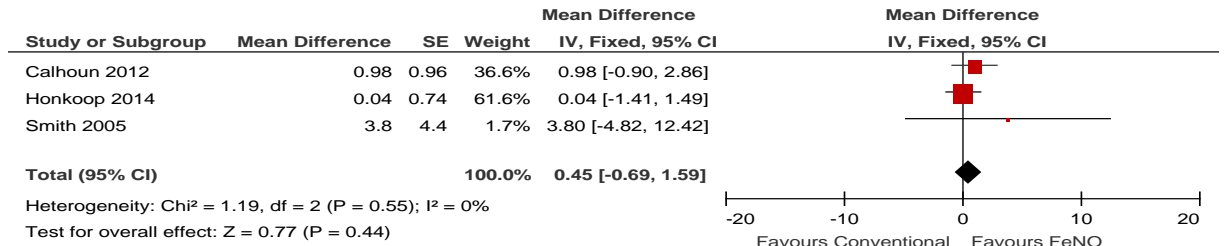
10

Figure 205: FeNO versus Conventional Monitoring in Adults, lung function (FEV1, litres) [≥6 months]



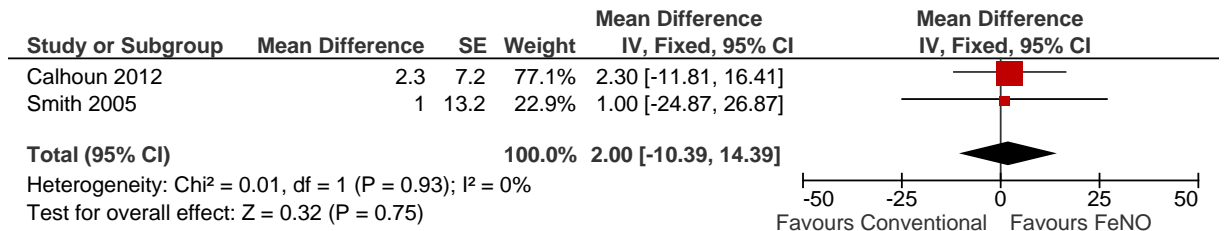
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Figure 206: FeNO versus Conventional Monitoring in Adults, lung function (FEV1, %) [≥6 months]



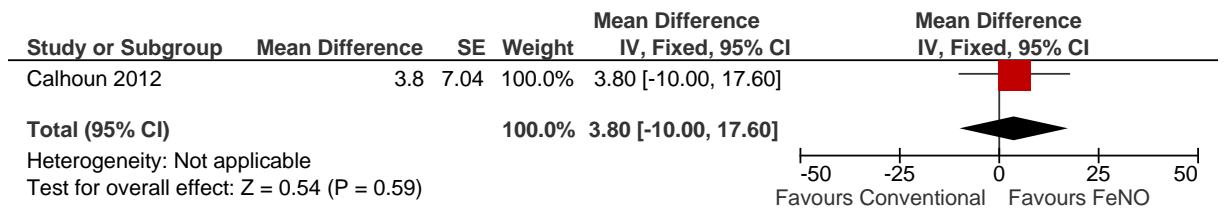
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Figure 207: FeNO versus Conventional Monitoring in Adults, lung function (PEF am, L/min) [≥6 months]



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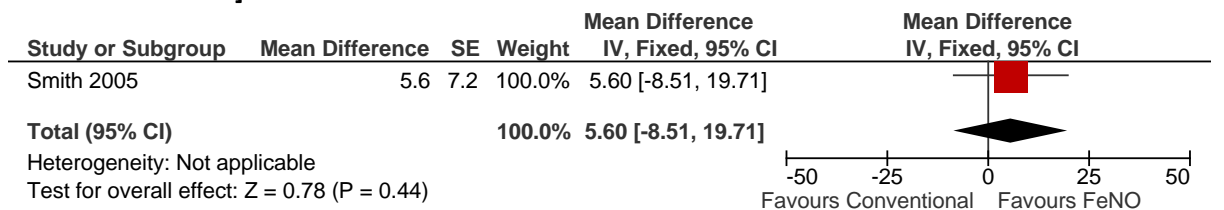
Figure 208: FeNO versus Conventional Monitoring in Adults, lung function (PEF pm, L/min) [<6 months]



12

13.17.1.6 Adults - Symptoms

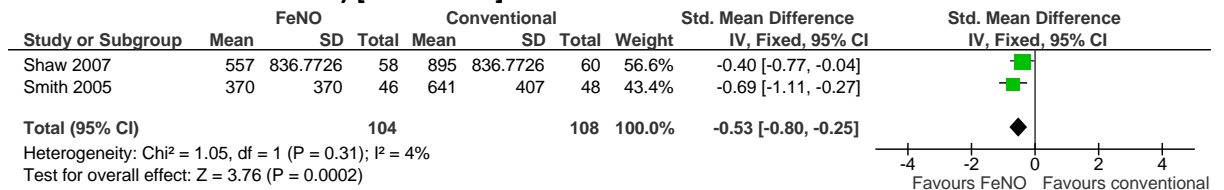
Figure 209: FeNO versus Conventional Monitoring in Adults, % symptom free days [≥6 months]



14

1.17.1.7 Adults - Dose of Regular Therapy

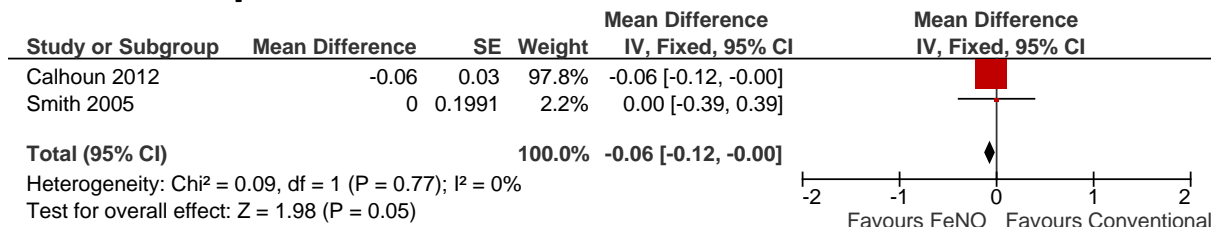
Figure 210: FeNO versus Conventional Monitoring in Adults, dose of regular therapy (ICS use, fluticasone dose) [≥6 months]



2

3.17.1.8 Adults - Rescue Medication

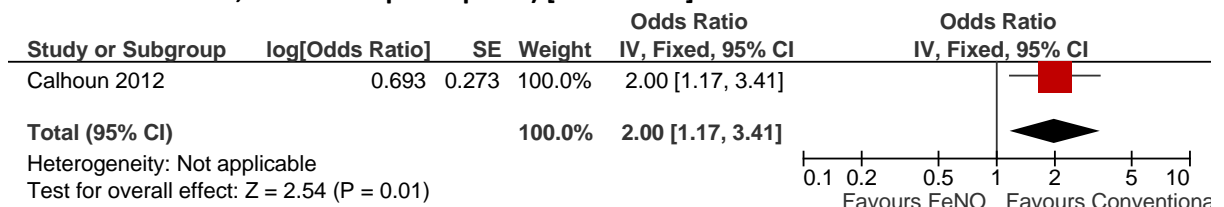
Figure 211: FeNO versus Conventional Monitoring in Adults, rescue medication (puffs/day) [≥6 months]



4

5.17.1.9 Adults - Time off school or work

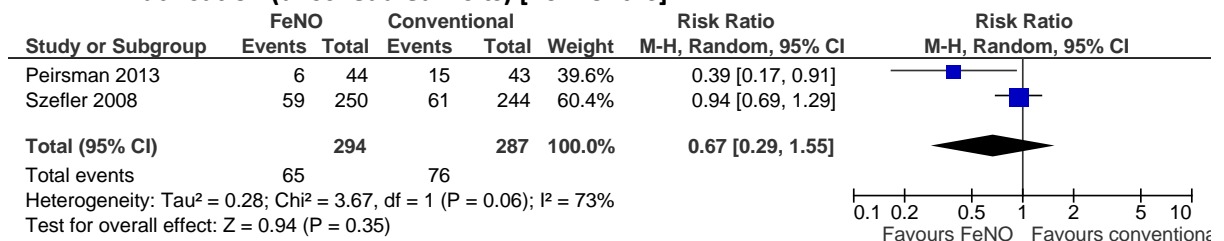
Figure 212: FeNO versus Conventional Monitoring in Adults, time off (missing days off school or work, number of participants) [≥6 months]



6

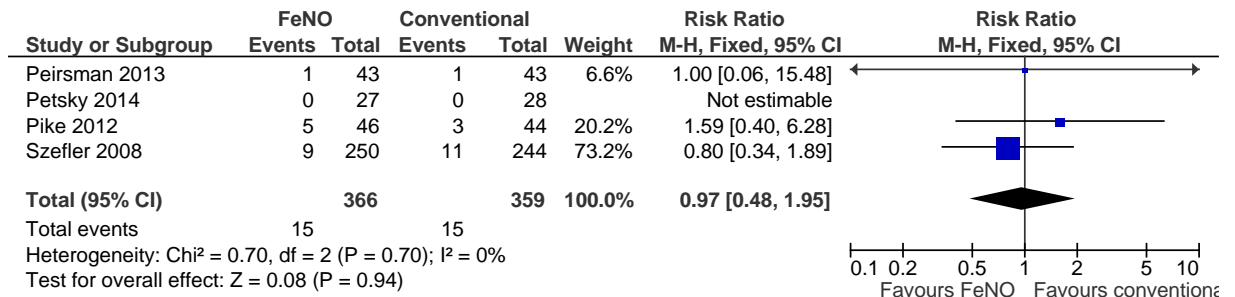
7.17.1.10 Children – Unscheduled Healthcare Utilisation

Figure 213: FeNO versus Conventional Monitoring in Children, unscheduled healthcare utilisation (unscheduled visits) [≥6 months]



8

1 **Figure 214: FeNO versus Conventional Monitoring in Children, unscheduled healthcare utilisation**
2 **(hospitalisation) [≥ 6 months]**



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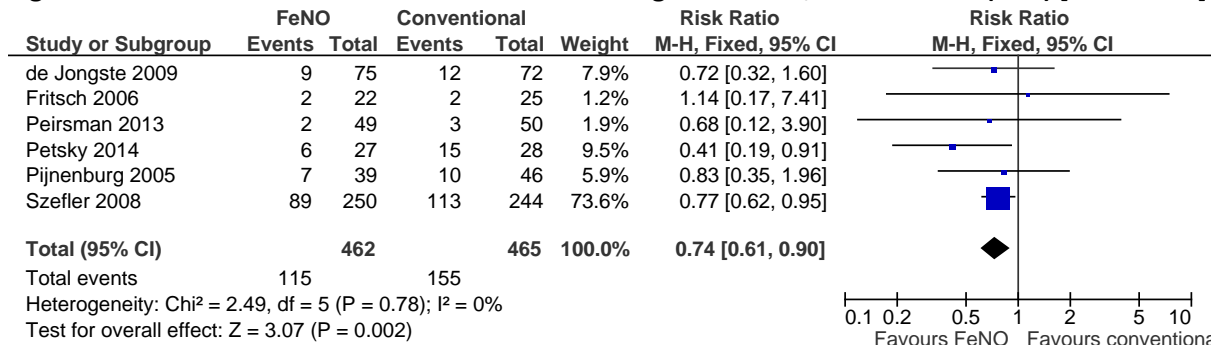
5 **Figure 215: FeNO versus Conventional Monitoring in Children, unscheduled healthcare utilisation**
6 **(number of children ≥ 1 emergency room admission) [≥ 6 months]**



7

17.1.11 Children – Exacerbation

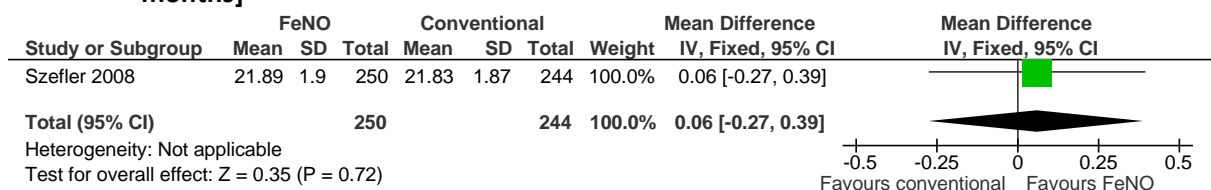
8 **Figure 216: FeNO versus Conventional Monitoring in Children, exacerbation (OCS) [≥ 6 months]**



9

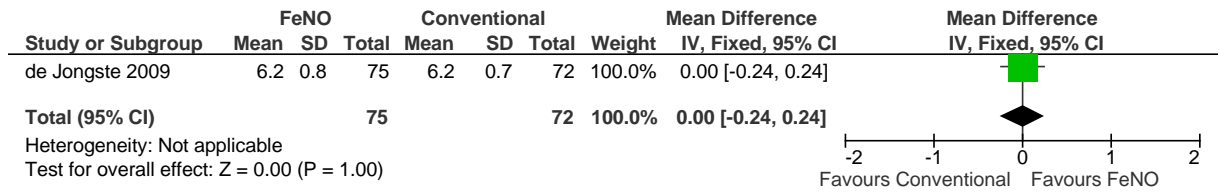
17.1.12 Children – Quality of Life

10 **Figure 217: FeNO versus Conventional Monitoring in Children, quality of life (ACT score) [≥ 6 months]**



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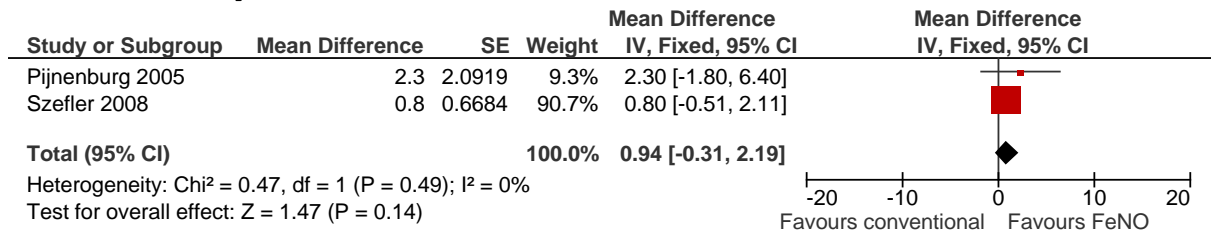
1 **Figure 218: FeNO versus Conventional Monitoring in Children, quality of life (Paediatric Asthma**
 2 **Caregiver Quality of Life Questionnaire) [≥6 months]**



3

J47.1.13 Children – Lung Function

Figure 219: FeNO versus Conventional Monitoring in Children, lung function (FEV1 % pred) [≥6 months]



J51.1.14 Children – Symptoms

Figure 220: FeNO versus Conventional Monitoring in Children, symptoms (% symptom free days) [≥6 months]

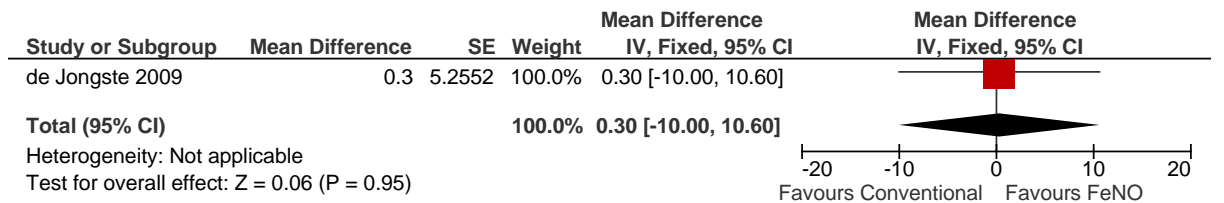
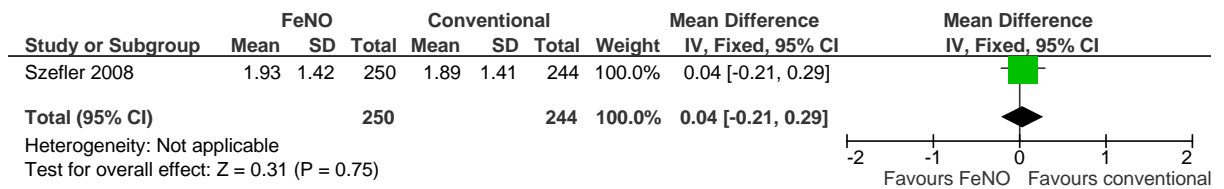


Figure 221: FeNO versus Conventional Monitoring in Children, symptoms (number of symptom days in last 2 weeks) [≥6 months]



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J117.1.15 Children – Dose of Regular Therapy

Figure 222: FeNO versus Conventional Monitoring in Children, dose of regular therapy (ICS use, daily dose) [≥6 months]

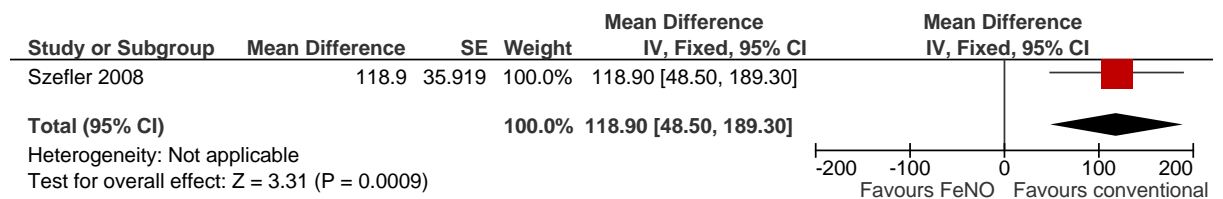
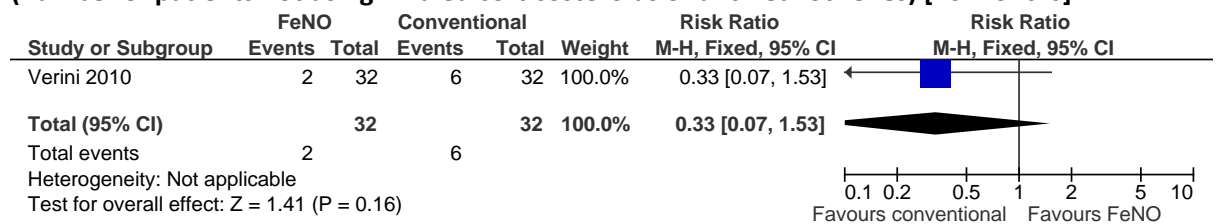
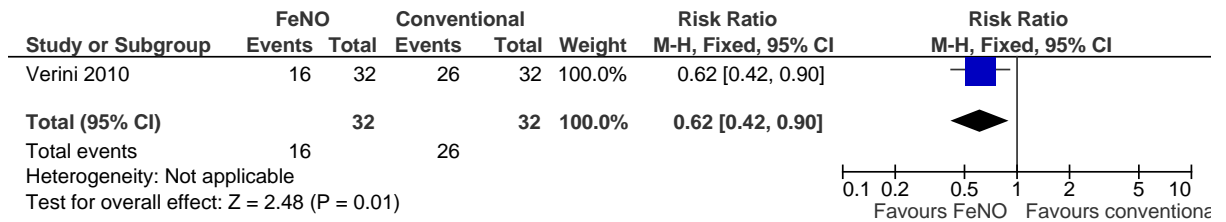


Figure 223: FeNO versus Conventional Monitoring in Children, dose of regular therapy (number of patients not using inhaled corticosteroids or anti-leukotrienes) [≥6 months]



J17.1.16 Children – Rescue Medication

Figure 224: FeNO versus Conventional Monitoring in Children, rescue medication (number of patients needed beta-agonist due to symptoms) [≥6 months]



J27.1.17 Children – Time Off school

Figure 225: FeNO versus Conventional Monitoring in Children, time off (number of days missed in last 2 weeks) [≥6 months]

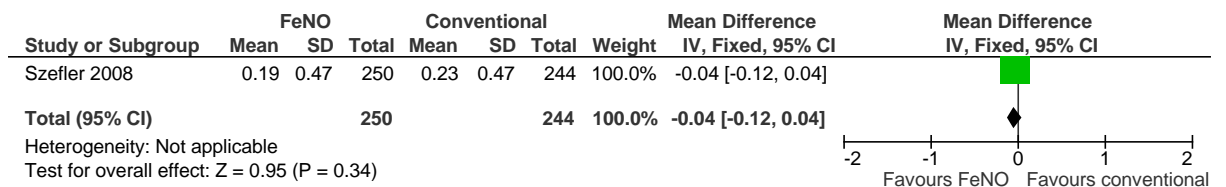
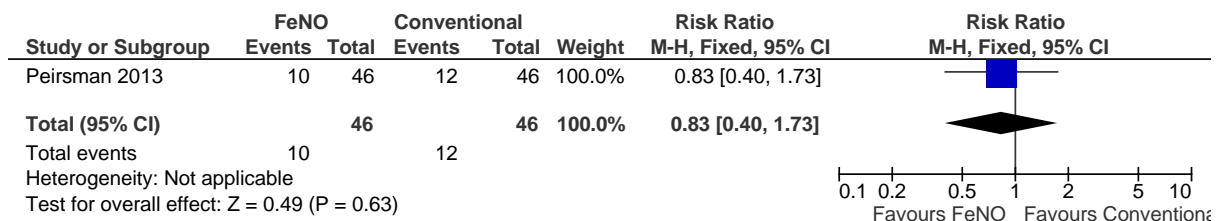


Figure 226: FeNO versus Conventional Monitoring in Children, time off (number of children missed school) [≥6 months]



3 J.18 Monitoring: Challenge tests

4.18.1.1 ADULTS Methacholine challenge test versus no challenge test for asthma monitoring

Figure 227: Mortality ≥6 months

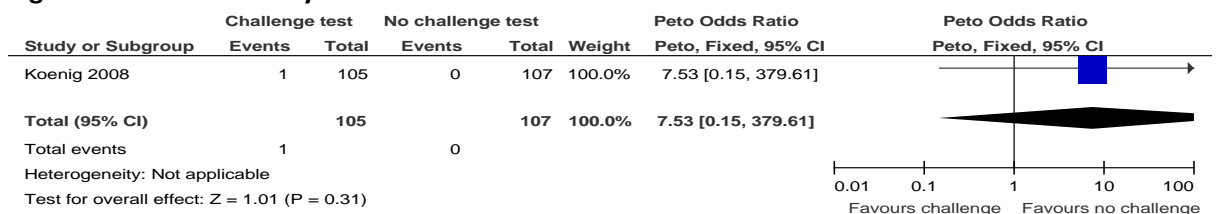


Figure 228: Exacerbations (undefined) ≥6 months

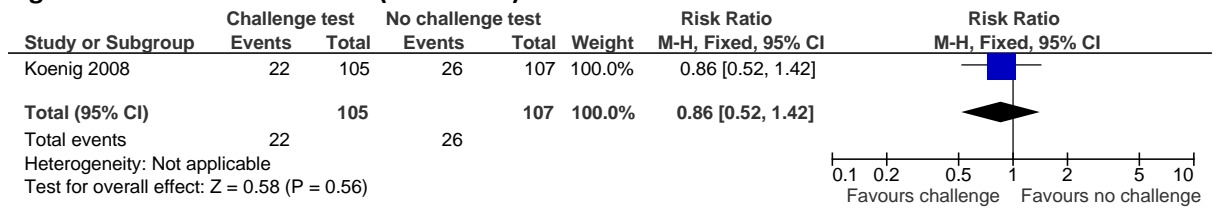


Figure 229: Rescue medications (puffs/day) ≥6 months

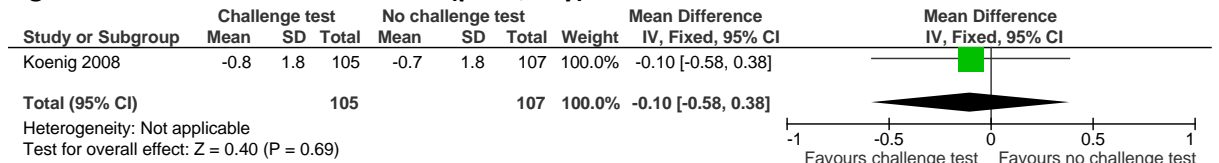
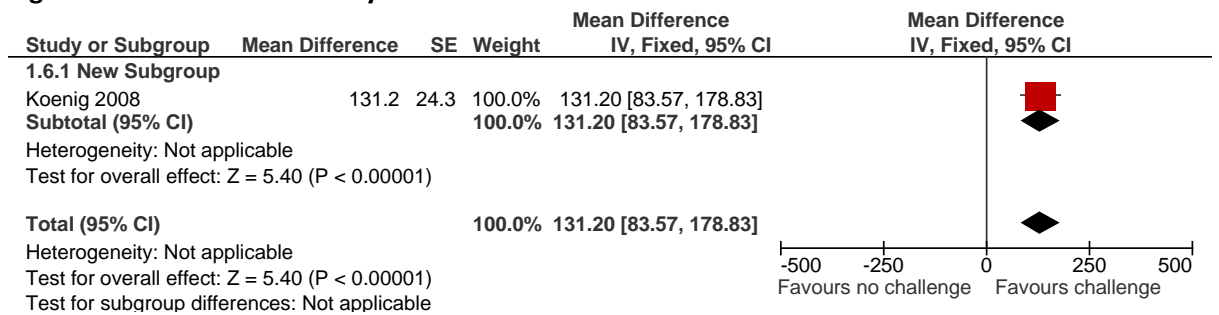


Figure 230: ICS mean daily dose ≥6 months



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Figure 231: FEV1 (L or L/year) ≥6 months

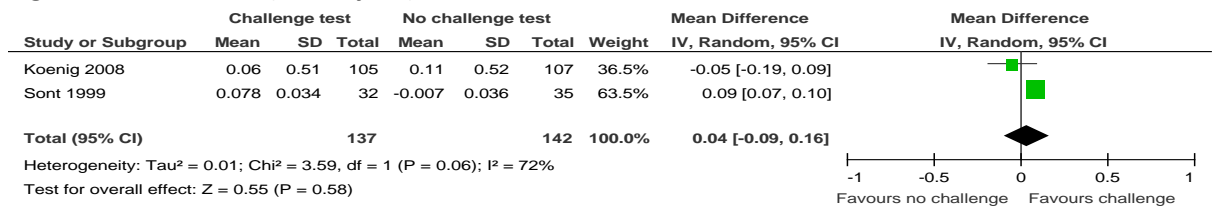


Figure 232: % symptom free days ≥6 months

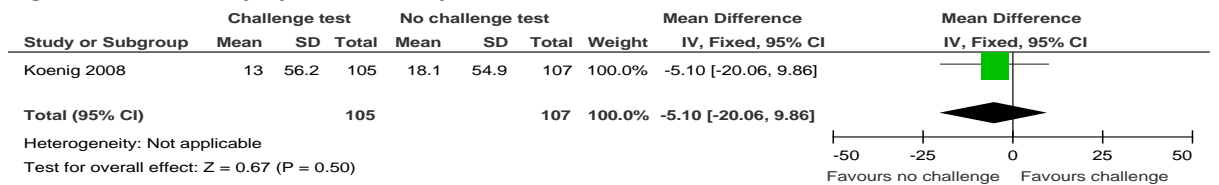


Figure 233: PEF am (L/min) ≥6 months

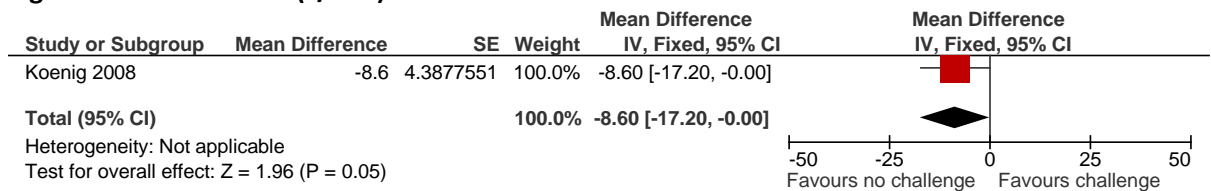
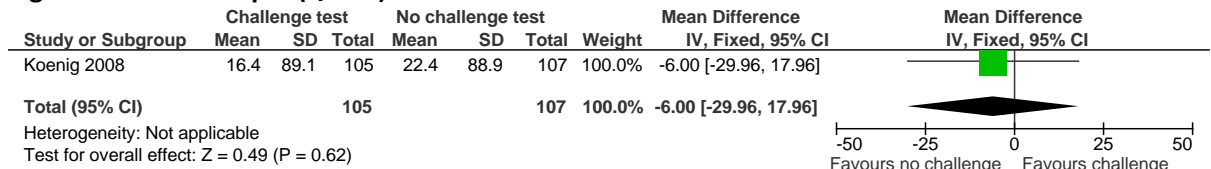


Figure 234: PEF pm (L/min) ≥6 months



1.18.1.2 ADULTS Mannitol challenge test versus no challenge test for asthma monitoring

Figure 235: QOL (miniAQLQ) ≥6 months

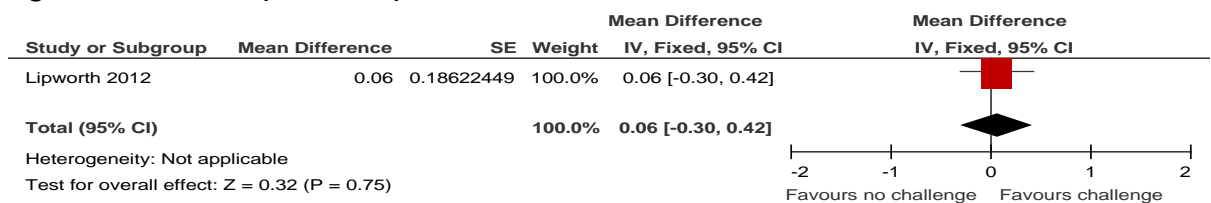


Figure 236: Exacerbations (OCS) ≥6 months

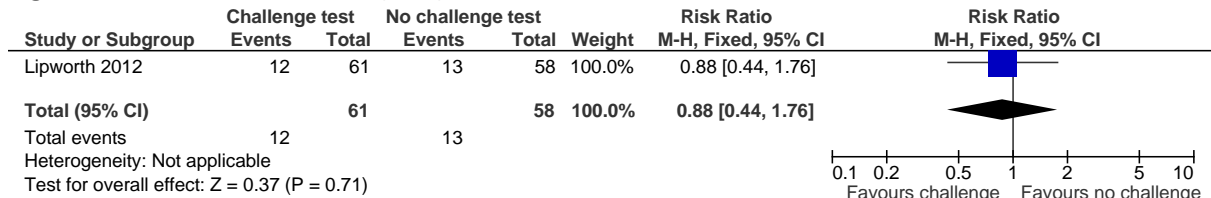
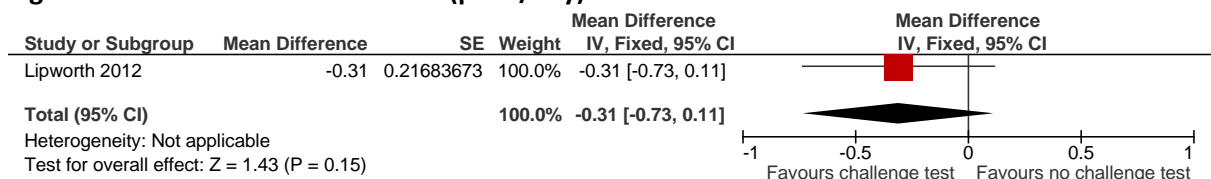


Figure 237: Rescue medications (puffs/day) ≥6 months



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Figure 238: ICS mean daily dose ≥6 months

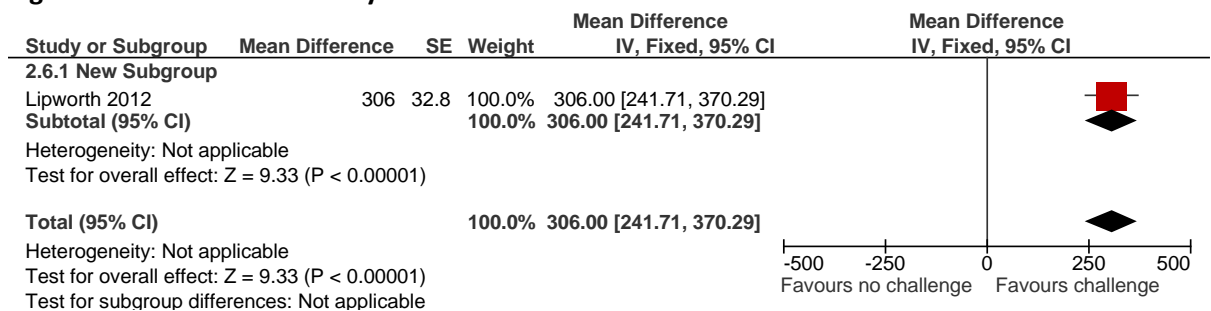


Figure 239: FEV1 (%) ≥6 months

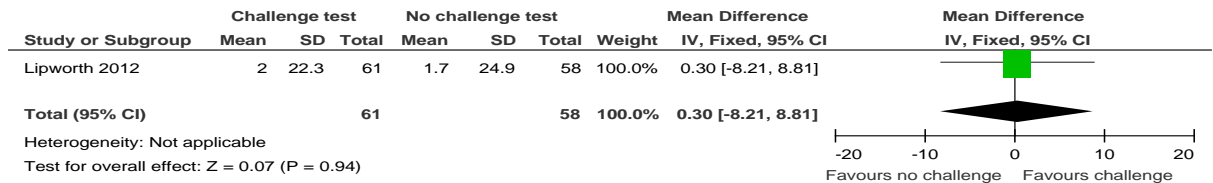


Figure 240: PEF (%) ≥6 months

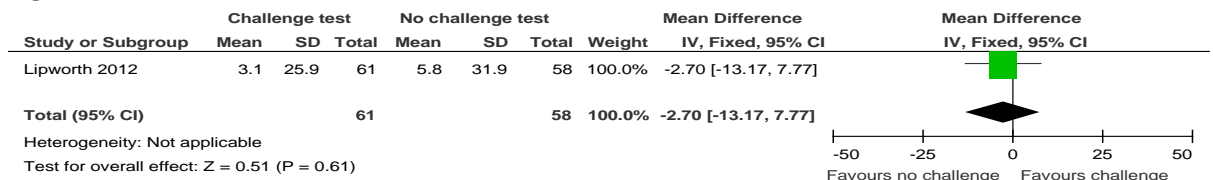
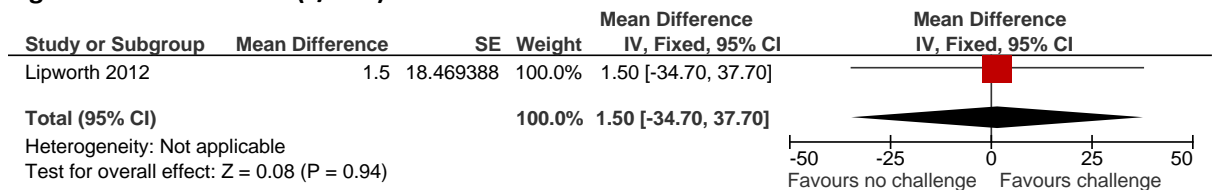


Figure 241: PEF am (L/min) ≥6 months



1.18.1.3 CHILDREN Methacholine challenge test versus no challenge test for asthma monitoring

Figure 242: Exacerbations (OCS) ≥6 months

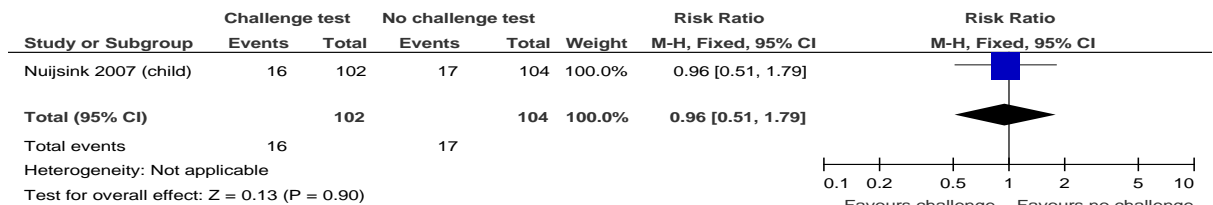


Figure 243: ICS mean daily dose for treatment period ≥6 months

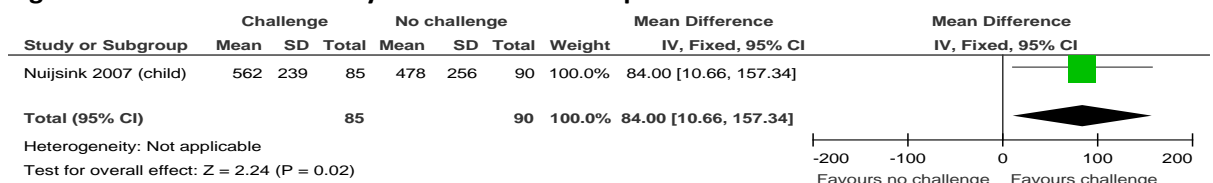


Figure 244: FEV1 (%) ≥6 months

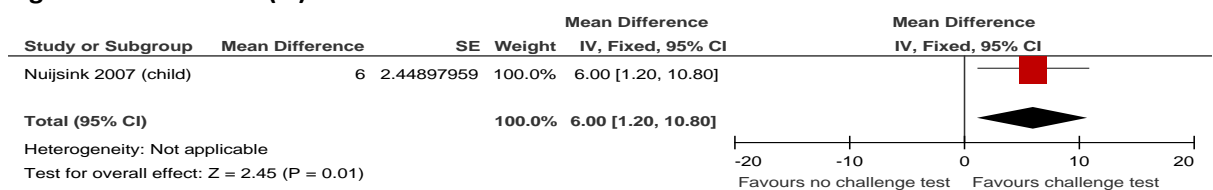
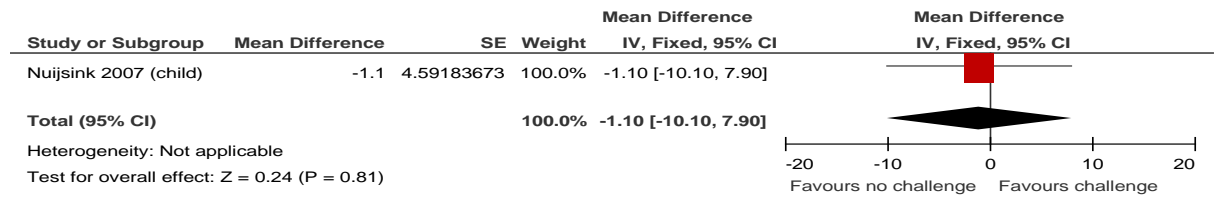


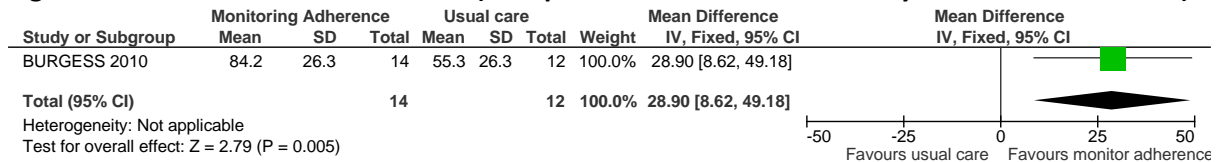
Figure 245: % symptom free days \geq 6 months



1 J.19 Monitoring adherence to treatment

2.19.1.1 Children (5-16 years) with uncontrolled asthma: Monitoring adherence + feedback vs no monitoring

Figure 246: Adherence <6 months (% of prescribed doses measured by the electronic inhaler)



4

5

Figure 247: Adherence ≥6 months (number of canister refills, 100% adherence = 3.0)

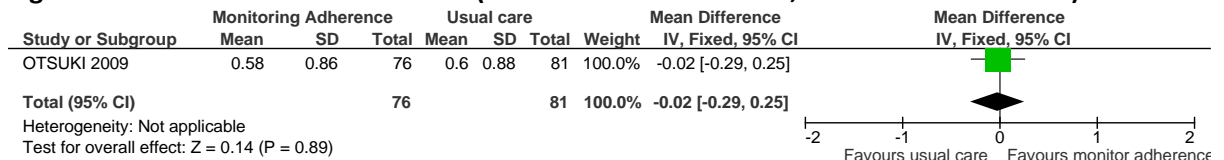


Figure 248: Self-reported adherence ≥6 months

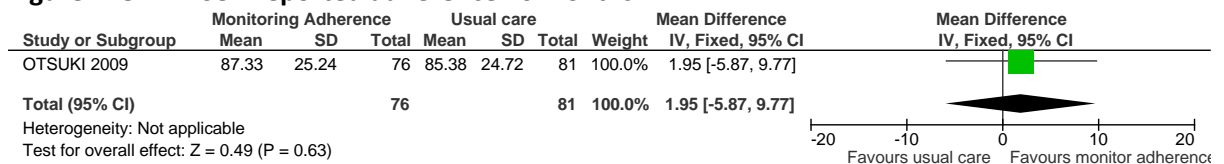


Figure 249: Exacerbation (OCS) <6 months

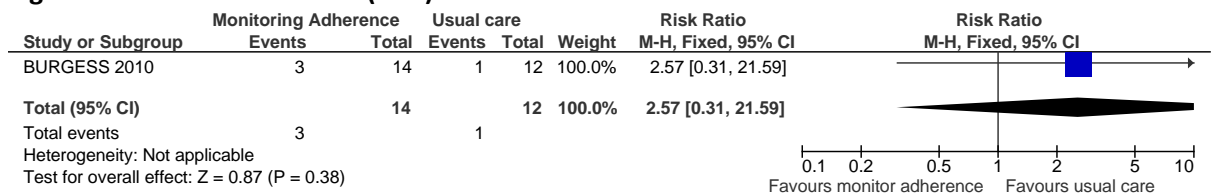


Figure 250: Exacerbation (OCS) ≥6 months (no. of OCS courses in 6 months)

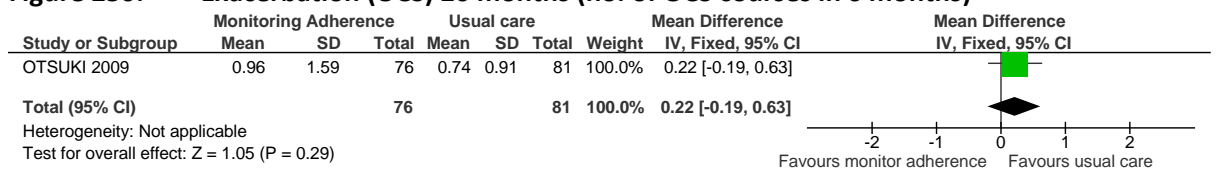


Figure 251: UHU (hospitalisation) ≥6 months (no. of hospitalisations in 6 months)

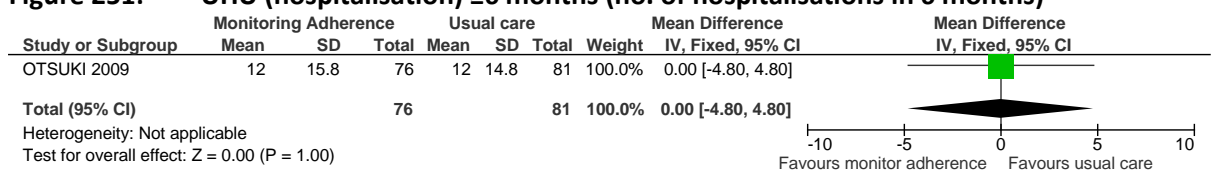
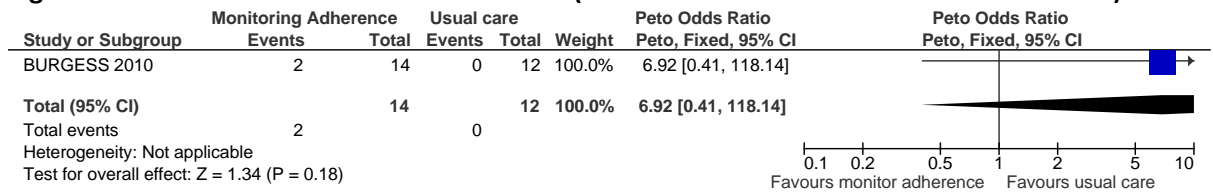


Figure 252: Rescue medication < 6months (reliever medication 3 or more times a week)



1

2.19.1.2 Adults (>16 years) overall: Monitoring adherence + feedback vs no monitoring

Figure 253: Adherence ≥6 months (% adherence to prescription refills in previous 3 months)

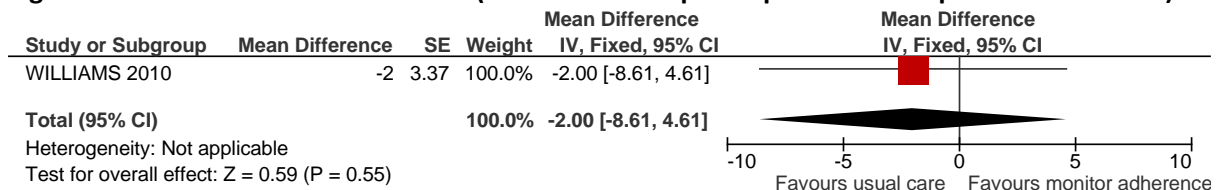


Figure 254: QOL <6 months (AQLQ, range 1-7)

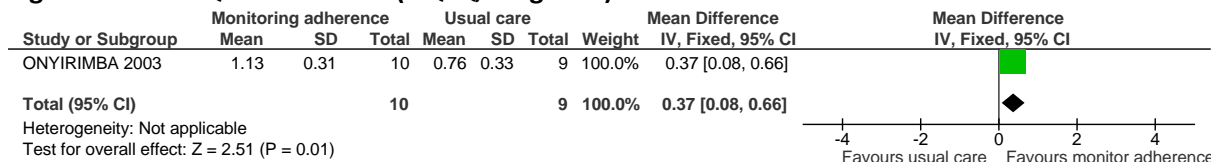


Figure 255: Exacerbation (OCS) ≥6months

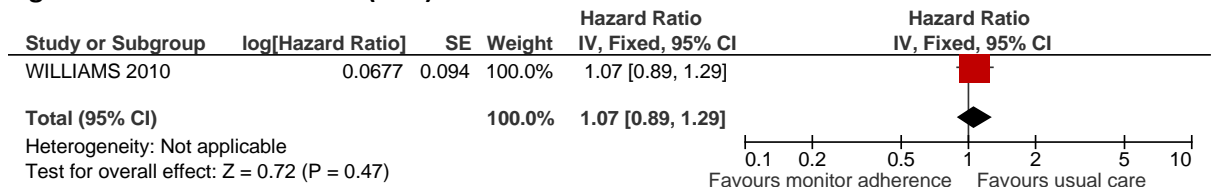


Figure 256: UHU (hospitalisation) ≥6months

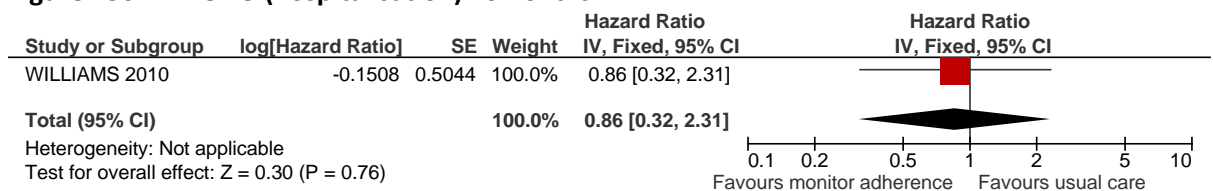


Figure 257: UHU (ED visit) ≥6months

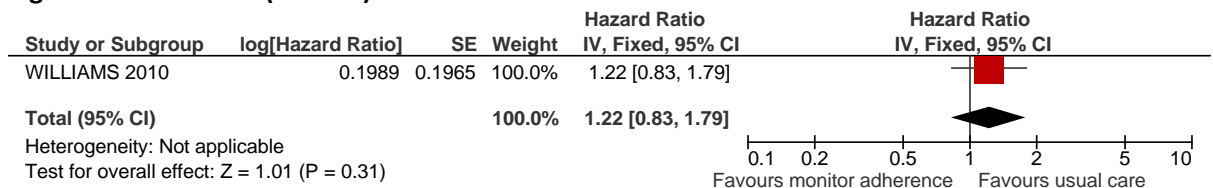
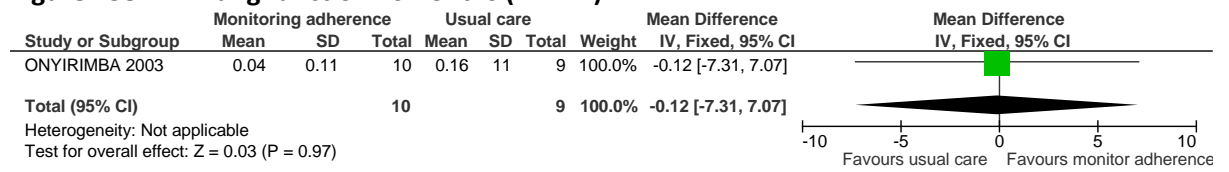


Figure 258: Lung function <6months (FEV1 L)



1 J.20 Monitoring inhaler technique

2.20.1.1 ADULTS: Monitoring inhaler technique vs no monitoring

Figure 259: Lung function <6 months (PEF Min%Max, higher is less variability)

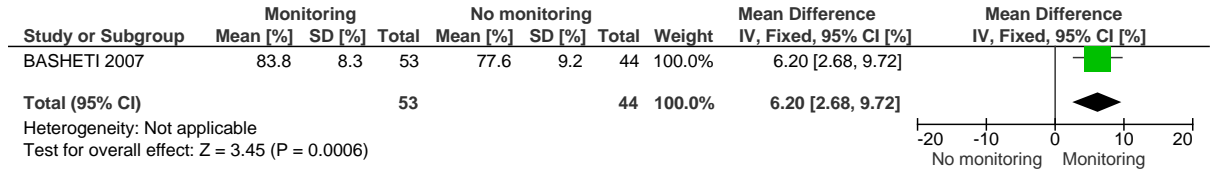


Figure 260: Lung function ≥6 months (PEF Min%Max, higher is less variability)

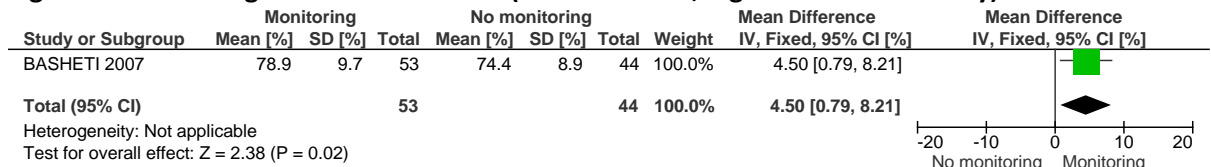


Figure 261: QOL <6 months (Marks AQLQ, 0-10, better indicated by lower values)

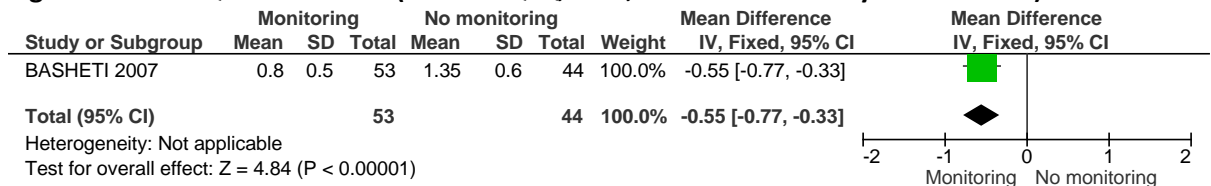
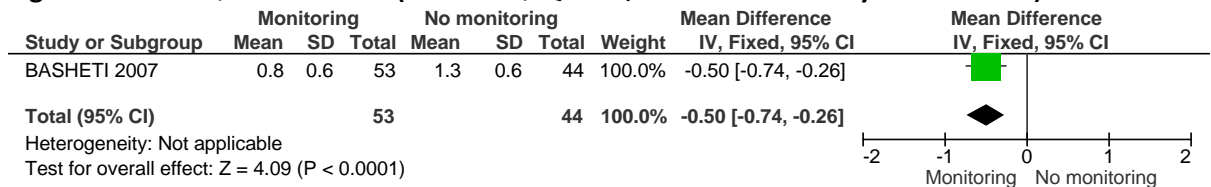


Figure 262: QOL ≥6 months (Marks AQLQ, 0-10, better indicated by lower values)



3.20.1.2 ADULTS: Monitoring (verbal and electronic) vs verbal monitoring only

Figure 263: QOL <6 months (mini AQLQ, 1-7, better indicated by higher values)

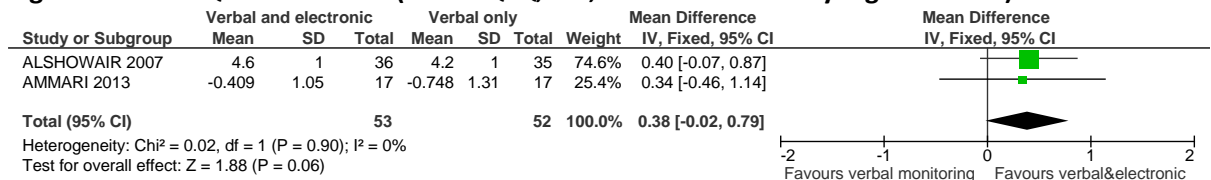


Figure 264: Lung function <6 months (FEV1 L)

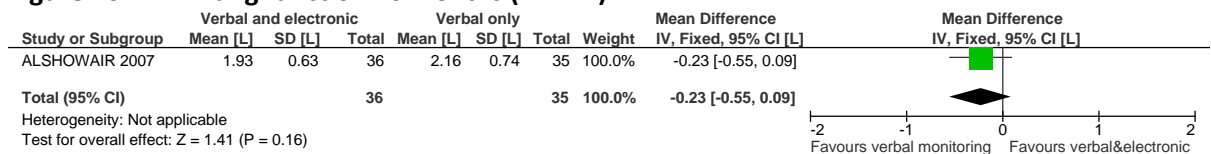
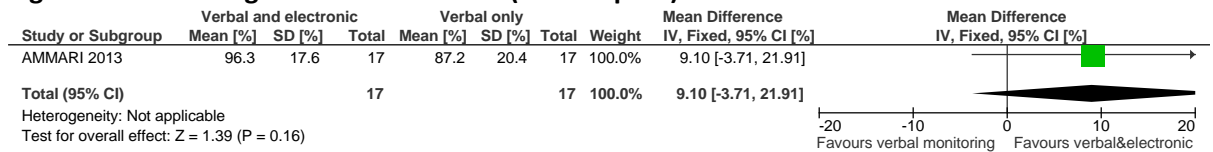


Figure 265: Lung function <6 months (FEV1 % pred)



1

2.20.1.3 CHILDREN: Monitoring (verbal and electronic) vs verbal monitoring only

Figure 266: Lung function <6 months (FEV1 % pred)

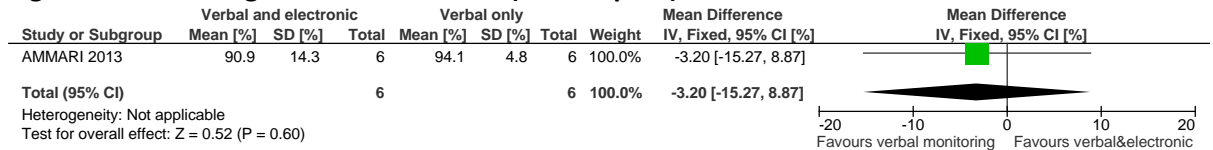
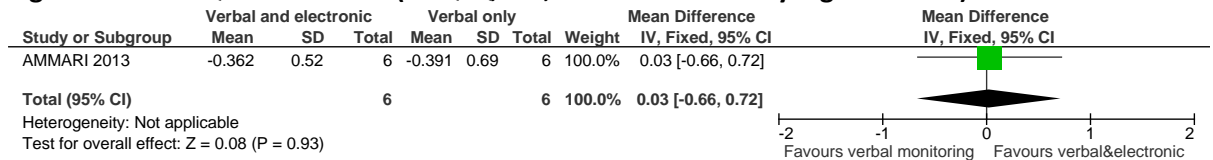


Figure 267: QOL <6 months (PAQLQ, 1-7, better indicated by higher values)



3 J.21 Monitoring: Tele-healthcare

4.21.1.1 Tele-healthcare for adults >17

Figure 268: Quality of life – Asthma Quality of Life Questionnaire (AQLQ)

5

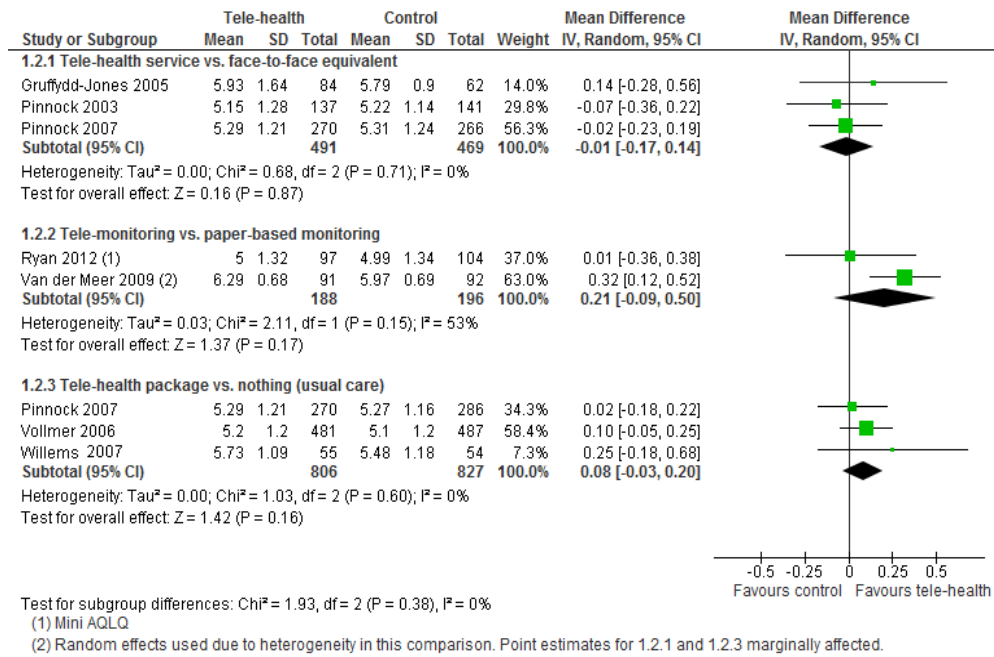


Figure 269: UHU hospitalisation

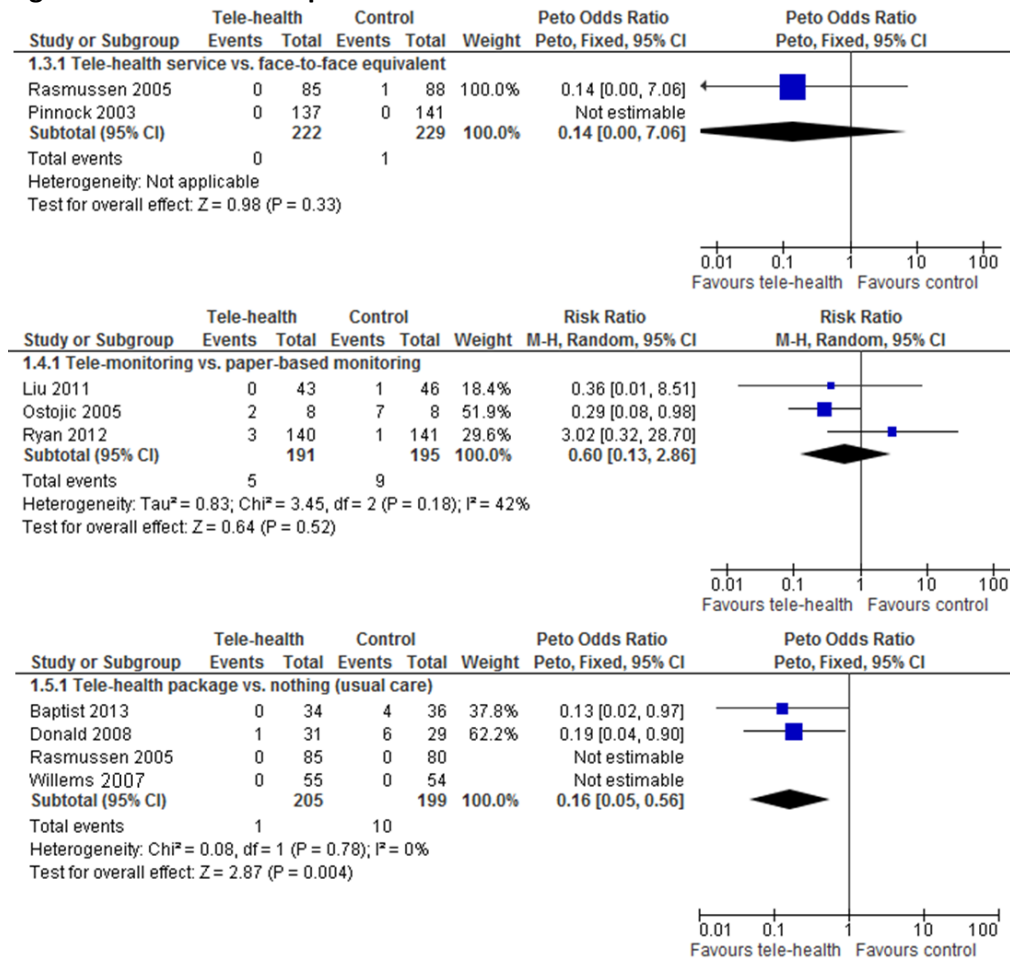
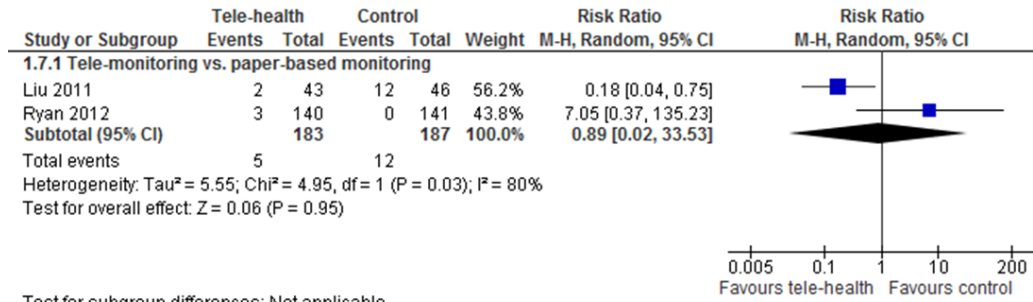
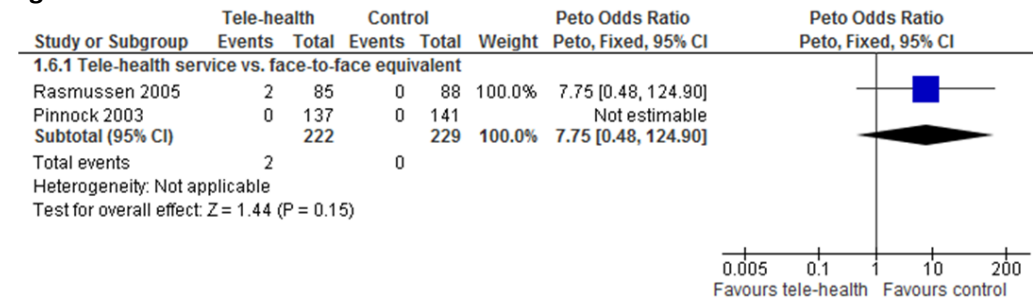
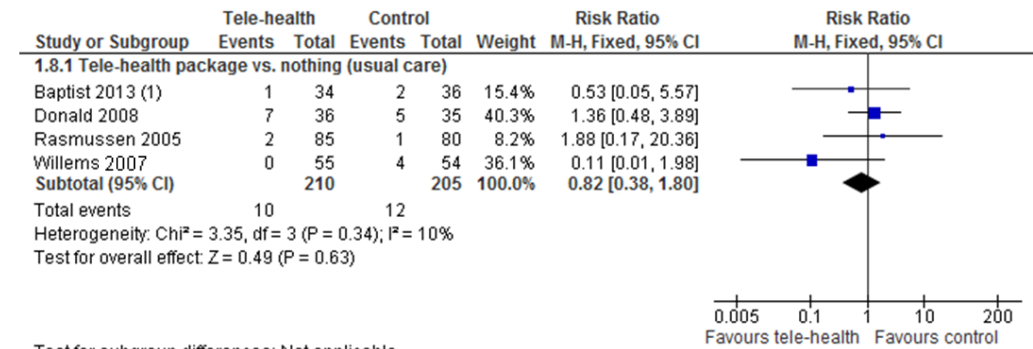


Figure 270: UHU ED visit



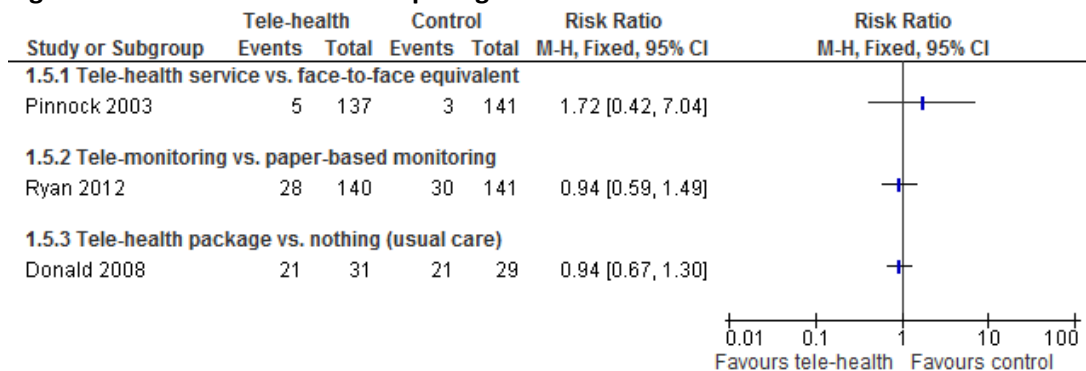
Test for subgroup differences: Not applicable



Test for subgroup differences: Not applicable
(1) End of study data (12 months)

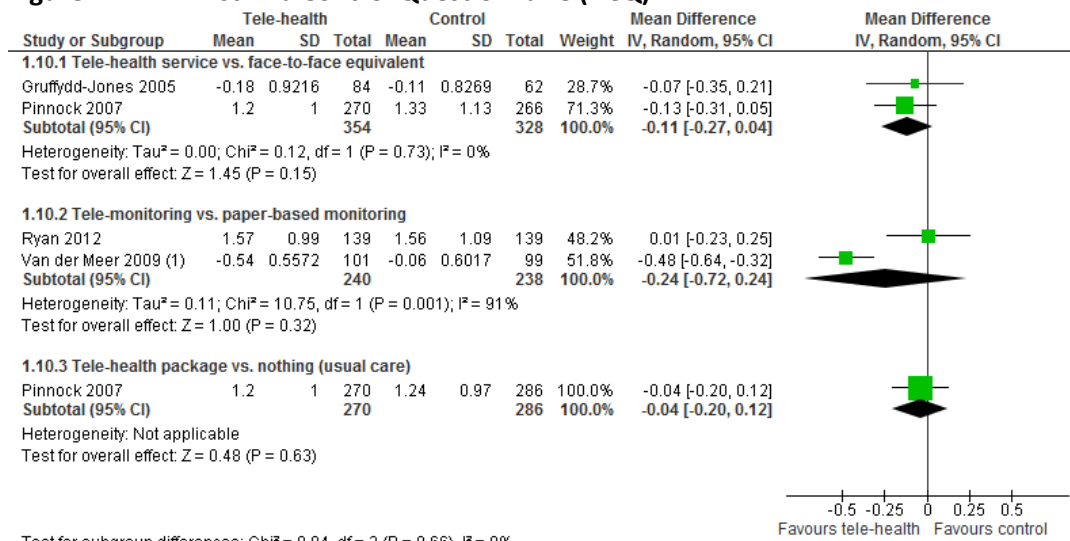
1

Figure 271: Exacerbations requiring oral steroids



2

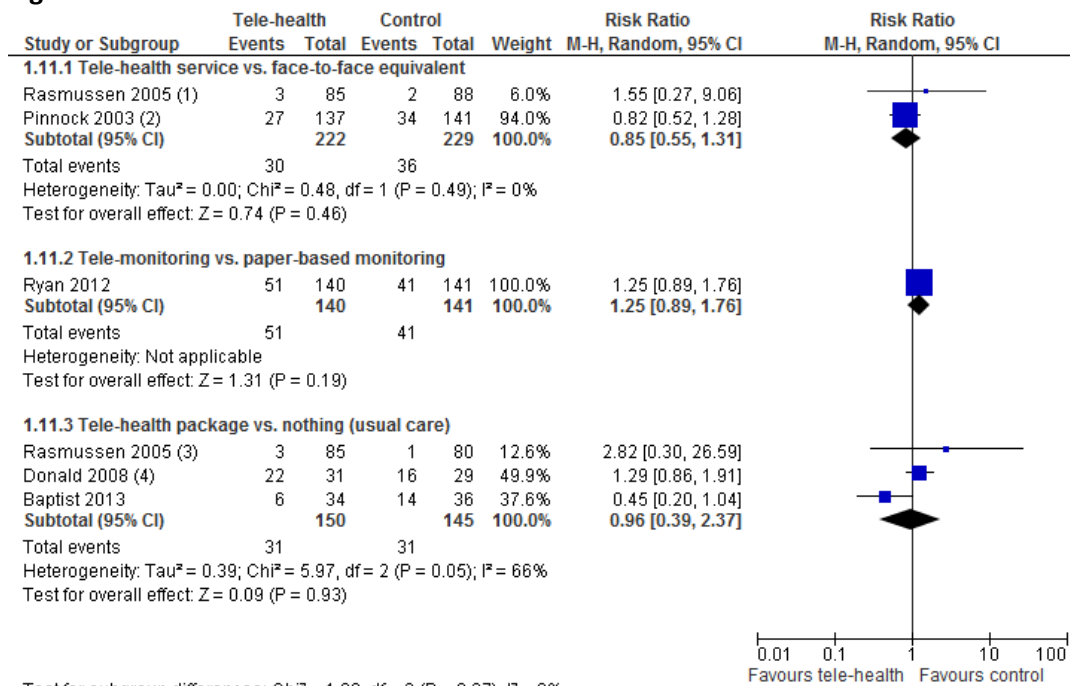
Figure 272: Asthma Control Questionnaire (ACQ)



Test for subgroup differences: Chi² = 0.84, df = 2 (P = 0.66), I² = 0%
(1) Random effects used due to heterogeneity in this comparison. Did not affect results for 1.10.1 and 1.10.3.

1

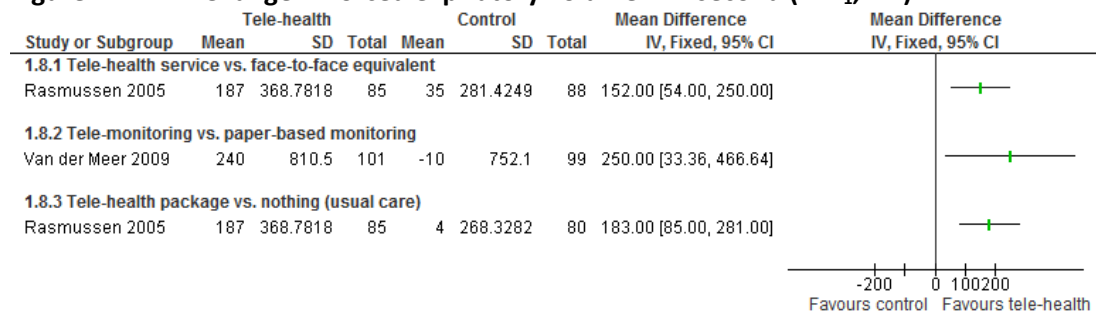
Figure 273: UHU GP visits



Test for subgroup differences: Chi² = 1.98, df = 2 (P = 0.37), I² = 0%
(1) Described as 'unscheduled visits'
(2) Unclear if unscheduled, or total GP visits during the study period
(3) Described as 'unscheduled healthcare visits'
(4) Random effects used due to heterogeneity in this comparison. Point estimates for 1.11.1 and 1.11.2 marginally affected.

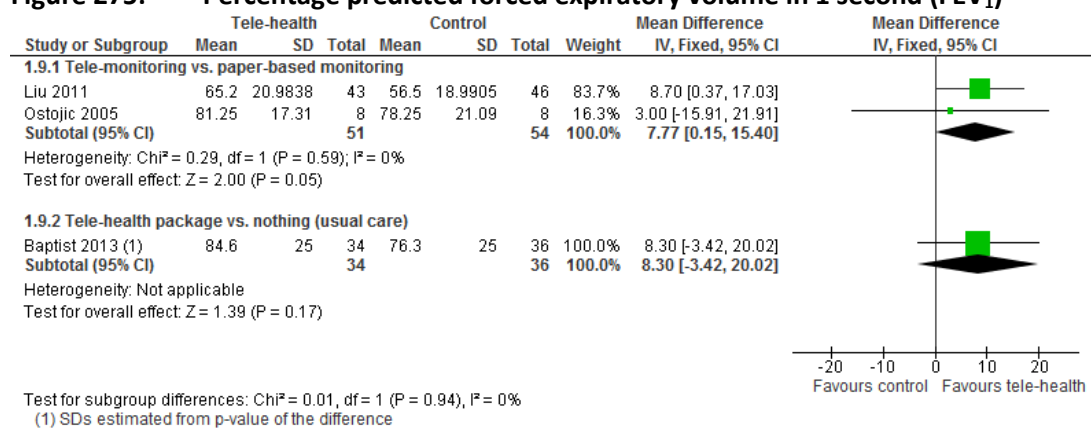
2

Figure 274: Change in forced expiratory volume in 1 second (FEV₁, mL)



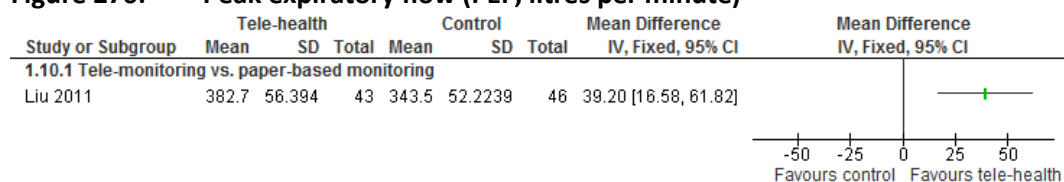
1

Figure 275: Percentage predicted forced expiratory volume in 1 second (FEV₁)



2

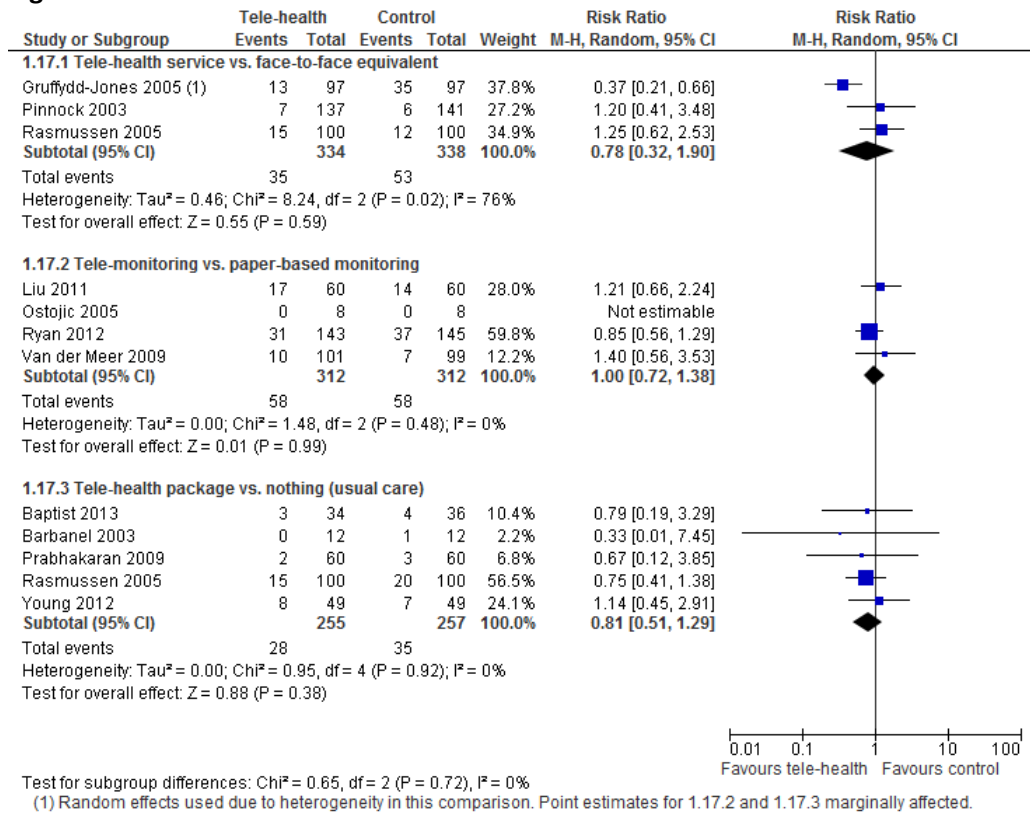
Figure 276: Peak expiratory flow (PEF, litres per minute)



3

4

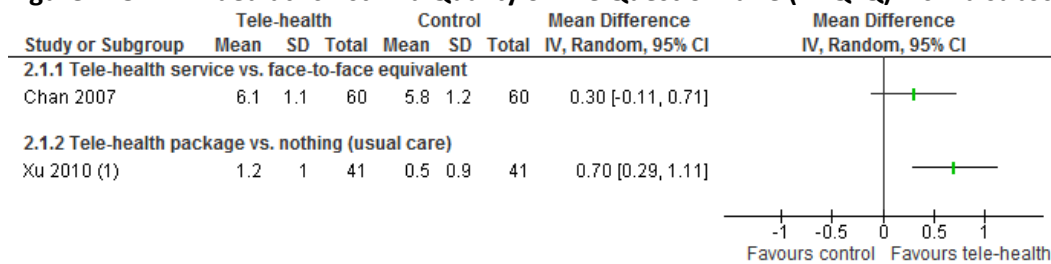
Figure 277: Withdrawal



1

2.21.1.2 Tele-healthcare for children aged 5 to 17

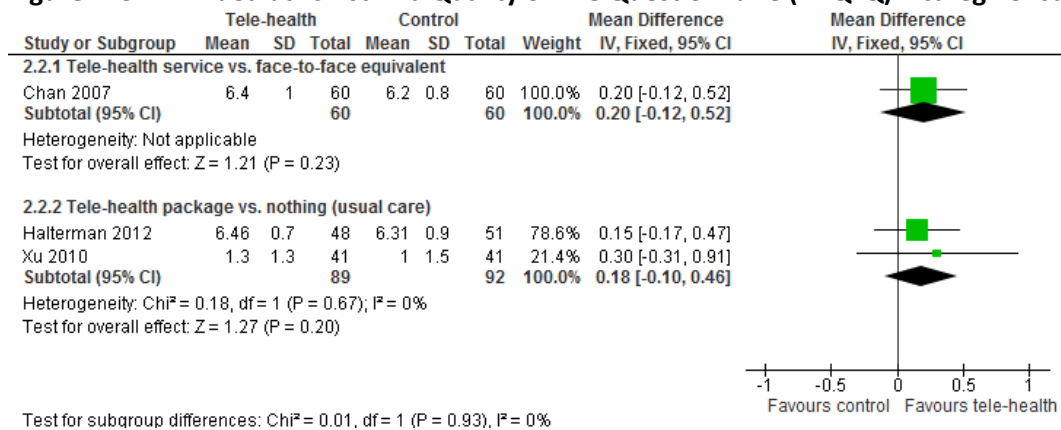
Figure 278: Paediatric Asthma Quality of Life Questionnaire (PAQLQ) – child subscale



(1) change scores

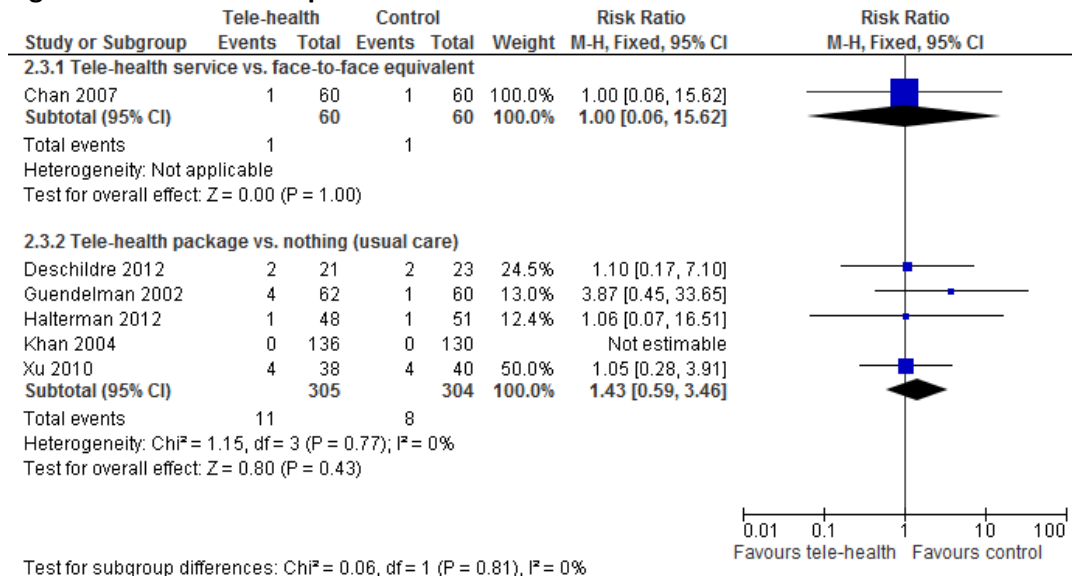
3

Figure 279: Paediatric Asthma Quality of Life Questionnaire (PAQLQ) – caregiver subscale



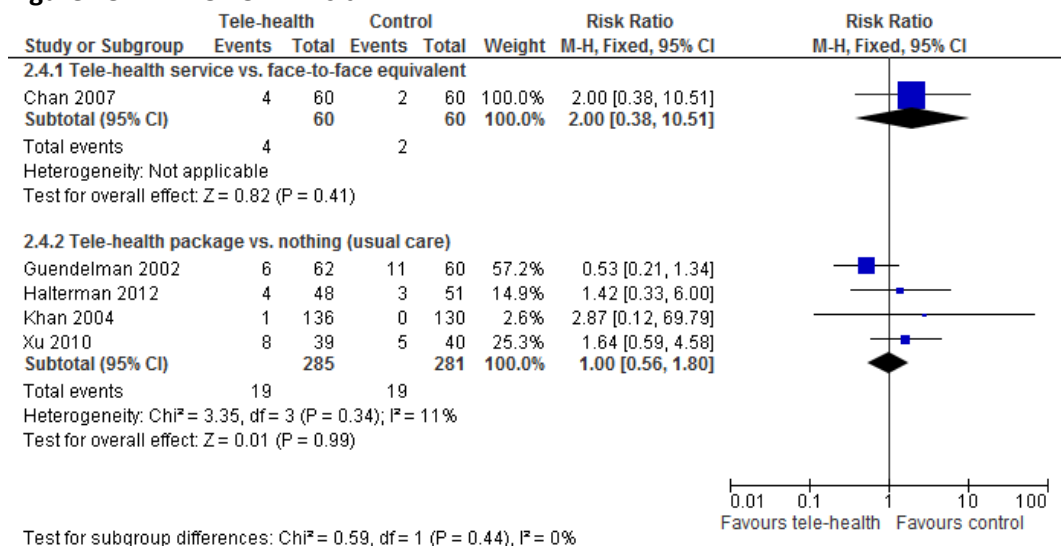
1

Figure 280: UHU hospitalisation



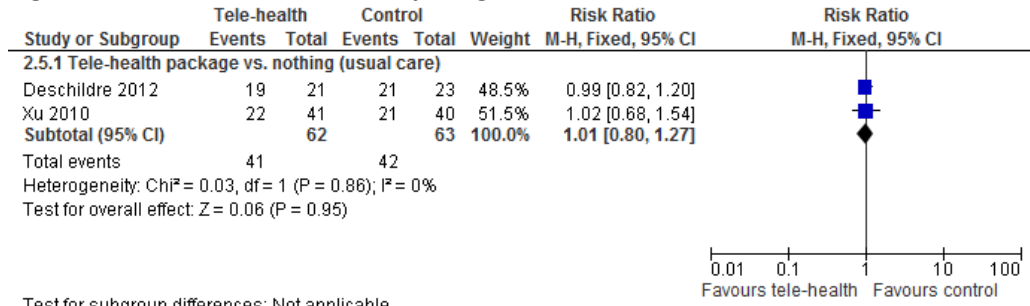
2

Figure 281: UHU ED visit



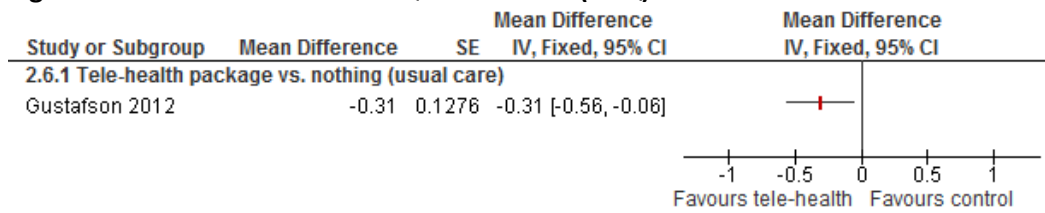
3

Figure 282: Exacerbations requiring oral steroids



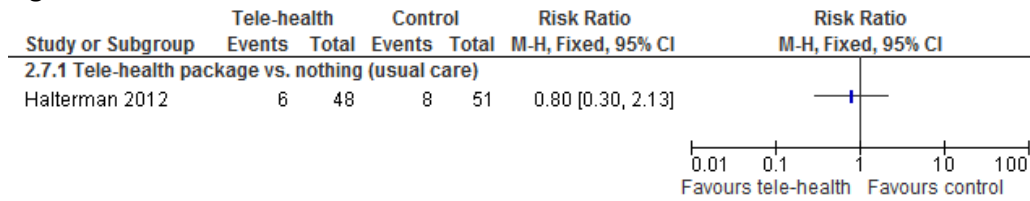
1

Figure 283: Asthma Control Questionnaire (ACQ)



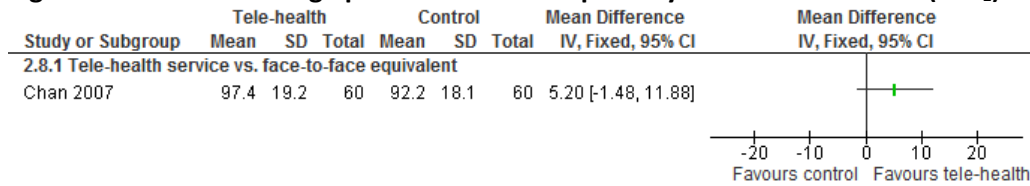
2

Figure 284: UHU GP visits



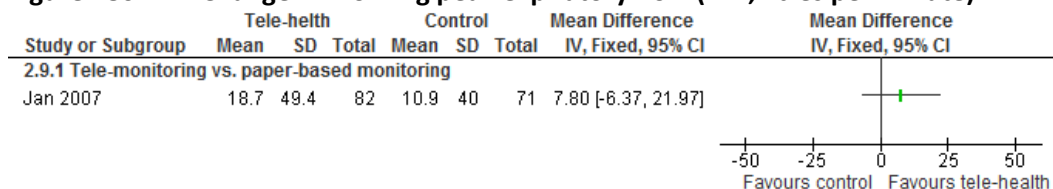
3

Figure 285: Percentage predicted forced expiratory volume in 1 second (FEV₁)



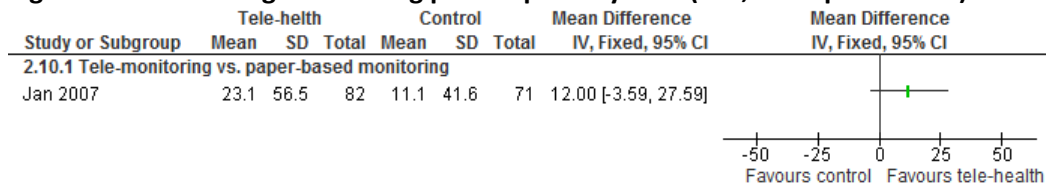
4

Figure 286: Change in morning peak expiratory flow (PEF, litres per minute)



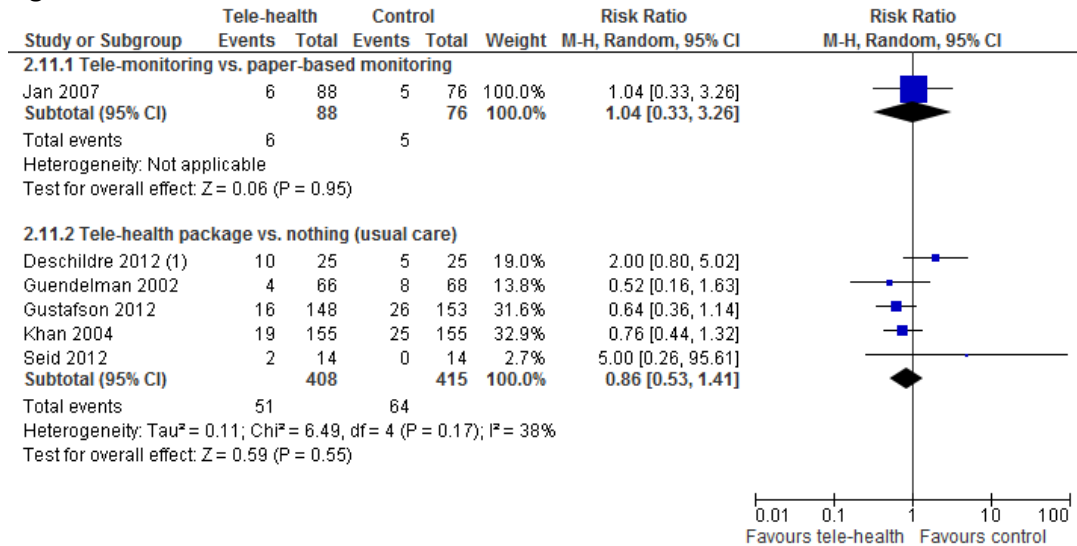
5

Figure 287: Change in evening peak expiratory flow (PEF, litres per minute)



1

Figure 288: Withdrawal



(1) Random effects used due to heterogeneity in this comparison. Point estimate for 2.11.1 not affected.

2

3.21.1.3 Adults and young people (>16 years): Telehealthcare without healthcare professional involvement vs usual care

4

Figure 289: QOL <6 months (AQLQ, range 0-7)

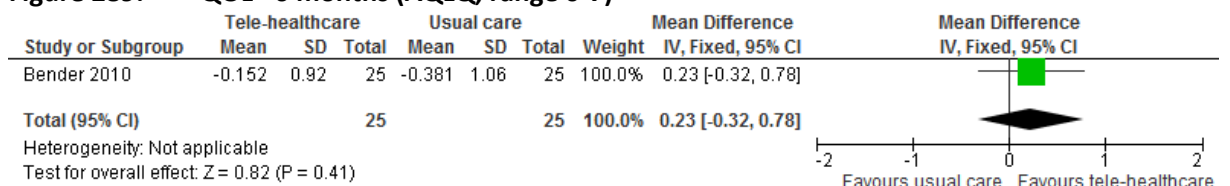
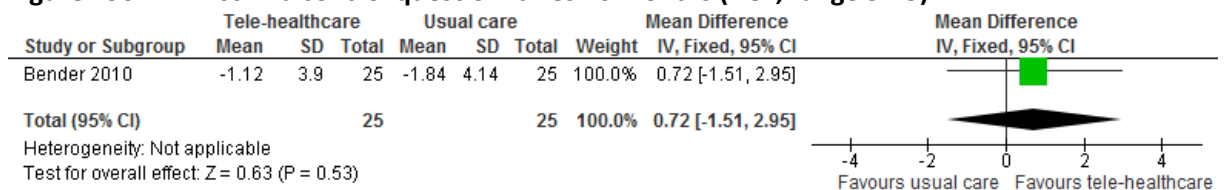


Figure 290: Asthma control questionnaires <6 months (ACT, range 5-25)



5

1.21.1.4 Children (5-16 years): Telehealthcare without healthcare professional involvement vs usual care

Figure 291: Exacerbations ≥6 months (OCS rescue use)

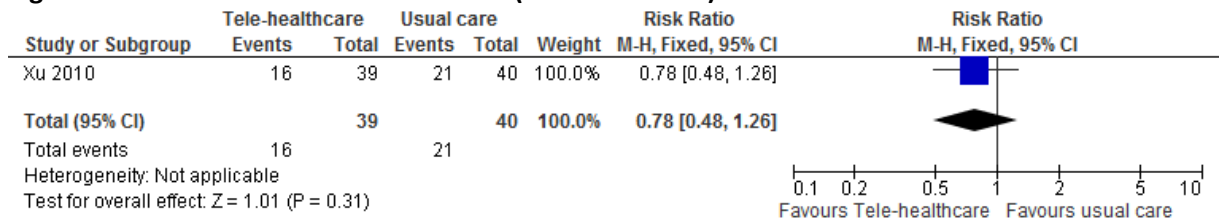


Figure 292: QOL ≥6 months (pAQLQ carer).

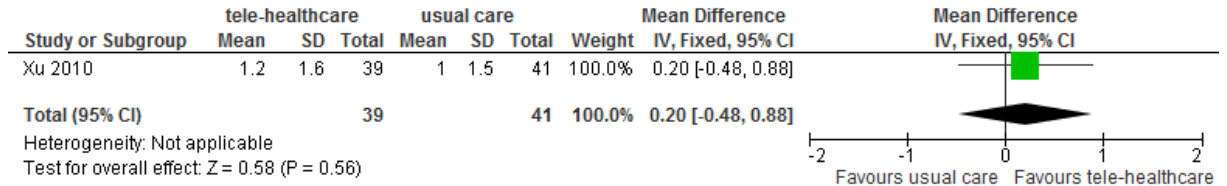


Figure 293: QOL ≥6 months (pAQLQ child).

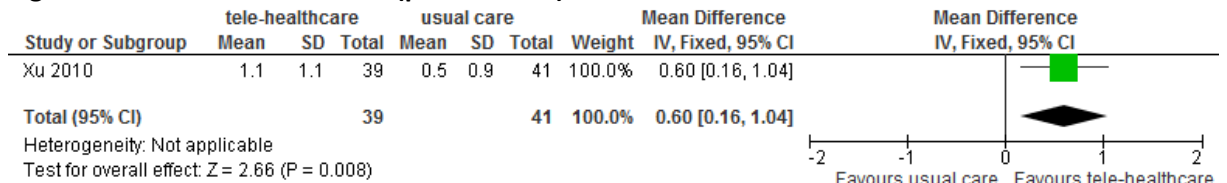


Figure 294: UHU ≥6 months (self-report ED presentation)

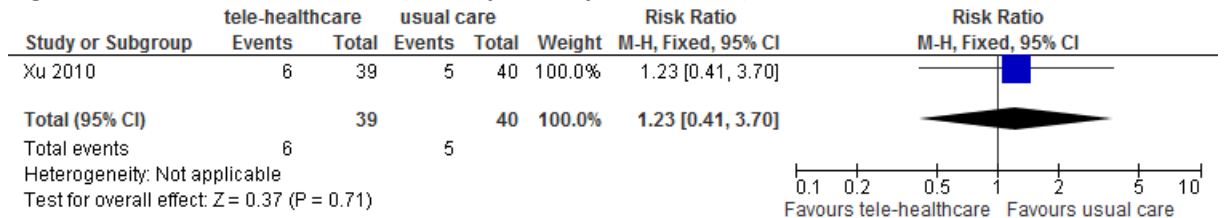
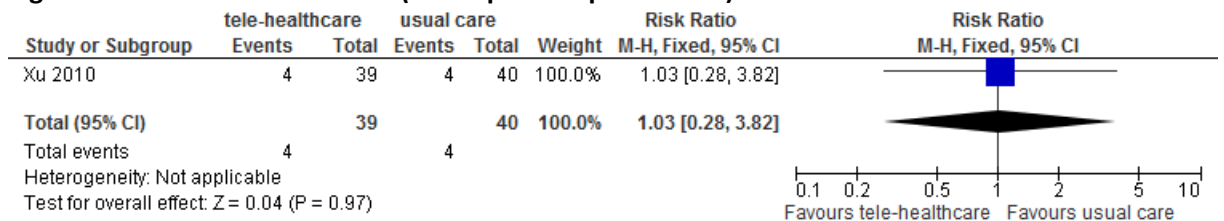


Figure 295: UHU ≥6 months (self-report hospitalisation)



2

Figure 296: School days lost ≥6 months (self-report yes/no)

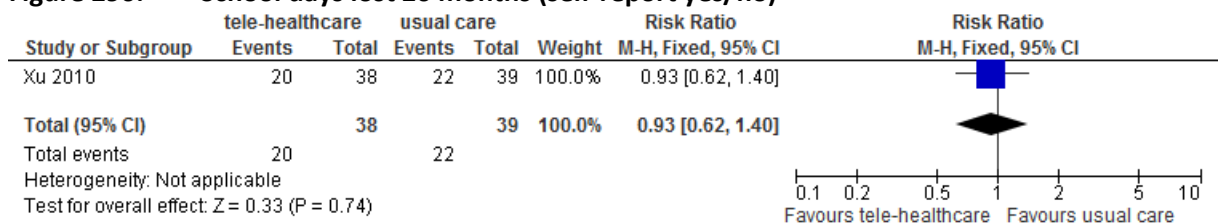


Figure 297: Parent work days lost ≥ 6 months (self-report yes/no)

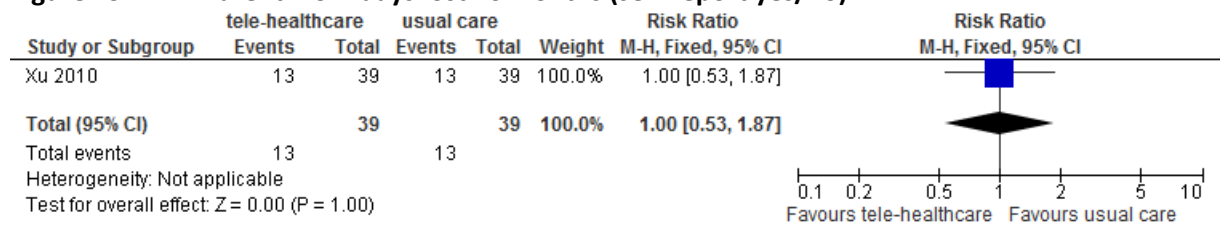


Figure 298: Patients who should have been on controllers at baseline (i.e. persistent asthma) but were not, who were on controllers at 6 months

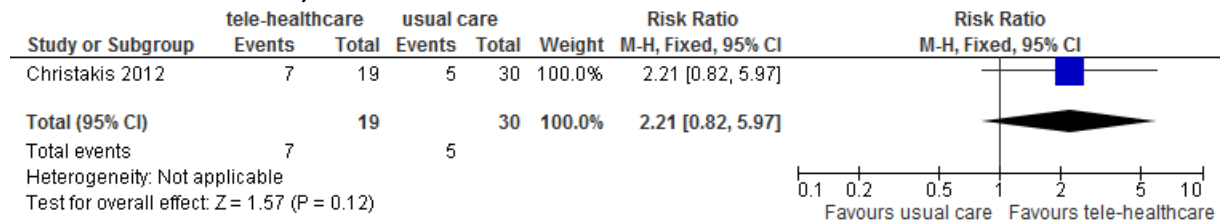


Figure 299: Persistent asthma on controllers at baseline but discontinued at 6 months.

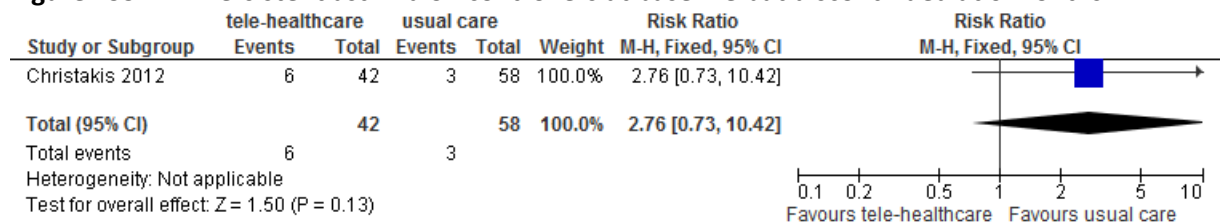
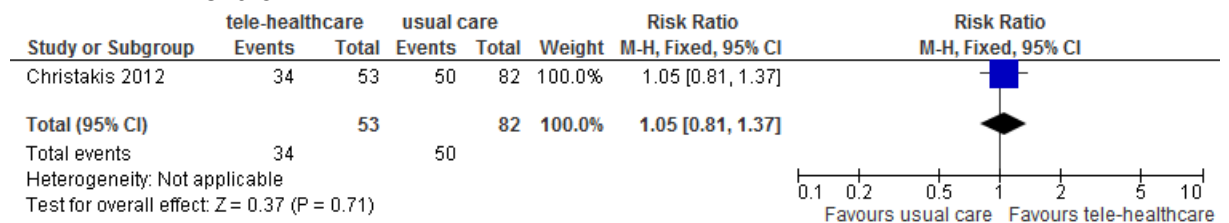


Figure 300: Of those who met severity criteria for controllers at baseline, number on them at 12 months



1
2

1 Appendix K: Excluded clinical studies

2 K.1 Diagnosis: Signs and symptoms

3 **Table 207: Studies excluded from the clinical review**

Reference	Reason for exclusion
ABRAMSON 1992 ⁹	General population and no subgroup analysis
ABRAMSON 1996A ¹⁰	General population and no subgroup analysis
ABRAMSON 2002 ¹²	Wrong definition of Phys Dx – no objective test.
AMAT 2011 ⁴¹	Wrong definition of Phys Dx – no objective test.
ANDERSON 1986 ⁴⁴	Wrong definition of Phys Dx – no objective test.
ANDERSON 1987 ⁴⁵	Wrong definition of Phys Dx – no objective test.
ANTOLINAMERIGO 2012 ⁵⁴	Conference abstract
ARIF 2003 ⁶⁷	General population and no subgroup analysis
ARIF 2004 ⁶⁶	Older children: wrong definition of Phys Dx – no objective test. Younger children: looks at wrong risk factors (not those specified in our protocol).
ARIF 2007 ⁶⁹	Wrong definition of Phys Dx – no objective test.
ARIF 2008 ⁶⁸	General population and no subgroup analysis; QoL only given in asthma subgroup.
ARNEDOPENA 2009 ⁷³	General population and no subgroup analysis
ARSHAD 2005 ⁷⁴	Wrong definition of Phys Dx – no objective test.
ASHER 2008 ⁷⁶	Wrong definition of Phys Dx – no objective test.
ATHERTON 1996 ⁷⁷	Wrong definition of Phys Dx – no objective test.
AUSTIN 1997 ⁷⁹	RFs for wheeze, not asthma.
BACHARIER 2012BACHARIER2012}	Asthma (wheeze in children) and no comparison group.
BACKER 2009 ⁸⁸	No comparison group – asthma only.
BAI 1998 ⁹²	Wrong definition of Phys Dx – no objective test.
BALL 2000 ⁹⁸	Gives prevalence of asthma but not symptoms.

Reference	Reason for exclusion
BARRY 2012 ¹¹⁶	General population and no subgroup analysis, and looks at the wrong risk factors (not those specified in our protocol),
BAUMAN 1992 ¹²⁷	Wrong definition of Phys Dx – no objective test.
BAUMANN 1986 ¹²⁸	Wrong comparison group: asthma vs. healthy controls.
BEACH 1995 ¹³³	Diurnal variation in methacholine results, not in symptoms.
BEEH 2003 ¹³⁶	Wrong population: only patients without asthma.
BELAMARICH 2000 ¹⁴²	Wrong definition of Phys Dx – no objective test.
BELLIA 2000 ¹⁴⁷	Wrong definition of Phys Dx – no objective test.
BENTUR 2004 ¹⁵³	Wrong definition of Phys Dx – no objective test.
BERG 2004 ¹⁵⁷	General population and no subgroup analysis
BERG 2011 ¹⁵⁴	Wrong definition of Phys Dx – no objective test.
BERZ 2007 ¹⁶⁵	Correct Phys Dx, but Looks at the wrong risk factors (not those specified in our protocol), and gives prevalence in people with asthma with no comparison group.
BISGAARD 2011 ¹⁷⁵	Wrong population for sens/spec: general population. Wrong population for prevalence data: asthma or general population, not asthma vs. other respiratory diseases. Predictors of asthma development are not given in useable categories.
BOLLAG 2000 ¹⁸²	Wrong outcomes: asthma attack rates.
BONER 2010 ¹⁸⁵	Wrong definition of Phys Dx – no objective test.
BORREGO 2009 A ¹⁹²	Does not give the % of people with asthma.
BORREGO 2010 ¹⁹³	Looks at the wrong risk factors (not those specified in our protocol).
BOUDREAU 1995 ¹⁹⁹	Wrong results: presence of

Reference	Reason for exclusion
	symptoms during histamine challenge.
BOULET 1991 ²⁰¹	Asthma pts only and no comparison group.
BOUSQUET 2004 ²⁰³	Wrong definition of Phys Dx of asthma only group – no objective test.
BRAUNFAHRLANDER 1998 ²¹⁸	Wrong definition of Phys Dx – no objective test.
BRAUNFAHRLANDER 2004 ²¹⁹	General population and no subgroup analysis
BRENNER 2001 ²²¹	Wrong definition of Phys Dx – no objective test.
BRESCIANINI 2009 ²²²	Wrong definition of Phys Dx – no objective test.
BROEKHUIZEN 2010 ²²⁷	Cannot calculate sensitivity and specificity
BROOKE 1998 ²³⁰	Wrong definition of Phys Dx – no objective test.
BRUTSCHE 2006 ²³⁹	Wrong outcomes/population: prevalence of symptoms in previously asymptomatic pts.
BURNEY 1989 ²⁴⁸	Wrong outcomes: sens/spec for wheeze, asthma attack, or bronchial irritability, not asthma Dx.
BURROWS 1991 ²⁵⁰	Wrong definition of Phys Dx – no objective test.
BUSINCO 1979 ²⁵³	Gives prevalence of people with asthma (wheezers) only, no comparison group.
CAREY 1996 ²⁷²	Wrong definition of Phys Dx – no objective test.
CARTER 2006 ²⁸⁷	Wrong definition of Phys Dx – no objective test.
CAUDRI 2007 ²⁹³	Wrong definition of Phys Dx – no objective test.
CAUDRI 2009 ²⁹⁴	Wrong definition of Phys Dx – no objective test.
CAUDRI 2010 ²⁹⁵	Wrong outcomes: risk factors for future asthma symptoms not asthma Dx. Prevalence of symptoms in suspected asthma but not in asthma vs. other respiratory diseases.
CHANG 2013 ³⁰¹	Population does not match protocol – family history of respiratory allergy
CHINN 2004 ³¹⁶	General population and no

Reference	Reason for exclusion
	subgroup analysis
CHRISTOFF 2013 ³²⁶	Conference abstract
COLEMAN 2001 ³⁵⁹	Wrong definition of Phys Dx – no objective test.
CORDEIRO 2011 ^{365,365}	Population does not match protocol – general allergic symptoms not respiratory symptoms only.
CORTESALVAREZ 2007 ³⁶⁸	Reference standard does not match protocol – history of atopic disorders in ≤ 3 yrs with wheezing, but no Dx of asthma made
COURT 2002 ³⁷²	Wrong definition of Phys Dx – no objective test.
CSONKA 2000A ³⁸²	Wrong definition of Phys Dx – no objective test.
CUIJPERS 1994 ³⁸³	Wrong definition of Phys Dx – no objective test.
DALES 1987 ³⁹¹	Wrong outcomes: sens/spec and predictors of AHR not asthma.
DALES 1988 ³⁹²	Wrong outcomes: predictors of AHR not asthma.
DAS 2003 ³⁹³	Levels of IgE in wheezers v. controls. Not signs and symptoms.
DEBENEDICTIS 1986 ³⁹⁶	Not known who had asthma, but only people with chronic cough who were MCT positive.
DEMARCO 2005 ⁴⁰⁴	Wrong definition of Phys Dx – no objective test.
DEMARCO 2006 ⁴⁰⁵	Prognostic factors for asthma severity, rather than for developing asthma.
DEN OTTER 1998 ⁴²³	Wrong outcomes; symptoms in people who consulted the GP vs. those who did not, rather than people with asthma.
DODGE 1994 ⁴⁴⁴	Wrong definition of Phys Dx – no objective test.
DODGE 1996 ⁴⁴⁵	Wrong definition of Phys Dx – no objective test.
FANIRAN 1999 ⁴⁹⁰	General population and no subgroup analysis
FLEMING 2000 ⁵⁰⁴	Prevalence of asthma over

Reference	Reason for exclusion
	time rather than symptoms.
FOUCARD 1984 ⁵¹³	Reference standard does not match protocol (children who reported asthma symptoms during the last year were regarded as having asthma)
FRANK 1996 ⁵¹⁶	Wrong definition of Phys Dx – no objective test.
FRANK 2001 ⁵¹⁷	Wrong definition of Phys Dx – no objective test.
FRANK 2008 ⁵¹⁸	Predictors of wheeze, not asthma.
FRISCHER 1993 ⁵²⁴	Wrong definition of Phys Dx – no objective test.
FUJIMURA 2005 ⁵³³	Looks at the wrong risk factors (not those specified in our protocol).
GARCINUNO 2013 ⁵⁵⁰	Wrong definition of Phys Dx – no objective test.
GERALD 2009 ⁵⁵⁶	Cannot calculate sensitivity and specificity
GLASGOW 2001 ⁵⁷⁴	General population and no subgroup analysis; and sens/spec not in suspected asthma.
GODDEN 1994 ⁵⁷⁵	Meets all inclusion criteria for prevalence study, except wrong sample size, N<200.
GOKSOR 2006 ⁵⁸²	Wrong definition of Phys Dx – no objective test.
GOKSOR 2008 ⁵⁸³	Wrong definition of Phys Dx – no objective test.
GUERRA 2004 ⁶¹²	Wrong definition of Phys Dx – no objective test.
GUILBERT 2004A ⁶¹⁴	Wrong definition of Phys Dx – no objective test.
GUILBERT 2004B ⁶¹³	Risk factors for wheeze in adults, not asthma.
GUILBERT 2011A ⁶¹⁵	Wrong definition of Phys Dx – no objective test.
HABBICK 1999 ⁶²⁰	Wrong definition of Phys Dx – no objective test.
HABY 2001 ⁶²¹	Looks at the wrong risk factors (not those specified in our protocol). Prevalence in general population.
HAFKAMP 2012 ⁶²⁵	Looks at the wrong risk factors (not those specified in our protocol).

Reference	Reason for exclusion
HAFKAMP 2013 ⁶²⁴	Wrong definition of Phys Dx – no objective test.
HAFKAMP 2013A ⁶²³	Prevalence in general population.
HAHN 1994 ⁶²⁶	Wrong definition of Phys Dx – no objective test.
HALL 2006 ⁶²⁸	Wrong definition of Phys Dx – no objective test.
HALLIDAY 1993 ⁶³⁰	Wrong definition of Phys Dx – no objective test.
HALONEN 1999 ⁶³¹	Looks at the wrong risk factors (not those specified in our protocol). Prevalence in general population.
HALONEN 2013 ⁶³²	Looks at the wrong risk factors (not those specified in our protocol). Prevalence in general population.
HANCOX 2004 ⁶³⁵	Wrong definition of Phys Dx – no objective test.
HANCOX 2005 ⁶³⁶	Looks at the wrong risk factors (not those specified in our protocol).
HANCOX 2006 ⁶³⁷	Wrong definition of Phys Dx – no objective test.
HANSEL 2011 ⁶³⁹	Cannot calculate sensitivity and specificity
HEINRICH 1998 ⁶⁶¹	Prevalence in general population.
HEINRICH 1999 ⁶⁶⁰	Prevalence in general population. Looks at the wrong risk factors (not those specified in our protocol).
HEINRICH 2002 ⁶⁵⁹	Wrong definition of Phys Dx – no objective test.
HENDERSON 1995 ⁶⁶⁴	Predictor of wheeze, not asthma.
HENDERSON 2005 ⁶⁶⁶	Prevalence in wrong population: RSV pts vs. controls, not asthma vs. other respiratory diseases.
HENDERSON 2008 ⁶⁶⁵	Wrong definition of Phys Dx – no objective test.
HENDERSON 2008A ⁶⁶⁷	Wrong definition of Phys Dx – no objective test.
HENSLEY 2003 ⁶⁷¹	Prevalence in wrong population: not asthma vs. other respiratory diseases.

Reference	Reason for exclusion
HERR 2012 ⁶⁷³	Age 18 months, but assessment of symptoms made in the previous 12 months.
HERR 2012A ⁶⁷²	Age 18 months, but assessment of symptoms made in the previous 12 months.
HICKSON 2009 ⁶⁷⁷	Prevalence in general population.
HIRSCH 1999 ⁶⁸³	Wrong definition of Phys Dx – no objective test.
HIRSCH 2004 ⁶⁸²	Looks at a new score for Dx of asthma. However the score contains other aspects as well as symptoms, and results are not given separately for the symptoms.
HODGE 1996 ⁶⁸⁴	Looks at the wrong risk factors (not those specified in our protocol).
HOEK 2012 ⁶⁸⁵	Prevalence in general population.
HOLSTER 2012 ⁶⁹¹	Wrong definition of Phys Dx – no objective test. Looks at the wrong risk factors (not those specified in our protocol).
HOLT 2010 ⁶⁹³	Prevalence in general population. Looks at the wrong risk factors (not those specified in our protocol).
HOMNICK 2007 ⁶⁹⁷	Wrong definition of Phys Dx – no objective test.
HOPP 1995 ⁷⁰³	Dx ability of questionnaire but looks at asthma a vs. controls in general population, not suspected asthma pts.
HOPPER 1995 ⁷⁰⁴	Prevalence in general population.
HOPPER 2012 ⁷⁰⁵	Wrong definition of Phys Dx – no objective test.
HORAK 2003 ⁷⁰⁶	Wrong definition of Phys Dx – no objective test.
HORAK 2006 ⁷⁰⁸	Prevalence in general population.
HORAK 2007 ⁷⁰⁷	Prevalence in general population. Looks at the wrong risk factors (not those specified in our protocol).

Reference	Reason for exclusion
HORWOOD 1985 ⁷¹¹	Meets all inclusion criteria for prognostic study in children, except wrong follow-up time: 6 years.
HU 1997 ⁷¹⁵	Prevalence in general population. Looks at the wrong risk factors (not those specified in our protocol).
HU 1997A ⁷¹⁴	Wrong definition of Phys Dx – no objective test.
HUBLET 2006 ⁷¹⁸	Prevalence in general population.
HUNGER 2010 ⁷²⁰	Wrong definition of Phys Dx – no objective test.
ILLI 2001 ⁷³³	Wrong definition of Phys Dx – no objective test.
ILLI 2001A ⁷³²	Prevalence in general population.
ILLI 2004 ⁷³⁴	Wrong definition of Phys Dx – no objective test.
ILLI 2006 ⁷³⁵	Wrong definition of Phys Dx – no objective test.
INKLEY 1967 ⁷³⁸	Prevalence in general population.
IRWIN 1990 ⁷³⁹	Gives the prevalence of asthma in people with cough, not the prevalence of cough in people who do not have asthma.
ISLAM 2007 ⁷⁴²	Wrong definition of Phys Dx – no objective test.
IVERSEN 2005 ⁷⁴³	Wrong definition of Phys Dx – no objective test.
JACKSON 2008 ⁷⁴⁷	Wrong definition of Phys Dx – no objective test.
JACOBS 2012 ⁷⁴⁸	Wrong definition of Phys Dx – no objective test.
JAMES 2010 ⁷⁵³	Wrong definition of Phys Dx – no objective test.
JAMES 2013 ⁷⁵⁴	Prevalence in general population.
JAMROZIK 2009 ⁷⁵⁶	Wrong definition of Phys Dx – no objective test.
JANSON 2001 ⁷⁶⁰	Wrong definition of Phys Dx – no objective test.
JANSON 2001A ⁷⁶¹	Wrong definition of Phys Dx – no objective test.
JARTTI 2008 ⁷⁶⁶	Wrong definition of Phys Dx –

Reference	Reason for exclusion
	no objective test.
JARVIS 1994 ⁷⁶⁹	Prevalence in general population.
JARVIS 1996 ⁷⁶⁷	Wrong definition of Phys Dx – no objective test.
JARVIS 2002 ⁷⁶⁸	Wrong definition of Phys Dx – no objective test.
JEFFS 2000 ⁷⁷¹	Unclear Physy Dx – but seems like ISAAC questionnaire.
JENKINS 1994A ⁷⁷⁴	Wrong definition of Phys Dx – no objective test.
JENKINS 2006 ⁷⁷³	Wrong definition of Phys Dx – no objective test.
JOHNSON 2013 ⁷⁸⁰	General population and no subgroup analysis
JOHNSTON 1998 ⁷⁸¹	Risk factors for other respiratory problems, not asthma. Prevalence of people with asthma with no comparison group.
JONES 2008 ⁷⁸⁵	Results separated for different ethnic groups. Mixed ages of children (<5 and >5 years with no subgroup analysis). Wrong definition of Phys Dx – no objective test.
JOSEPH 1996 ⁷⁸⁸	Wrong definition of Phys Dx – no objective test.
JOSEPH 1999 ⁷⁸⁹	Reference standard does not match protocol (self-reported physician Dx of asthma – no objective test).
JOSEPH-BOWEN 2004 ⁷⁹¹	Reference standard does not match protocol; physician diagnosis + symptoms of wheeze in last 12 months + asthma meds in last 12 months (no objective test)
JUHN 2005 ⁷⁹²	Looks at the wrong risk factors (not those specified in our protocol). Unclear percentage who had objective test with the Phys Dx.
JUNG 2012 ⁷⁹⁵	Looks at the wrong risk factors (not those specified in our protocol). Prevalence in general population.
JUNG 2012A ⁷⁹⁴	Predictors of wheeze, not asthma.
JUST 2010 ⁸⁰⁹	Predictors of wheeze, not

Reference	Reason for exclusion
	asthma.
JUST 2013 ⁸¹⁰	Wrong outcome: predictors of different types of wheeze.
KABESCH 2004 ⁸¹¹	Looks at the wrong risk factors (not those specified in our protocol). Prevalence in general population.
KABIR 2009 ⁸¹²	Wrong definition of Phys Dx – no objective test.
KABLE 2001 ⁸¹³	Prevalence and sens/spec in general population.
KAGEN 2014 ⁸¹⁴	Conference abstract
KAPPELLE 2012 ⁸²⁰	Wrong definition of Phys Dx – no objective test.
KARAKOC 2002 ⁸²⁵	Prevalence in general population, and looks at wrong risk factors (not those specified in our protocol).
KAUFFMANN 1997 ⁸³⁰	Wrong definition of Phys Dx – no objective test.
KAUFFMANN 2011 ⁸³¹	Epidemiology.
KAUGARS 2008 ⁸³³	Looks at wrong risk factors (not those specified in our protocol).
KEALL 2012 ⁸³⁷	Prevalence in general population.
KEARNEY 1998 ⁸³⁸	Wrong definition of Phys Dx – no objective test.
KEIL 1996 ⁸⁴¹	General population and no subgroup analysis
KEIL 2006 ⁸⁴⁰	Review – used as a source of references
KELLY 1987 ⁸⁴²	Unclear Phys Dx. Case-control study.
KELLY 1995 ⁸⁴³	Wrong definition of Phys Dx – no objective test.
KELLY 1996 ⁸⁴⁴	Wrong definition of Phys Dx – no objective test.
KERCSMAR 2008 ⁸⁴⁹	Conference summary.
KERKHOF 2009 ⁸⁵¹	Wrong definition of Phys Dx – no objective test.
KHARITONOV 1996 ⁸⁶⁰	Asthma only – no comparison group. Correct Phys Dx with objective test.
KHOSHOO 2009 ⁸⁶³	Meets all inclusion criteria for prevalence study, except

Reference	Reason for exclusion
	sample size N<200.
KIEFTEDE 2012 ⁸⁶⁴	Looks at wrong risk factors. Prevalence in general population.
KING 2004 ⁸⁷⁷	Predictors of lung function, not asthma. Does not give prevalence in asthma pts.
KISS 2003 ⁸⁷⁸	Symptoms as predictors of angina, not asthma! Unclear asthma Dx.
KLAASSEN 2012 ⁸⁸⁴	Does not give prevalence of symptoms, or predictors, or ability to diagnose.
KLINNERT 2001 ⁸⁸⁹	Wrong definition of Phys Dx – no objective test.
KLINNERT 2008 ⁸⁹⁰	General population and no subgroup analysis, and looks at wrong risk factors (not those specified in out protocol).
KLJAKOVIC 1991 ⁸⁹¹	General population and no subgroup analysis
KNEYBER 2000 ⁸⁹²	Does not give symptoms in asthma, but bronchiolitis and control group.
KOLLER 1997 ⁹⁰³	Age < 1 year
KOLNAAR 1995 ⁹⁰⁴	Reference standard does not match protocol - comparison of histamine test to presence of asthma symptoms (not to physician Dx)
KOPONEN 2012 ⁹¹¹	Wrong definition of Phys Dx – no objective test.
KOSHY 2010 ⁹¹³	General population and no subgroup analysis
KOZYRSKYJ 2003 ⁹²⁶	Wrong definition of Phys Dx – no details given or mention of objective test.
KOZYRSKYJ 2004 ⁹²⁷	Wrong definition of Phys Dx – no objective test.
KOZYRSKYJ 2009 ⁹²⁵	Wrong definition of Phys Dx – no objective test.
KUEHNI 2000 ⁹³¹	Wrong definition of Phys Dx – no objective test.
KUEHNI 2001 ⁹³²	Prevalence of symptoms in people with asthma only, no comparison group.
KUEHR 1995 ⁹³⁴	Wrong comparison group:

Reference	Reason for exclusion
	asthma vs. non-asthma (not other respiratory symptoms).
KUHNI 1995 ⁹³⁶	Does not mention asthma definition of Dx.
KUMAR 2008 ⁹⁴¹	General population and no subgroup analysis
KURUKULAARATCHY 2002 ⁹⁴⁶	Gives prevalence data in people with asthma but no other respiratory comparison group. Prognostic data not used as wrong follow-up time: baseline (birth) to 10 years later (does not match our protocol criteria).
KURUKULAARATCHY 2003 ⁹⁴⁸	Risk of wheeze not asthma (older children).
KURUKULAARATCHY 2003A ⁹⁵⁰	Asthma only - no comparison group.
KURUKULAARATCHY 2004 ⁹⁴⁵	Wrong population: wheeze not asthma (older children).
KURUKULAARATCHY 2004A ⁹⁴⁹	General population and no subgroup analysis
KURUKULAARATCHY 2005 ⁹⁵¹	General population and no subgroup analysis; looks at wrong risk factors (not those in our protocol).
KURUKULAARATCHY 2005A ⁹⁴⁷	Prevalence and risk factors for atopy, not asthma.
LABRUZZO 2007 ⁹⁵⁶	Review.
LAI 2009 ⁹⁶⁰	General population and no subgroup analysis
LANGE 2010 ⁹⁶⁴	General population and no subgroup analysis
LAU 2000 ⁹⁷²	General population and no subgroup analysis
LAU 2002 ⁹⁷⁴	Prevalence in wheezers (young children) but no comparison group.
LAU 2003 ⁹⁷³	Predictors of impaired lung function not asthma.
LAU 2005 ⁹⁷¹	Wrong definition of Phys Dx – no objective test.
LAUBEREAU 2002 ⁹⁷⁵	General population and no subgroup analysis
LEERMAKERS 2013 ⁹⁸⁶	General population and no subgroup analysis
LEONARDI 2011 ⁹⁹³	Wrong definition of Phys Dx –

Reference	Reason for exclusion
	no objective test.
LEONE 2012 ⁹⁹⁴	Wrong definition of Phys Dx – no objective test.
LESOUF 1995 ⁹⁸⁰	General population and no subgroup analysis
LEUNG 1994 ⁹⁹⁷	Wrong definition of Phys Dx – no objective test.
LEVESQUE 2004 ¹⁰⁰⁰	Wrong definition of Phys Dx – no objective test.
LEWIS 1995 ¹⁰⁰⁴	Predictors of wheeze not asthma (in young people).
LEWIS 1996 ¹⁰⁰³	General population and no subgroup analysis
LI 2006B ¹⁰¹⁰	Wrong definition of Phys Dx – no objective test.
LIEM 2007 ¹⁰¹³	RFs for transient tachypnea and wheeze, not asthma.
LINEHAN 2007 ¹⁰²²	General population and no subgroup analysis.
LINEHAN 2009 ¹⁰²¹	Prevalence in people with respiratory symptoms, not asthma.
LINEHAN 2012 ¹⁰²⁰	General population and no subgroup analysis.
LOERBROKS 2012 ¹⁰³⁶	Prevalence in general population but not in asthma subgroup.
LUYT 1993 ¹⁰⁵³	General population or asthma subgroup (no comparison group).
LUYT 1994 ¹⁰⁵²	Wrong definition of Phys Dx for children up to 5 years old: no objective test, just symptoms ascertained by questionnaire.
LUYT 1995 ¹⁰⁵¹	General population or asthma subgroup (no comparison group). Looks at wrong risk factors (not those specified in our protocol).
MAAS 2009 ¹⁰⁵⁴	Does not answer the question. Effect of allergen-reduction interventions on the prevention of asthma.
MAGDALIJNS 2011 ¹⁰⁵⁹	General population and no subgroup analysis
MAHER 2004 ¹⁰⁶³	Cannot calculate sensitivity and specificity
MAITRA 2004 ¹⁰⁶⁶	General population and no

Reference	Reason for exclusion
	subgroup analysis
MALLOL 2010 ¹⁰⁷⁴	Percentage of wheezers who had asthma, rather than % of asthma who had wheeze.
MANDHANE 2005 ¹⁰⁸²	RFs for wheeze, not asthma.
MANFREDA 2001 ¹⁰⁸³	Wrong definition of Phys Dx – no objective test.
MANNING 2007 ¹⁰⁸⁴	Conference abstract.
MARBURY 1996 ¹⁰⁸⁸	General population and no subgroup analysis
MAROSSY 2007 ¹⁰⁹¹	Wrong definition of Phys Dx – no objective test.
MARTINDALE 2005 ¹⁰⁹²	General population and no subgroup analysis
MARTINEZ 1995 ¹⁰⁹³	General population and no subgroup analysis
MARTINEZ 2006 ¹⁰⁹⁴	General population and no subgroup analysis
MATHESON 2006 ¹⁰⁹⁹	Looks at the wrong risk factors (not those specified in our protocol).
MATRICARDI 2008 ¹¹⁰¹	Predictors of wheeze not asthma (in young people).
MAZIAK 2002 ¹¹⁰⁹	Wrong definition of Phys Dx – no objective test.
MAZIAK 2004 ¹¹¹⁰	Wrong definition of Phys Dx – no objective test.
MCCONNELL 1999 ¹¹¹³	Wrong definition of Phys Dx – no objective test.
MCCONNELL 2002 ¹¹¹⁴	Wrong definition of Phys Dx – no objective test.
MCHEDLISHVILI 2013 ¹¹²⁰	Conference abstract
MCKEEVER 2002 ¹¹²¹	Unclear age of children and follow-up time.
MICHEL 2006 ¹¹⁴¹	Dx of wheeze in older children (not asthma).
MIDODZI 2010 ¹¹⁴³	Wrong definition of Phys Dx for children up to 5 years old: no objective test, just symptoms ascertained by questionnaire.
MIEDINGER 2007 ¹¹⁴⁶	Good definition of Phys Dx, but gives sens/spec in general population (not suspected asthma), and prevalence in

Reference	Reason for exclusion
	asthma pts only (no comparison group).
MILAM 2008 ¹¹⁴⁸	No comparison group: wheeze only.
MILLSTEIN 2004 ¹¹⁵⁴	Wrong definition of Phys Dx – no objective test. Wrong definition of Phys Dx – no objective test.
MITCHELL 1989 ¹¹⁶²	General population and no subgroup analysis.
MITCHELL 1994 ¹¹⁶⁰	Wrong definition of Phys Dx – no objective test.
MITCHELL 1997 ¹¹⁶⁴	Methods paper – not study results.
MITCHELL 2009 ¹¹⁶³	Predictors of wheeze, not asthma (older children)
MOHANGOO 2010 ¹¹⁷¹	Good definition of Phys Dx, but gives sensitivity/specificity in general population (not suspected asthma), and prevalence in general population (not people with asthma).
MOMAS 1998 ¹¹⁷²	Wrong definition of Phys Dx – no objective test.
MOMMERS 2005 ¹¹⁷³	Wrong comparison group - - prevalence in asthma vs. controls (not vs. other respiratory diseases), and looks at the wrong risk factors (not those specified in our protocol).
MORASS 2008 ¹¹⁷⁸	General population and no subgroup analysis; looks at the wrong risk factors (not those specified in our protocol).
MORGAN 2005 ¹¹⁷⁹	Literature review.
MUSK 2011 ¹¹⁹⁷	Wrong definition of Phys Dx – no objective test.
MVULA 2005 ¹²⁰¹	General population and no subgroup analysis
NAGEL 2009A ¹²⁰⁵	Looks at the wrong risk factors (not those specified in our protocol).
NAGEL 2010 ¹²⁰⁷	Looks at the wrong risk factors (not those specified in our protocol). Prevalence of asthma in general population

Reference	Reason for exclusion
NAGEL 2012 ¹²⁰⁶	Wrong definition of Phys Dx – no objective test.
NANKANI 1990 ¹²⁰⁸	Wrong definition of Phys Dx – no objective test.
NEJJARI 1994 ¹²²⁰	Case-control study: asthma vs. healthy controls (not other respiratory diseases).
NEUMAN 2012 ¹²²²	Wrong definition of Phys Dx – no objective test.
NEVILLE 1992 ¹²²⁴	Wrong definition of Phys Dx – no objective test.
NEVILLE 2001 ¹²²⁵	Prevalence in asthma pts only (no comparison group).
NGMANKWONG 2001 ¹²²⁷	General population and no subgroup analysis
NGMANKWONG 2002 ¹²²⁶	Wrong definition of Phys Dx – no objective test.
NICOLAI 2003 ¹²³⁴	General population and no subgroup analysis
NINAN 1993 ¹²⁴⁸	Prevalence data only given in the symptomatic group who are BHR+ (ie people with asthma), not in any comparison group.
NINAN 1995 ¹²⁴⁷	Reference standard does not match protocol – Dx made on the basis of symptoms
NWARU 2013 ¹²⁶³	General population and no subgroup analysis; wrong risk factors (not those specified in the protocol).
OBERLE 2003 ¹²⁶⁶	Wrong definition of Phys Dx – no objective test.
ODDY 1999 ¹²⁶⁹	Wrong definition of Phys Dx – no objective test.
ODDY 2000 ¹²⁶⁷	Wrong definition of Phys Dx – no objective test.
ODDY 2002 ¹²⁶⁸	Wrong definition of Phys Dx – no objective test.
ODDY 2002A ¹²⁷⁰	General population and no subgroup analysis
ODDY 2004 ¹²⁷¹	Wrong definition of Phys Dx – no objective test.
OSMAN 2007 ¹²⁸⁸	Wrong definition of Phys Dx – no objective test.
PALMER 2004 ¹²⁹⁹	Wrong definition of Phys Dx – no objective test.
PANICO 2007 ¹³⁰²	General population and no

Reference	Reason for exclusion
	subgroup analysis
PARARAJASINGAM 1992 ¹³⁰⁸	General population and no subgroup analysis
PARK 1986 ¹³¹¹	Wrong definition of Phys Dx – no objective test.
PATERSON 1997 ¹³¹⁸	General population and no subgroup analysis
PATTEMORE 1990 ¹³²⁰	Reference standard does not match protocol (asthma diagnosis by previous report of a diagnosis but no objective test)
PEARLMAN 2005 ¹³²²	Wrong comparison group: people with asthma on Tx vs. Tx-naïve people with asthma.
PEAT 1991A ¹³²³	Predictors of wheeze, not asthma (older children).
PEAT 1993 ¹³²⁶	Good Phys Dx definition, but looks at wrong risk factors for asthma (not in our protocol).
PEAT 1994 ¹³²⁷	Good Phys Dx definition, but only gives prevalence in General population and no subgroup analysis.
PERSKY 1998 ¹³⁴⁰	Asthma and no comparison group.
PERZANOWSKI 2008A ¹³⁴²	General population and no subgroup analysis
PETERS 1999 ¹³⁴⁷	Wrong definition of Phys Dx – no objective test.
PINTO 2010 ¹³⁶⁶	General population and no subgroup analysis
PIZZICHINI 2000 ¹³⁶⁷	Wrong definition of Phys Dx – no objective test.
PLESSMULLOLI 2000 ¹³⁷¹	General population and no subgroup analysis
PLESSMULLOLI 2001 ¹³⁷²	General population and no subgroup analysis
PONSONBY 2000 ¹³⁷⁶	General population - gives prevalence of symptoms in asthma vs. no asthma (not other respiratory diseases).
PONSONBY 2004 ¹³⁷⁸	General population and no subgroup analysis
PONSONBY 2008 ¹³⁷⁹	General population and no subgroup analysis
POWELL 1995 ¹³⁸⁷	Wrong definition of Phys Dx – no objective test.

Reference	Reason for exclusion
POWELL 1996 ¹³⁸⁸	Wrong definition of Phys Dx – no objective test.
POWELL 1999 ¹³⁸⁶	General population and no subgroup analysis
POWER 1995 ¹³⁹¹	Wrong definition of Phys Dx – no objective test.
PRABHU 2010 ¹³⁹⁴	Prevalence in general population and asthma, but no comparison group.
PUJADESRODRIGUEZ 2009 ¹⁴¹³	General population and no subgroup analysis
PUJADESRODRIGUEZ 2009A ¹⁴¹⁴	Wrong definition of Phys Dx – no objective test.
RADON 2002 ¹⁴²¹	Wrong definition of Phys Dx – no objective test.
RAHERISON 2006 ¹⁴²⁴	Prevalence in asthma, but no comparison group.
RASMUSSEN 2002 ¹⁴³⁵	Wrong definition of Phys Dx – no objective test.
RAZA 2012 ¹⁴³⁸	Wrong definition of Phys Dx – no objective test.
REDLINE 2003 ¹⁴⁴²	Cannot calculate sensitivity and specificity
REGNIER 2013 ¹⁴⁴⁴	Looks at the wrong risk factors (not those specified in our protocol).
REMES 2001 ¹⁴⁴⁷	General population and no subgroup analysis; and looks at the wrong risk factors (not those specified in our protocol).
RENNIE 2004 ¹⁴⁴⁹	Prevalence in asthma subgroup, but no comparison group.
RIETVELD 1996 ¹⁴⁶⁰	Wrong population for Dx accuracy – asthma vs. controls rather than suspected asthma.
RIETVELD 1998 ¹⁴⁶¹	Wrong definition of Phys Dx – no objective test.
RIZWAN 2004 ¹⁴⁶⁵	General population and no subgroup analysis
ROBINSON 2012A ¹⁴⁶⁷	Correct definition of Phys Dx, but looks at the wrong risk factors (not those specified in our protocol).
RODRIGO 2013 ¹⁴⁶⁹	Treatment study
RODUIT 2009 ¹⁴⁷¹	General population and no

Reference	Reason for exclusion
	subgroup analysis
RONA 1995 ¹⁴⁷⁶	General population and no subgroup analysis
ROORDA 2001 ¹⁴⁷⁷	Prevalence of symptoms in suspected asthma, but not asthma vs. other respiratory diseases.
ROSIER 1994 ¹⁴⁸³	Does not answer the question. Gives data on prevalence of symptoms in patients with asthma vs. patients without asthma. Divides data into severity categories and measures of function within each category.
SALAM 2004 ¹⁵⁰¹	Looks at the wrong risk factors (not those specified in our protocol).
SALOME 1987 ¹⁵⁰³	Wrong definition of Phys Dx – no objective test.
SAVENIJE 2011 ¹⁵¹⁹	Wrong definition of Phys Dx – no objective test.
SCARLETT 1995 ¹⁵²⁰	General population and no subgroup analysis
SCHACHTER 2001 ¹⁵²³	Looks at the wrong risk factors (not those specified in our protocol).
SCHACHTER 2003 ¹⁵²²	General population and no subgroup analysis
SCHACHTER 1984 ¹⁵²¹	Wrong definition of Phys Dx – no objective test.
SCHAPER 2010 ¹⁵²⁴	Wrong definition of Phys Dx – no objective test.
SCHERNHAMMER 2008 ¹⁵²⁸	Wrong definition of Phys Dx – no objective test.
SCHOLTENS 2009 ¹⁵³⁹	General population and no subgroup analysis
SCHOLTENS 2009A ¹⁵⁴¹	General population and no subgroup analysis
SCHOLTENS 2010 ¹⁵⁴⁰	General population and no subgroup analysis
SCHONBERGER 2004 ¹⁵⁴²	Meets all inclusion criteria for prognostic study, but wrong follow-up time: >5 years. Children with wheeze followed for development of asthma in adolescence.
SCHUMPERT 2006 ¹⁵⁴⁴	Wrong definition of Phys Dx – no objective test.

Reference	Reason for exclusion
SCOTT 2010 ¹⁵⁵⁰	Wrong definition of Phys Dx – no objective test.
SEARS 1996 ¹⁵⁵⁴	Prevalence in General population and no subgroup analysis. Looks at the wrong risk factors (not those specified in our protocol).
SENNHAUSER 1995 ¹⁵⁶⁰	Wrong definition of Phys Dx – no objective test.
SENTHILSELVAN 1993 ¹⁵⁶¹	Wrong definition of Phys Dx – no objective test.
SHAHEEN 1998 ¹⁵⁶⁷	General population and no subgroup analysis
SHAHEEN 1999 ¹⁵⁶⁵	General population and no subgroup analysis
SHAHEEN 2005 ¹⁵⁶³	General population and no subgroup analysis
SHAHEEN 2000 ¹⁵⁶⁶	General population and no subgroup analysis
SHAHEEN 2002 ¹⁵⁶⁴	Prevalence of wheeze in future wheezers vs. non-wheezers (wrong comparison group).
SHANKARDASS 2009 ¹⁵⁶⁹	General population and no subgroup analysis
SHAVIT 2007 ¹⁵⁷³	Wrong definition of Phys Dx – no objective test.
SHERRIFF 2009 ¹⁵⁷⁵	General population and no subgroup analysis
SHIN 2010 ¹⁵⁸¹	Good definition of Phys Dx – uses objective test. BUT wrong comparison group: asthma vs. healthy controls, not other respiratory symptoms.
SHREWSBURY 2000 ¹⁵⁸⁸	Meta-analysis of Tx studies – shows symptoms in asthma only (no comparison group).
SIBBALD 1992 ¹⁵⁸⁹	General population and no subgroup analysis
SILVER 1998 ¹⁵⁹³	Wrong definition of Phys Dx – no objective test.
SILVERS 2009 ¹⁵⁹⁴	General population and no subgroup analysis; and looks at the wrong risk factors (not those specified in our protocol).
SILVERS 2012 ¹⁵⁹⁵	Looks at the wrong risk factors (not those specified in

Reference	Reason for exclusion
	our protocol).
SIMPSON 2010 ¹⁶⁰⁷	Prevalence in General population and no subgroup analysis. Looks at the wrong risk factors (not those specified in our protocol).
SIN 2002 ¹⁶¹¹	Wrong definition of Phys Dx – no objective test.
SISTEK 2001A ¹⁶¹⁷	Wrong definition of Phys Dx – no objective test.
SISTEK 2006 ¹⁶¹⁸	Reference standard does not match protocol – asthma Dx based on questionnaire responses to doctor diagnosed asthma and attack in the last 12 months (no mention of objective test)
SMIT 2009 ¹⁶²⁶	Does not give prevalence of symptoms.
SNIJDERS 2007 ¹⁶³⁴	Looks at the wrong risk factors (not those specified in our protocol).
SOCKRIDER 2001 ¹⁶³⁶	Wrong definition of Phys Dx – no objective test.
SOLOMON 2003 ¹⁶³⁷	General population and no subgroup analysis
SONNENSCHNEIN 2012 ¹⁶⁴¹	Looks at the wrong risk factors (not those specified in our protocol).
SONNENSCHNEIN VAN DER VOORT 2012 ¹⁶⁴⁰	General population and no subgroup analysis
SORIANO 2003 ¹⁶⁴⁷	All asthma pts – no comparison group; does not give prevalence of symptoms.
SOTIR 2006 ¹⁶⁴⁸	Prevalence of asthma and wheeze in RTI pts, not symptoms in asthma.
SOTORAMIREZ 2013 ¹⁶⁴⁹	Wrong definition of Phys Dx – no objective test.
SPEEVANDERWEKKE 1998 ¹⁶⁵⁶	General population and no subgroup analysis
SPYCHER 2008 ¹⁶⁶⁴	General population and no subgroup analysis
SPYCHER 2009 ¹⁶⁶⁶	General population and no subgroup analysis
SPYCHER 2012 ¹⁶⁶⁵	Wrong definition of Phys Dx – no objective test.
STERN 2008 ¹⁶⁷⁷	Wrong definition of Phys Dx – no objective test.

Reference	Reason for exclusion
STINGONE 2008 ¹⁶⁸¹	Asthma and no comparison group.
STINGONE 2011 ¹⁶⁸²	Asthma and no comparison group.
STODDARD 1995 ¹⁶⁸³	General population and no subgroup analysis
STRACHAN 1985 ¹⁶⁸⁷	General population and no subgroup analysis
STRACHAN 1988A ¹⁶⁸⁸	Wrong definition of Phys Dx – no objective test.
STRACHAN 1994 ¹⁶⁸⁹	Wrong definition of Phys Dx – no objective test.
STRACHAN 1996 ¹⁶⁹¹	Unclear definition of diagnosis – seems like self-reported.
STRACHAN 1996B ¹⁶⁹⁰	Wrong definition of Phys Dx – no objective test.
STRUNK 2002 ¹⁶⁹³	RFs for night-awakening due to asthma, not for asthma. Prevalence of symptoms in people with asthma but no comparison group.
SUN 2011 ¹⁷⁰⁰	General population and no subgroup analysis. Looks at the wrong risk factors (not those specified in our protocol).
SUN 2013 ¹⁶⁹⁹	General population and no subgroup analysis. Looks at the wrong risk factors (not those specified in our protocol).
SUNYER 2004 ¹⁷⁰²	Wrong outcomes: fraction of asthma caused by atopy.
SUTHERLAND 2007 ¹⁷⁰⁴	Wrong definition of Phys Dx – no objective test.
TAGIYEVA 2010 ¹⁷¹⁴	General population and no subgroup analysis
TAI 2009 ¹⁷¹⁵	General population and no subgroup analysis
TAKENOUE 2012 ¹⁷¹⁹	Meta-analysis of the influence of NO in the Dx of asthma.
TAN 2013 ¹⁷²⁴	Wrong population: prevalence in obstructive airways combined, not asthma separated.
TAUSSIG 2003 ¹⁷³⁴	Review of a study (TUSCON study).
TAVERAS 2006 ¹⁷³⁵	Correct definition of Phys Dx, but looks at the wrong risk

Reference	Reason for exclusion
	factors (not those specified in our protocol).
TAYLOR 1983 ¹⁷³⁶	General population and no subgroup analysis
TAYLOR 2005 ¹⁷³⁷	Wrong definition of Phys Dx – no objective test.
THOMAS 2010 ¹⁷⁴⁹	Wrong definition of Phys Dx – no objective test.
THOMSON 2012 ¹⁷⁵¹	General population and no subgroup analysis
THORNE 2005 ¹⁷⁵³	Looks at the wrong risk factors (not those specified in our protocol). Does not give prevalence in asthma vs. other respiratory diseases.
TIMONEN 2002 ¹⁷⁵⁸	Wrong definition of Phys Dx – no objective test (older children).
TO 2004 ¹⁷⁶²	Wrong definition of Phys Dx – no objective test.
TO 2009 ¹⁷⁶⁰	Looks at the wrong risk factors (not those specified in our protocol). Does not give prevalence in asthma vs. other respiratory diseases, only in general population.
TO 2012A ¹⁷⁶¹	Wrong definition of Phys Dx – no objective test.
TOLLERUD 1991 ¹⁷⁶⁹	Wrong definition of Phys Dx – no objective test.
TOLPPANEN 2013 ¹⁷⁷⁰	General population and no subgroup analysis
TOOP 1985 ¹⁷⁷⁴	Wrong definition of Phys Dx – no objective test.
TOREN 1993 ¹⁷⁷⁵	Literature review.
TORRENT 2007 ¹⁷⁷⁷	Wrong definition of Phys Dx – no objective test.
TROMP 2012 ¹⁷⁸⁷	Looks at the wrong risk factors (not those specified in our protocol).
TSE 1993 ¹⁷⁸⁹	Wrong definition of Phys Dx – no objective test.
TURBYVILLE 2011 ¹⁷⁹⁹	Wrong definition of Phys Dx – no objective test.
TURCOTTE 2003 ¹⁸⁰⁰	Prevalence and sens/spec in general population of athletes vs. controls (not suspected asthma, or asthma vs. other

Reference	Reason for exclusion
	respiratory diseases).
TURNER 2008 ¹⁸⁰⁵	Wrong symptoms: rattles, purrs, and whistles.
TURNER 2010A ¹⁸⁰⁶	General population and no subgroup analysis
TURNERWARWICK 1988 ¹⁸⁰⁷	Prevalence in people with asthma, but no comparison group.
VALERY 2001 ¹⁸¹⁵	Not UK-relevant population.
VALERY 2004 ¹⁸¹⁶	Older children: looks at the wrong risk factors (not those specified in our protocol). Younger children: no comparison group (just prevalence in asthma)
VANBEVER 1999 ¹⁸²⁰	Wrong population: croup and not compared with people without asthma.
VANDERGUGTEN 2012 ¹⁸²²	General population and no subgroup analysis
VANDERMARK 2014 ¹⁸²³	Longitudinal study – symptoms occurring aged 1-5 years as a predictor for asthma at 6 years
VANDERVALK 2012B ¹⁸³⁰	General population and no subgroup analysis
VANDERVALK 2013 ¹⁸³¹	General population and no subgroup analysis
VANDEVEN 2006 ¹⁸²¹	General population and no subgroup analysis
VANGENT 2007 ¹⁸³⁴	Wrong definition of Phys Dx – no objective test (older children).
VANGYSEL 2007 ¹⁸³⁵	General population and no subgroup analysis
VANMAANEN 2013 ¹⁸³⁶	Wrong definition of Phys Dx – no objective test.
VANNIMWEGEN 2011 ¹⁸³⁷	General population and no subgroup analysis
VANSCHAYCK 1991 ¹⁸⁴⁰	Meets all inclusion criteria for prevalence study except sample size is N<200.
VANSCHAYCK 2000 ¹⁸³⁹	Does not give the specific symptoms in the asthma subgroup.
VANZAANE 2007 ¹⁸⁴¹	Validation of a questionnaire; but does not give prevalence of symptoms in subgroup with

Reference	Reason for exclusion
	asthma.
VARGAS 2007 ¹⁸⁴⁶	Only gives data for the asthma group (no comparison group).
VEDAL 1998 ¹⁸⁵⁰	Wrong definition of Phys Dx – no objective test.
VELLINGA 2005 ¹⁸⁵¹	Wrong definition of Phys Dx – no objective test.
VENABLES 1993 ¹⁸⁵³	Sens/spec in general population; symptoms in asthma vs. control (wrong comparison group).
VENN 2000 ¹⁸⁵⁴	General population and no subgroup analysis; Looks at the wrong risk factors: (not those specified in our protocol).
VENN 2001 ¹⁸⁵⁵	Risk factors for wheeze, not asthma (in mostly older children).
VIALDUPUY 2011 ¹⁸⁶¹	Wrong definition of Phys Dx – no objective test.
VOGELMEIER 2011 ¹⁸⁷⁰	Post-Tx symptoms.
VOLKMER 1995 ¹⁸⁷²	General population and no subgroup analysis
VONEHRENSTEIN 2000 ¹⁸⁷⁵	General population and no subgroup analysis
VONMUTIUS 1999 ¹⁸⁷⁶	Looks at the wrong risk factors: (not those specified in our protocol).
VUGT 2012 ¹⁸⁸¹	Gives prevalence in people with obstruction, but does not subgroup into asthma or COPD etc.
WAKE 2013 ¹⁸⁸³	General population and no subgroup analysis
WANG 2008 ¹⁸⁹⁰	Wrong definition of Phys Dx – no objective test.
WANG 2008A ¹⁸⁸⁸	General population and no subgroup analysis
WANG 2010 ¹⁸⁸⁹	Wrong definition of Phys Dx – no objective test.
WASSALL 2005 ¹⁸⁹⁷	Wrong definition of Phys Dx – no objective test.
WATELET 2010 ¹⁸⁹⁸	Looks at the wrong risk factors: chronic cough (for the development of concomitant asthma).

Reference	Reason for exclusion
WEINMAYR 2007 ¹⁹⁰³	Wrong definition of Phys Dx – no objective test.
WEINMAYR 2013 ¹⁹⁰²	Prevalence in General population and no subgroup analysis.
WHITROW 2010 ¹⁹¹⁰	Wrong definition of Phys Dx – no objective test.
WICKENS 2005 ¹⁹¹¹	Wrong definition of Phys Dx – no objective test.
WICKENS 2008 ¹⁹¹²	Prevalence in General population and no subgroup analysis.
WIJGA 2003 ¹⁹¹⁶	Prevalence in general population and no subgroup analysis. Prevalence of asthma in wheezers, not prevalence of wheeze in people with asthma.
WILLERS 2007 ¹⁹²⁰	General population and no subgroup analysis; and looks at the wrong risk factors: (not those specified in our protocol).
WILLERS 2008 ¹⁹²¹	Wrong definition of Phys Dx – no objective test.
WITHERS 1998 ¹⁹²⁶	Wrong definition of Phys Dx – no objective test.
WJST 1994 ¹⁹²⁹	Wrong definition of Phys Dx – no objective test.
WJST 1998 ¹⁹³¹	Wrong definition of Phys Dx – no objective test.
WJST 2001 ¹⁹³⁰	General population and no subgroup analysis; and looks at the wrong risk factors: (not those specified in our protocol).
WOLF 2003A ¹⁹³³	Wrong definition of Phys Dx – no objective test.
WOODS 2000 ¹⁹⁴⁰	General population and no subgroup analysis; and looks at the wrong risk factors: (not those specified in our protocol).
WOODS 2001 ¹⁹⁴¹	General population and no subgroup analysis
WOODS 2001A ¹⁹³⁹	Wrong outcomes: predictors of breathlessness or food allergy intolerance in adults, not asthma.
WOODS 2002 ¹⁹⁴²	General population and food

Reference	Reason for exclusion
	allergies, no asthma subgroup analysis
WRIGHT 2001 ¹⁹⁴⁴	General population and no subgroup analysis
WRIGHT 2006 ¹⁹⁴⁵	Wrong definition of Phys Dx – no objective test.
WUTHRICH 1995 ¹⁹⁴⁷	General population and no subgroup analysis
YEATTS 2000 ¹⁹⁵⁷	Wrong definition of Phys Dx – no objective test.
YEATTS 2000A ¹⁹⁵⁶	Prevalence in subgroup with asthma, but no comparison group.
YEATTS 2003 ¹⁹⁵⁸	General population and no subgroup analysis and looks at the wrong risk factors: (not those specified in our protocol).
YUNGINGER 1992 ¹⁹⁶⁷	Dx sens/sepc data: wrong population – general population. Prevalence data: wrong comparison group – asthma vs. probable asthma or single episode wheezers.
ZHOU 2013 ¹⁹⁷⁸	General population and no subgroup analysis
ZOLLNER 2005 ¹⁹⁹⁰	General population and no subgroup analysis
ZUIDGEEST 2008 ¹⁹⁹¹	Wrong definition of Phys Dx – use of asthma medication to indicate asthma.
ZUIDGEEST 2009 ¹⁹⁹²	Looks at the wrong risk factors: (not those specified in our protocol). Prevalence in asthma but no comparison group.
ZWAR 2011 ¹⁹⁹⁴	Correct Phys Dx but does not give prevalence of symptoms in the asthma vs. COPD groups and does not look at the correct RFs (not those specified in our protocol).

1 K.2 Diagnosis: History of atopic disorders

2 Table 208: Studies excluded from the clinical review

Reference	Reason for exclusion
ALBUQUERQUE2013 ³⁴	Conference abstract
ALVAREZPUEBLA 2002 ³⁹	Index test does not match protocol – total

Reference	Reason for exclusion
	asthma symptoms questionnaire, not history of atopic disorders
ANDERSON 2009 ⁴⁸	Index test does not match protocol – history of atopic disorders not reported
BACKER 1991 ⁸⁷	Reference standard does not match protocol – Dx made on the basis of questionnaire
BACKER 2014 ⁹¹	Index test and reference standard do not match protocol – sn/sp of FeNO to predict positive mannitol in suspected asthma (not physician diagnosis and objective test)
BEAUSOLEIL 2007 ¹³⁴	Review article
BEEH 2000 ¹³⁷	No relevant outcomes – prevalence in allergic vs non-allergic patients
BEEH 2001 ¹³⁸	Index test does not match protocol – atopy defined as family history or positive SPT (cannot calculate the sn/sp of family history alone)
BEEH 2004 ¹³⁹	Index test does not match protocol – total symptom score with no breakdown of atopy history alone
BENGASHIR 2004 ¹⁴⁸	Population does not match protocol – all patients positive for atopic dermatitis (all positive for index test)
BOCCACCINO 2007 ¹⁸¹	Population does not match protocol - patients with respiratory symptoms picked up using a screening questionnaire
BONNER 1984 ¹⁸⁸	Review article
BREGAS 2000 ²²⁰	Not in English
BURR 1975 ²⁴⁹	No relevant outcomes and does not match review question – cannot calculate sn/sp of family history
CAFFARELLI 2005 ²⁶⁰	Population does not match protocol – all patients positive atopic eczema (all positive for index test)
CANTANI 2003 ²⁶⁸	Reference standard does not match protocol – no objective test
CARTER 2000 ²⁸⁶	No relevant outcomes and does not match review question - sn/sp of patients report of allergy for positive SPT in people with confirmed asthma
CHEN 2014 ³¹⁰	Population does not match protocol – general population
CHRISTOFF 2013 ³²⁷	Conference abstract
CIRILLO 2003 ³⁴¹	Population does not match protocol – general population
CORTESALVAREZ 2007 ³⁶⁸	Reference standard does not match protocol – history of atopic disorders in ≤ 3 yrs with wheezing, but no Dx of asthma made

Reference	Reason for exclusion
CVITANOVIC 2007 ³⁸⁸	Population does not match protocol – all SPT positive.
DEBLEY 2012 ⁴⁰⁹	Population does not match protocol – children aged 4-36 months with ≥ 3 episodes of physician Dx wheezing (all people with asthma according to protocol criteria)
DELRIO 2004 ⁴¹⁵	Case-control study – asymptomatic and symptomatic patients.
DELIU 2013 ⁴¹⁹	Conference abstract
DENG 2010 ⁴²⁴	Population does not match protocol - patients with respiratory symptoms picked up using a screening questionnaire, not presenting to GP
DING 2012 ⁴⁴³	Population does not match protocol - patients with respiratory symptoms picked up using a screening questionnaire
ELIZUR 2007 ⁴⁷⁴	No relevant outcomes and does not match review question – prevalence study in general population
ERIKSSON 1978 ⁴⁸⁰	Population does not match protocol – all asthma and/or rhinitis
ERIKSSON 1990 ⁴⁸¹	Population does not match protocol – all asthma and/or rhinitis
EYSINK 2005 ⁴⁸⁷	Case-control study – IgE positive and IgE negative
FANIRAN 1998 ⁴⁸⁹	Index test does not match protocol – sn/sp of first Dx by a physician in primary healthcare
FARHOUDI 2005 ⁴⁹²	Population does not match protocol – allergic patients with asthma and/or rhinitis
FONSECA 2004 ⁵⁰⁶	Population does not match protocol – not suspected asthma only, population consisted of people with confirmed asthma
FRANK 1998 ⁵¹⁹	Population does not match protocol – general population
GALVEZ 1987 ⁵⁴³	Reference standard objective test does not match protocol – methacholine challenge test positive defined as PC20 <25mg/ml.
GUILBERT 2004 ⁶¹⁴	Population does not match protocol – all had a personal or family history of atopic disorders
GULSVIK 1979 ⁶¹⁶	No relevant outcomes – prevalence of symptoms in the general population
GUSTAFSSON 2000 ⁶¹⁸	Population does not match protocol – children with atopic dermatitis
HAFKAMPDEGROEN 2013 ⁶²²	Longitudinal prognostic study
HEDMAN 1998 ⁶⁵⁶	Index test does not match protocol – history of atopic disorders not reported
JENKINS 1996 ⁷⁷²	Index test does not match protocol – sn/sp of symptoms questionnaire. Reference

Reference	Reason for exclusion
	standard does not match protocol – Dx based on a history of wheeze in the past 12 months
KARAKAYA 2012 ⁸²⁴	No relevant outcomes – sn/sp of physician Dx of atopy with SPT as the gold standard
KILPELAINEN 2001B ⁸⁶⁶	Index test does not match protocol – sn/sp of symptoms questionnaire
KUMAR 2010 ⁹⁴⁰	No relevant outcomes – allergy Dx in patients with asthma or allergic rhinitis
KUMARI 2006 ⁹⁴²	Case-control study – atopic and non-atopic patients
LOMBARDI 2008 ¹⁰³⁸	No relevant outcomes – prevalence of asthma and allergy in general population
LOMBARDI 2011 ¹⁰³⁷	No relevant outcomes – prevalence of asthma and allergy in general population
MILLER 2007 ¹¹⁵³	Population does not match protocol – general population
MONTNEMERY 2002 ¹¹⁷⁴	Index test does not match protocol – sn/sp of first Dx of asthma in primary healthcare
NANTANDA 2013 ¹²⁰⁹	Population does not match protocol – includes severe asthma and >50% <12 months old.
NJA 2001 ¹²⁵²	Case-control study. Reference standard does not match protocol – Dx made on the basis of symptoms, no objective test
NINAN 1995 ¹²⁴⁷	Case-control study – asymptomatic and symptomatic patients. Reference standard does not match protocol – Dx made on the basis of symptoms
PEDROSA 2009 ¹³²⁹	No relevant outcomes – cannot calculate sn/sp of family history
RIEDLER 1994 ¹⁴⁵⁹	Case control study
RUGINA 2002 ¹⁴⁹⁰	No relevant outcomes - prevalence of symptoms in nasal polyposis
SCHLEICH 2012 ¹⁵³⁰	Index test does not match protocol – FeNO and symptoms
SMITH 2009 ¹⁶³²	Population does not match protocol – all currently Dx with rhinitis or asthma
SNIDER 1985 ¹⁶³³	Review article
STAIKUNIENE 2008 ¹⁶⁷²	Case-control study - chronic rhinosinusitis vs controls
TIMONEN 1997 ¹⁷⁵⁷	Population does not match protocol - patients with chronic respiratory symptoms picked up using a screening questionnaire
VALERY 2003 ¹⁸¹⁷	Case-control study. Index test does not match protocol – sn/sp of symptoms

Reference	Reason for exclusion
	questionnaire
WOO 2012 ¹⁹³⁷	Index test does not match protocol - FeNO
ZARAGOZA 2014 ¹⁹⁷²	Conference abstract

1 K.3 Diagnosis: Symptoms after exercise

2 **Table 209: Studies excluded from the clinical review**

Reference	Reason for exclusion
ANDERSON 2009 ^{44,48}	Index test does not match protocol.
ANDERSON 2010A ^{44,46}	Conference abstract
ANTOLINAMERIGO 2012 ⁵⁴	Conference abstract
BRANNAN 1998 ^{216,216}	No relevant outcomes and does not match review question (sensitivity and specificity of mannitol challenge test to predict EIA in participants with a positive response to exercise challenge test or eucapnic hyperventilation).
BROZEK 2009 ^{234,234}	Conference abstract. Index test does not match protocol (exercise challenge test)
CARLSEN 2000 ^{273,274}	No relevant outcomes and does not match review question (comparing methods of exercise challenge test in people with confirmed asthma with exercise-induced bronchoconstriction)
CHEW 1999 ^{312,312}	Reference standard does not match protocol (asthma Dx made on the basis of the question 'have you (your child) ever had asthma?')
CHINELLATO 2012 ^{315,315}	Population does not match protocol – all people with asthma on treatment
DEMISSIE 1998 ^{421,421}	Population does not match protocol (general population, not suspected asthma); index test does not match protocol (general symptom questions, not symptoms after exercise); reference standard does not match protocol (Dx by questionnaire)
DRYDEN 2010 ^{457,457}	Review including 2 studies with exercise symptoms as the index test (population does not match protocol for both studies – general population of athletes, not suspected asthma)
FOUCARD 1984 ^{512,513}	Reference standard does not match protocol (children who reported asthma symptoms during the last year were regarded as having asthma)
FUENTES 2011 ^{531,531}	Case control study. Reference standard for Dx in the group with asthma does not match protocol (no mention of objective test) so cannot use index test vs exercise challenge test.

Reference	Reason for exclusion
GREEN 1997 ^{595,595}	No relevant outcomes and does not match review question (cannot calculate sensitivity and specificity of 'symptoms in response to exercise' in the Dx of asthma).
HETLEVIK 2000 ^{675,675}	Reference standard does not match protocol (current asthma Dx if affirmative response to the question 'has your child ever had asthma?' and 'does your child still have asthma?')
HILDEBRAND 2011 ^{680,680}	Not in English
JONES 1994 ^{782,782}	Reference standard does not match protocol (not all had objective test)
JOSEPH 1999 ^{788,789}	Reference standard does not match protocol (self-reported physician Dx of asthma – no objective test).
KERSTEN 2009 ^{852,852}	Index test does not match protocol – exercise challenge test not history of symptoms with exercise
KIVILLOOG 1975 ^{881,881}	Reference standard does not match protocol - all people with confirmed asthma and possible to calculate test vs test (sn/sp of IT in detecting positive exercise challenge) but no mention of how asthma Dx was made (no mention of objective test).
LAI 1997 ^{959,959}	Reference standard does not match protocol
LEX 2007 ^{1006,1007}	Index test does not match protocol – sn/sp of symptoms to detect EIB in people with asthma but includes symptoms induced by exercise and other factors such as allergy, no breakdown of those who only had symptoms to exercise
LOWHAGEN 1999 ^{1042,1042}	Review article checked for references
LUKRAFKA 2010 ^{1046,1046}	Reference standard does not match protocol, no objective test (asthma Dx based on affirmative answer to 'Have you ever been told by a physician that you have asthma or bronchitis?')
MAJAK 2013 ^{1067,1067}	Population does not match protocol (groups with and without a history of exercise symptoms, but group without symptoms in response to exercise included patients whose asthma was in remission).
MANSOURNIA 2007 ^{1087,1087}	Target condition does not match protocol - sn/sp of exercise symptoms to Dx EIB in the general population
NEVILLE 1992 ^{1224,1224}	No relevant outcomes and does not match review question (prevalence of symptoms in general population)
PEDROSA 2009 ^{1329,1329}	Index test does not match protocol – cannot calculate sn/sp of index test in Dx of asthma.

Reference	Reason for exclusion
PONSONBY 1996 ^{1377,1377}	Population does not match protocol – general population (including healthy asymptomatic children) not suspected asthma alone
RANDOLPH 1997 ^{1431,1431}	Population does not match protocol – general population (including healthy asymptomatic children) not suspected asthma alone
RANDOLPH 2011A ^{1431,1432}	Conference abstract
RANDOLPH 2012 ^{1431,1434}	Conference abstract
RANDOLPH 2013 ^{1431,1433}	Conference abstract
REMES 2002 ^{1447,1448}	Population does not match protocol – general population (including healthy asymptomatic children) not suspected asthma alone
SEEAR 2005 ^{1556,1556}	No relevant outcomes and does not match review question (exercise challenge test to determine the accuracy of EIA Dx)
SIERSTED 1996 ^{1590,1591}	Index test does not match protocol
SINCLAIR 1995 ^{1612,1612}	Index test does not match protocol – exercise challenge test not history of symptoms with exercise
SMEETON 2006 ^{1625,1625}	No relevant outcomes and does not match review question (prevalence of symptoms in general population)
STORMS 2000 ^{1685,1685}	Review article
TERBLANCHE 1990 ^{1741,1741}	Index test does not match protocol – exercise challenge test not history of symptoms with exercise
TERNESTENHASSEUS 2008 ¹⁷⁴³	No relevant outcomes and does not match review question (gives levels and changes after exercise test, cannot calculate sn/sp)
TSYBULKINA 2009 ^{1794,1795}	Conference abstract
WEST 1996 ^{1907,1907}	Index test and reference standard do not match protocol
ZIAEE 2009 ^{1979,1979}	Conference abstract

1 K.4 Diagnosis: Symptoms after drugs

2 Table 210: Studies excluded from the clinical review

Reference	Reason for exclusion
AHMETAJ 2009 ²⁵	Not addressing review question (prevalence of aspirin-sensitive asthma using challenge test in people with confirmed asthma)
ALONSO 2002 ³⁸	Not addressing review question (diagnostic accuracy of challenge test vs. physician Dx of aspirin-induced asthma)
AMEISEN 1985 ⁴²	Wrong population (asthma vs. healthy)

Reference	Reason for exclusion
	controls). Wrong study type (case control)
BARLES 1988 ¹⁰⁸	Wrong population (all aspirin-sensitive asthma patients). Not Dx of asthma
BARRANCO 2009 ¹¹³	Not addressing review question (aspirin challenge test to diagnose aspirin-sensitive asthma in people with confirmed asthma)
BAVBEK 2010 ¹³¹	Conference abstract. Not addressing review question (prevalence of aspirin-sensitive asthma in people with confirmed asthma)
BAVBEK 2012 ¹³⁰	Not addressing review question (index test as a predictor of aspirin-sensitive asthma in people with confirmed asthma, not for asthma Dx)
BERGES 2002 ¹⁵⁸	Wrong population (all aspirin-sensitive asthma patients). Not Dx of asthma
BOTEY 1988 ¹⁹⁷	Wrong population (all people with asthma)
CALADO 2011 ²⁶²	Conference abstract. Full paper (CALADO 2012) obtained
CALADO 2012 ²⁶³	Non-English language publication (Portuguese)
CARNIMEO 1981 ²⁷⁹	Not addressing review question (index test as a predictor of positive aspirin challenge test not for asthma Dx)
CASADEVALL 2000 ²⁸⁹	Wrong population (asthma vs. healthy controls). Wrong study type (case control)
CASTILLO 1986 ²⁹¹	Wrong population (all asthma patients)
CHANG 2011 ³⁰⁰	Not addressing review question (diagnostic accuracy of index test as a predictor of AERD in people with confirmed asthma, not for asthma Dx)
CROCE 1992 ³⁷⁹	Wrong population (asthma vs. healthy controls). Wrong study type (case control)
DAHLEN 1990 ³⁹⁰	Not addressing review question (aspirin challenge test to diagnose aspirin-sensitive asthma in people with confirmed asthma)
DELANEY 1976 ⁴¹⁷	Not addressing review question (index test as a predictor of positive aspirin challenge test not for asthma Dx)
GENTON 1985 ⁵⁵⁵	Wrong population (asthma or urticarial)
GONZALEZ 2011 ⁵⁸⁷	Wrong population (all asthma patients)
GRZELEWSKA 1981 ⁶⁰⁴	Not addressing review question (index test as a predictor of aspirin-sensitive asthma)
HONG 1989 ⁶⁹⁸	Wrong population (all asthma patients)
HUSSEIN 1989 ⁷²⁵	Not addressing review question (index test as a predictor of positive aspirin

Reference	Reason for exclusion
	challenge test not for asthma Dx)
KARAKAYA 2000 ⁸²²	No comparison with reference standard
MAKOWSKA 2008 ¹⁰⁶⁸	Not addressing review question (aspirin challenge test to diagnose aspirin-sensitive asthma in people with confirmed asthma)
MASCIA 2005 ¹⁰⁹⁶	Index test vs. objective test but does not give the number of patients +ve/-ve for objective test so sensitivity and specificity of IT cannot be calculated
MELILLO 1991 ¹¹³¹	Not addressing review question (index test as a predictor of positive aspirin challenge test not for asthma Dx)
MILEWSKI 1998 ¹¹⁵⁰	Wrong population (asthma vs. healthy controls). Wrong study type (case control)
MILLER 2013 ¹¹⁵²	Not addressing review question (challenge test to diagnose AERD in people with asthma)
MIRAKIAN 2012 ¹¹⁵⁷	Wrong population (all aspirin-sensitive asthma patients). Not Dx of asthma
MUNOZ 2013 ¹¹⁹²	Wrong population (patients with aspirin-sensitive asthma)
NIKLAS 1973 ¹²³³	Wrong population (all asthma patients with no history of symptoms to aspirin)
NIZANKOWSKA 2000 ¹²⁵¹	Not addressing review question (aspirin challenge test to diagnose aspirin-sensitive asthma in people with confirmed asthma)
RACHELEFSKY 1975 ¹⁴²⁰	Not addressing review question (prevalence of aspirin-sensitive asthma using challenge test in people with confirmed asthma)
RAM 2013 ¹⁴²⁵	Wrong outcomes (not Dx of asthma)
RAMIREZ 2011 ¹⁴²⁷	Not addressing review question (reliability study of provocation test – not Dx of asthma)
STENIUS 1976 ¹⁶⁷⁵	Not addressing review question (prevalence of aspirin-sensitive asthma using challenge test in people with confirmed asthma)
SUETSUGU 1981 ¹⁶⁹⁷	Wrong population (all aspirin-sensitive asthma patients)
VAIDYANATHAN 2012 ¹⁸¹³	Conference abstract. Not addressing review question (index test as a predictor of positive aspirin challenge test not for asthma Dx)
WEBER 1979 ¹⁸⁹⁹	Wrong population (all asthma patients)

Reference	Reason for exclusion
WISMOL 2012 ¹⁹²⁵	Wrong population (all aspirin-sensitive asthma patients). Not Dx of asthma
ZAMBONINO 2013 ¹⁹⁷¹	Conference abstract. Not addressing review question (index test not used for asthma Dx)

1 K.5 Diagnosis: Occupational asthma

2 **Table 211: Studies excluded from the clinical review**

Reference	Reason for exclusion
ANEES2003 ⁵¹	Not asking if symptoms better away from work
ARCHAMBAULT 2001 ⁶²	Not all patients had gold standard test
BALDWIN 2002 ⁹⁶	Not asking if symptoms better away from work
BARBER 2007 ¹⁰⁷	Survey of diagnostic approach to single case scenario, not diagnostic value of asking if symptoms better away from work
BERNSTEIN 1993 ¹⁶¹	Not all patients had gold standard test
BLANC 1996 ¹⁷⁹	Not asking if symptoms better away from work
CAMPBELL 2007 ²⁶⁶	Not asking if symptoms better away from work
CARTIER 2003 ²⁸⁸	No usable data
COTE 1990 ³⁷⁰	Only includes people with positive history so cannot calculate specificity
COTE 1993 ³⁷¹	Not asking if symptoms better away from work
CRESPO 2001 ³⁷⁸	Not asking if symptoms better away from work
CRUZ 2010 ³⁸⁰	Not asking if symptoms better away from work
DELLABIANCA 1996 ⁴²⁰	Not asking if symptoms better away from work
DESCATHA 2005 ⁴³⁰	Not asking if symptoms better away from work
DOSTALER 2011 ⁴⁴⁹	No gold standard for occupational asthma, only questionnaire development
DUCE 1988 ⁴⁶⁰	Not asking if symptoms better away from work
ELSHABRAWI 2011 ⁴⁷⁷	Not asking if symptoms better away from work
ENARSON 1988 ⁴⁷⁸	Not asking if symptoms better

Reference	Reason for exclusion
	away from work
GAUTRIN 2010 ⁵⁵³	Not asking if symptoms better away from work
GIRARD 2004 ⁵⁷²	Not asking if symptoms better away from work
GORDON 1997 ⁵⁸⁸	Not asking if symptoms better away from work
GRAMMER 1992 ⁵⁹³	Not asking if symptoms better away from work
GRAMMER 1998 ⁵⁹²	Not asking if symptoms better away from work
HANNU 2013 ⁶³⁸	Not asking if symptoms better away from work
HAYATI 2008 ⁶⁵¹	Not asking if symptoms better away from work
HAYATI 2006 ⁶⁵⁰	Not asking if symptoms better away from work
HUR 2008 ⁷²³	Reference standard is for diagnosis of occupational asthma or occupational eosinophilic bronchitis
JARES 2012 ⁷⁶⁵	No usable data
KARVALA 2010 ⁸²⁷	Not asking if symptoms better away from work
KIM 1998 ⁸⁶⁸	Not occupational asthma
KONGERUD 1992A ⁹⁰⁹	All participants positive for history and bronchial challenge test
KRAW 1999 ⁹²⁸	Not asking if symptoms better away from work
LABRECQUE 2011 ⁹⁵⁵	Not asking if symptoms better away from work
LEMIERE 1999 ⁹⁹²	Not asking if symptoms better away from work
LEMIERE 2011 ⁹⁹⁰	Not asking if symptoms better away from work
LEMIERE 2011A ⁹⁹¹	Not asking if symptoms better away from work
LIPINSKA 2011 ¹⁰²⁹	Not asking if symptoms better away from work
MALO 1993 ¹⁰⁷⁸	Not asking if symptoms better away from work
MALO 1995 ¹⁰⁸¹	Not asking if symptoms better away from work
MERGET 1991 ¹¹³⁶	Not asking if symptoms better away from work
MIEDINGER 2013 ¹¹⁴⁴	Not asking if symptoms better away from work
MIRMOHAMMADI 2010 ¹¹⁵⁹	Assesses a questionnaire but

Reference	Reason for exclusion
	asking if symptoms better away from work was not part of the definition of questionnaire-positive responses
MOORE 2009 ¹¹⁷⁷	Not asking if symptoms better away from work
MOORE 2010 ¹¹⁷⁶	Not asking if symptoms better away from work
MOSCATO 1993 ¹¹⁸¹	Not asking if symptoms better away from work
MURPHY 2002 ¹¹⁹⁴	Not asking if symptoms better away from work
NASIR 2011 ¹²¹¹	Not asking if symptoms better away from work
OLAGUIBEL 1989 ¹²⁷⁹	Not asking if symptoms better away from work
PERRIN 1992 ¹³³⁷	Not asking if symptoms better away from work
PHAKTHONGSUK 2007 ¹³⁵⁵	Not assessing asking if symptoms better away from work versus gold standard
QUIRCE 1995 ¹⁴¹⁹	Not asking if symptoms better away from work
SCHLUNSEN 2011 ¹⁵³¹	Not asking if symptoms better away from work
SCHWAIBLMAIR 1997 ¹⁵⁴⁵	Not asking if symptoms better away from work
SHOFER 2006 ¹⁵⁸⁴	Not asking if symptoms better away from work
SKOVSTED 2003 ¹⁶²¹	Not asking if symptoms better away from work
SMITH 1987 ¹⁶²⁷	Not asking if symptoms better away from work
STENTON 1993 ¹⁶⁷⁶	Not asking if symptoms better away from work
SUARTHANA 2010 ¹⁶⁹⁵	Outcome is wheat sensitisation not asthma
SURANGE 2011 ¹⁷⁰³	Single case report not diagnostic test value
TALINI 2002 ¹⁷²¹	Not asking if symptoms better away from work
TARLO 1991 ¹⁷²⁸	Not asking if symptoms better away from work
TARLO 2000 ¹⁷²⁹	not all participants had gold standard test
TARLO 2008 ¹⁷³⁰	Not assessing asking if symptoms better away from

Reference	Reason for exclusion
	work versus gold standard
TARLO 2009 ¹⁷³¹	Not assessing asking if symptoms better away from work versus gold standard
TEE 1998 ¹⁷³⁸	Not asking if symptoms better away from work
TORRESDA 2002 ¹⁷⁷⁸	non-English
TURNER 2010 ¹⁸⁰⁴	Not asking if symptoms better away from work
VOGELMEIER 1991 ¹⁸⁶⁹	Not asking if symptoms better away from work
WIESLANDER 1994 ¹⁹¹⁵	Not asking if symptoms better away from work
WITTCZAK 2012 ¹⁹²⁷	Not asking if symptoms better away from work
WHITE 2013 ¹⁹⁰⁹	General population
HATHAWAY 2014 ⁶⁴⁹	General population
WALTERS 2012A ¹⁸⁸⁷	General population
KAYHAN 2013 ⁸³⁶	General population

1 K.6 Diagnosis: Spirometry

2 **Table 212: Studies excluded from the clinical review**

Reference	Reason for exclusion
AHFMR 2002 ³⁰	Full article not available
ALBERTS 1994 ^{32,32}	Index test does not match protocol – sn/sp of FEF25-75%
BROUWER 2010 ^{232,233}	Index test does not match protocol – sn/sp of PEFv and FEV1 variation for Dx of asthma
BUFFELS 2012 ^{242,242}	Reference standard does not match review protocol – Dx with spirometry taken as reference.
CERVERI 2009 ^{296,296}	No relevant outcomes - sn/sp of FEV1/FVC in predicting airflow obstruction with lower limit of normality as gold standard in people with confirmed asthma
CIPRANDI 2010 ^{331,337}	Population does not match protocol – all people with asthma or rhinitis. Index test does not match protocol – FeNO
CIPRANDI 2011B ^{331,336}	Population does not match protocol – all Dx with allergic rhinitis and excluded if a history of asthma or referred with asthma symptoms
CIPRANDI 2011C ^{331,333}	Population does not match protocol – patients with allergic rhinitis; exclusion criteria was previous asthma Dx or presence of asthma symptoms.
CIPRANDI 2012 ^{331,334}	No relevant outcomes - sn/sp of FEV1 or FVC in predicting airways obstruction with

Reference	Reason for exclusion
	FEF25-75% as gold standard in people with confirmed asthma
CIRILLO 2006 ^{339,341}	No relevant outcomes – association between positive MCT and the ratio between FEV1 and FEF25-75%
CORDEIRO 2011 ^{365,365}	No relevant outcomes – cannot calculate the sn/sp of FEV1/FVC for asthma Dx. Only gives ROC AUC for FEV1/FVC
COUTO 1997 ^{373,373}	Index test does not match protocol - MCT
DI LORENZO 2007 ⁴³⁶	Case control study – study gives sn/sp values for FEV1/FVC, but this includes asymptomatic healthy control group
DUNDAS 2006 ^{462,463}	Review article
DUPONT 2003 ^{464,464}	Index test does not match protocol - FeNO
DWYER 2012 ^{466,466}	Review article
EID 2000 ^{470,470}	No relevant outcomes – sn/sp of PEF to predict abnormal FEV1
FOWLER 2000 ^{514,514}	Index test does not match protocol – MCT and correlation of FEV1 with MCT
FRANKLIN 2003 ^{520,520}	Population does not match protocol – general population
FUKUHARA 2011 ^{535,535}	Index test does not match protocol - FeNO
GALVEZ 1987A ^{542,543}	No relevant outcomes – correlation between FEV1 and PC20 in people with confirmed asthma
GERALD 2004 ^{557,558}	Population does not match protocol – general population. Index test does not match protocol – sn/sp of procedures including symptoms questionnaire, spirometry and exercise test.
GILBERT 1985 ^{569,569}	Target condition does not match protocol – sn/sp of FEV1/FVC to Dx obstruction (asthma and COPD) with reference standard of clinical and body plethysmographic data
GILBERT 1986 ^{568,569}	Target condition and reference standard do not match protocol – Dx of obstruction based on history, physical examination, chest radiographs, biopsy and body plethysmographic data
GOEDHART 2006 ^{578,578}	Case control type study – confirmed asthma and COPD. Reference standard does not match protocol – without objective test.
GRZELEWSKI 2014 ^{606,607}	Study does not report results in such a way that it is possible to calculate sensitivity and specificity.
HARGREAVE 2009 ^{641,643}	Review article
HEDENSTROM 1987 ^{655,655}	Case control study – sn/sp of FEV1 in people with asthma vs healthy controls
HOLT 2006 ^{692,692}	No relevant outcomes – comparing treatment plans made by physicians using

Reference	Reason for exclusion
	symptoms alone or with spirometry
HUNTER 2002 ^{721,721}	Case control study – calculation of sn/sp in people with confirmed asthma, healthy controls and pseudoasthma, with no breakdown.
JERZYNSKA 2014 ^{776,776}	Study does not report results in such a way that it is possible to calculate sensitivity and specificity.
KING 1998 ^{875,876}	Case report
KOMAROW 2012 ^{906,906}	Index test does not match protocol – impulse oscillometry or BDR
LAMBERT 2013 ^{963,963}	Meeting abstract
LEBECQUE 1993 ^{981,981}	No relevant outcomes – comparing different spirometry measures in people with confirmed asthma
LEHMANN 2008 ^{988,988}	Population does not match protocol – general population
LIAM 2001 ^{1011,1011}	No relevant outcomes - association between FEV1 and symptoms or BDR in people with confirmed asthma
LIM 2005 ^{1016,1017}	Review article
LINNA 1996 ^{1024,1026}	Population does not match protocol – all people with asthma and cannot calculate sn/sp of test vs test.
LIU 2009 ^{1028,1028}	Review article
LUTFI 2011 ^{1050,1050}	Case-control study – people with confirmed asthma and healthy controls
MAGYAR 1998 ^{1062,1062}	Review article
MELBYE 2011 ^{1129,1129}	Population and reference standard does not match protocol – confirmed asthma, COPD and asthma+COPD. Reference standard for Dx not reported.
MELTZER 1989 ^{1132,1132}	No relevant outcomes- comparison of PEF and FEV1 in people with confirmed asthma
MENDONCA 2011 ^{1133,1133}	Case-control study. Asthma Dx with clinical Dx, no mention of objective test
MILLER 1990 ^{1151,1151}	No relevant outcomes – comparing different spirometry measures in people with confirmed asthma with normal FEV1/FVC
MINAKATA 2008 ^{1155,1155}	Population does not match protocol – presenting with diseases other than respiratory diseases
MIRAVITLLES 2012 ^{1158,1158}	No relevant outcomes – cannot calculate the sn/sp of spirometry for asthma
MODRYKAMIEN 2009 ^{1167,1167}	Target condition does not match protocol – sn/sp of spirometry to detect upper airway obstruction with reference standard of bronchoscopy, laryngoscopy and tomogram
NEVE 2012 ^{1223,1223}	Population does not match protocol –

Reference	Reason for exclusion
	preschool children aged 3-5 years old with wheezing disorders
NICOLAI 1993 ^{1235,1235}	Population does not match protocol – general populations. Index test does not match protocol – cold air challenge
NIKKHAH 2011 ^{1245,1245}	Case control study
OTTER 1997 ⁴²²	Index test does not match protocol
OZAREKHANC 2012 ¹²⁹³	Article not in English
PEDROSA 2009 ^{1329,1329}	Population and index test do not match protocol – all patients normal spirometry and index test is challenge test
SATO 2008 ^{1514,1515}	Index test does not match protocol - FeNO
SAURO 2005 ^{1517,1517}	Populations does not match protocol – general population
SCHERMER 2000 ^{1526,1526}	Review article
SIMON 2010 ^{1604,1604}	All people with asthma (test vs test) – can calculate sn/sp of FEV1/FVC for detecting BDR. FEV1/FVC at 95% cut-off (best cut-off determined from ROC curve) for detecting BDR 20% increase in FEV1
SLIEKER 2003A ^{1624,1624}	No relevant outcomes – sn/sp of PEF to predict abnormal FEV1 pre- and post-bronchodilator
STENTON 1993 ^{1676,1676}	Population does not match protocol – screening shipyard workers and job applicants
TEETER 1999 ^{1739,1739}	Review article
THIADENS 1999 ^{1746,1747}	No relevant outcomes – comparison of Δ PEF and Δ FEV1 for BDR
TINKELMAN 2006 ^{1759,1759}	Target condition does not match protocol – sn/sp of questionnaire in the Dx of COPD
TODA 2009 ^{1763,1763}	Index test does not match protocol – FEV1/FVC used as reference standard for obstruction
WALAMIES 1998A ^{1884,1884}	Case control study. Index test vs comparator test in people with asthma – cut-off values do not match protocol (FEV1/FVC 89% and BDR Δ FEV1pred \geq 15%)
YARTSEV 2006A ^{1953,1953}	Case- control study
YU 2004 ^{1965,1965}	Population does not match protocol – general populations. Reference standard does not match protocol – parental report of doctor Dx asthma.
YURDAKUL 2005 ^{1968,1968}	Case-control study. Index test does not match protocol

1 K.7 Diagnosis: Bronchodilator reversibility

2 **Table 213: Studies excluded from the clinical review**

Reference	Reason for exclusion
ADAMS 2003 ¹⁷	No data on bronchodilator response in diagnosed asthma group
BIBI 1991 ¹⁷¹	Wrong cut-off for FEV1: change >6%.
BIRING 2001 ¹⁷³	Asthma and COPD together
BONINI 2007 ¹⁸⁶	Not all participants had reference standard tests
BORREGO 2012 ¹⁹¹	Not in English
BORREGO 2013 ¹⁹⁴	Not bronchodilator response over/under threshold versus asthma status
BOSSLEY 2009 ¹⁹⁶	Number with bronchodilator response reported but not comparison/gold standard test
BUSSAMRA 2005 ²⁵⁴	Reference standard is the same test (bronchodilator response) with American Thoracic Society specified cut-off rather than 95 th percentile cut off
CARLSEN 1995 ²⁷³	Case control study
CHOI 2007 ³¹⁸	Bronchodilator response is part of gold standard (index test = questionnaire)
CIPRANDI 2011 ³³⁶	Allergic rhinitis patients not asthma
CIPRANDI 2011A ³³²	Unavailable
CIPRANDI 2013 ³³⁸	Bronchial reversibility as gold standard (index test = FeNO)
CORDEIRO 2011 ³⁶⁵	Bronchial reversibility as part of gold standard (index test = FeNO)
CORSICO 2007 ³⁶⁷	Bronchial reversibility as part of asthma diagnosis (not all participants had this test)
COTE 1990 ³⁷⁰	Occupational asthma
DELRIO 2004 ⁴¹⁵	Not bronchial reversibility versus doctor diagnosis (all had asthma) or versus other tests for diagnosis of asthma (symptomatic versus asymptomatic on ISAAC questionnaire)
DIAS 2010 ⁴³⁷	Not in English
DUMAS 2010 ⁴⁶¹	Bronchodilator test was gold standard as well as index test
DUNDAS 2005 ⁴⁶²	Case control study
ELLIOTT 2013	Population does not match protocol – children less than 1 year old
FABBRI 2003 ⁴⁸⁸	Variability to inhaled albuterol part of gold standard as well as index test
FISH 1978 ⁵⁰⁰	Workshop not primary study
FRUCHTER 2009 ⁵³⁰	Not all participants had bronchodilator reversibility test; longitudinal follow up

	for later diagnosis of asthma
FRUCHTER 2009 ⁵²⁹	Correlation between PC20 and Δ FEV1 not reversibility over/under threshold versus positive/negative methacholine challenge test
GALANT 2007 ⁵⁴¹	Population does not match protocol – general population
GHARAGOZLOU 2004 ⁵⁶¹	Not all participants had bronchodilator test
GIBSON 1995 ⁵⁶⁴	Not bronchodilator response
GINGO 2012 ⁵⁷¹	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
GJEVRE 2006 ⁵⁷³	Subjects selected for meeting ATS bronchodilator response criteria
GOLDSTEIN 2001 ⁵⁸⁶	Longitudinal follow up for later diagnosis of asthma
GRIFFITHS 1999 ⁵⁹⁹	Bronchodilator reversibility = definition of asthma (gold standard not index test)
HELLINCKX 1998 ⁶⁶²	Not PEF, PEFR or FEV ₁
HUNTER 2002 ⁷²¹	Case-control study. Mixed population of cases, controls and pseudoasthma in the results. Not separated out the data.
HYVARINEN 2006 ⁷²⁷	Not PEF, PEFR or FEV ₁
IRWIN 1997 ⁷⁴⁰	Not PEF, PEFR or FEV ₁
JAIN 2013 ⁷⁵⁰	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
JOSEPH 2011A ⁷⁹⁰	Not bronchodilator reversibility versus doctor diagnosis or eligible comparator test for asthma
KESTEN 1994 ⁸⁵³	Lung function tests part of gold standard as well as index test
KJAER 2008A ⁸⁸²	Case control study; bronchodilator test part of gold standard as well as index test
KONSTANTINOOU 2010 ⁹¹⁰	Longitudinal study: bronchodilator response during exacerbation compared with no exacerbation
KOWAL 2009 ⁹²⁴	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
LEHMANN 2008 ⁹⁸⁸	Bronchodilator reversibility = gold standard not index test; not shown versus doctor diagnosis of asthma or other comparator tests (only questionnaire symptoms or other measures of FEV1 or FVC)
LERDLUEDEEPORN 1999 ⁹⁹⁵	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma

LINNA 1999 ¹⁰²⁴	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
LORBER 1978 ¹⁰⁴⁰	Wrong population – general population
MALMBERG 2003 ¹⁰⁷⁶	Case control study
MEHRPARVAR 2013 ¹¹²⁷	Occupational asthma
MELE 2010 ¹¹³⁰	Not PEF, PEFR or FEV ₁
MESLIER 1989 ^{1137,1137}	Only reports change in FEV1 as % initial or absolute volume alone
MIRAVITLLES 2010 ¹¹⁵⁸	Bronchodilator test part of gold standard (doctor diagnosis) as well as index test
MUNNIK 2010 ¹¹⁹¹	Bronchodilator test part of gold standard (doctor diagnosis) as well as index test
MUSK 2011 ¹¹⁹⁷	Not all participants had bronchodilator test
NOWAK 1996 ¹²⁵⁹	Not all participants had bronchodilator test
OHKURA 2013 ¹²⁷⁴	Conference abstract – have enough fully published data already
OOSTVEEN 2010 ¹²⁸³	Age <5 years; not PEF, PEFR or FEV ₁
PATON 2010 ¹³¹⁹	Not primary study
PEDROSA 2010 ¹³³⁰	All participants selected for negative bronchodilator test
PETANJEK 2007 ¹³⁴⁶	All participants selected for positive bronchodilator test
PINO 1996 ¹³⁶⁵	Wrong outcome measure of FEV1 (Change in FEV1% >15% - not clinically relevant)
POSTMA 1995 ¹³⁸⁵	Longitudinal study – bronchodilator test and diagnosis not at the same time
PRUITT 2012 ¹⁴¹²	Not primary study
REED 2010 ¹⁴⁴³	Not primary study
RENWICK 1996 ¹⁴⁵¹	Not all participants had bronchodilator test
RHEE 2013 ¹⁴⁵³	Bronchodilator test part of gold standard (doctor diagnosis) as well as index test
RICHTER 2008 ^{1456,1456}	Only reports change in FEV1 as % initial or absolute volume alone
ROBINSON 2010 ¹⁴⁶⁶	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma (same study as Robinson 2012 below)
ROBINSON 2012 ¹⁴⁶⁷	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
RUPPEL 2012 ¹⁴⁹²	Not a primary study
SALLAWAY 2011 ¹⁵⁰²	Not all participants had bronchodilator

	test
SALOME 1999 ¹⁵⁰⁴	Not all participants had bronchodilator test
SANCHEZ 2012 ¹⁵⁰⁵	Participants selected for negative bronchodilator test
SANCHEZ 2013 ¹⁵⁰⁶	Bronchodilator test part of gold standard not index test
SCHNEIDER 2013 ¹⁵³⁶	Not all participants had bronchodilator test
SCOTT 2012 ¹⁵⁵¹	Not all participants had bronchodilator test
SILVESTRI 2008 ¹⁵⁹⁶	Bronchodilator test part of gold standard (doctor diagnosis) as well as index test(from guidelines cited references 13 and 14: asthma info page 6 of asthma guideline and COPD info on p 11 of COPD guideline; both pdfs accessed from: http://www.jornaldepneumologia.com.br/detalhe_suplemento.asp?id=40 (in Portuguese)
SIN 2006 ¹⁶⁰⁹	Bronchodilator test part of gold standard (doctor diagnosis) as well as index test
SINGH 2012 ¹⁶¹⁴	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
SLIEKER 2003 ¹⁶²⁴	Not all participants had bronchodilator test
SMITH 2004 ¹⁶³⁰	Bronchodilator test part of gold standard (doctor diagnosis) as well as index test
SOBOL 1985 ¹⁶³⁵	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
SPOSATO 2008 ¹⁶⁶¹	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma
THIADENS 1998A ¹⁷⁴⁵	Bronchodilator test as gold standard (doctor diagnosis) not index test
THIADENS 1999 ¹⁷⁴⁷	Bronchodilator test as gold standard (doctor diagnosis) as well as index test
TOMITA 2013 ¹⁷⁷³	Bronchodilator test part of gold standard (doctor diagnosis) not index test. Scoring system of signs and symptoms, algorithm based on BDR or reversibility.
TSE 2013 ¹⁷⁹⁰	Case control study
ULRIK 2005 ¹⁸¹⁰	Wrong outcome measure of FEV1 (Change in FEV1% >10% - not clinically relevant)
VUGT 2012 ¹⁸⁸¹	Bronchodilator test used as gold

	standard as well as index test
WALAMIES 1998 ¹⁸⁸⁴	Wrong cut-off value for FEV1: change $\geq 5\%$
WALRAVEN 2001 ¹⁸⁸⁶	Not all participants had bronchodilator test
WARDMAN 1986 ¹⁸⁹⁵	Not all participants had bronchodilator test
WOLFF 2012 ¹⁹³⁵	Not all participants had bronchodilator test
YANG 2011A ¹⁹⁵⁰	Case control study; bronchodilator test part of gold standard (doctor diagnosis) not index test
YAO 2011 ¹⁹⁵²	FeNO not bronchodilator response
YOO 2007 ¹⁹⁶⁰	Not doctor diagnosed asthma; not bronchodilator reversibility versus doctor diagnosis or other test for asthma
ZWAR 2011 ¹⁹⁹⁴	Not bronchodilator reversibility versus doctor diagnosis or other test for asthma

1 K.8 Diagnosis: PEF variability

2 Table 214: Studies excluded from the clinical review

Reference	Reason for exclusion
AGGARWAL2002 ^{21,21}	Case control study
AITKHALED2006 ²⁶	Not PEF over/under a certain threshold versus asthma status
ALBERTINI1989 ^{31,31}	Case control study
ANEES2011 ^{50,51}	Not PEF over/under a certain threshold versus asthma status
BARUA2005 ^{117,117}	Not a primary study
BASER2007 ^{118,118}	Not PEF versus another test for asthma (PEF included in the definition of asthma)
BECKETT2006 ^{135,135}	Not PEF over/under a certain threshold versus asthma status
BELLIA1985 ^{146,146}	Not PEF for diagnosis (prognosis of morning dip)
BERNSTEIN1993 ^{161,161}	Occupational asthma
BERRY1985 ^{164,164}	Not PEF over/under a certain threshold versus asthma status
BOULET1994 ^{201,202}	Not PEF over/under a certain threshold versus asthma status
BRAND1991 ^{210,210}	Not PEF over/under a certain threshold

Reference	Reason for exclusion
	versus asthma status
BRAND1997 ^{B210,212}	Not PEF over/under a certain threshold versus asthma status
BRITTON1997 ^{224,225}	Not PEF over/under a certain threshold versus asthma status
BROUWER2006 ^{232,232}	Not PEF over/under a certain threshold versus asthma status
CHU2008 ^{328,328}	Not primary study; not PEF over/under a certain threshold versus asthma status
COTE1990 ^{370,370}	Occupational asthma
CURRIE2005 ^{385,385}	Not PEF over/under a certain threshold versus asthma status
DESALU2009 ^{429,429}	Wrong population. Reference standard – no objective test.
DICKINSON1999 ^{440,440}	Not PEF versus another test for asthma (PEF included in the definition of asthma)
DOW2001 ^{451,451}	Not PEF versus another test for asthma (PEF included in the definition of asthma)
ENRIGHT1997 ^{479,479}	Not PEF over/under a certain threshold versus asthma status or other test
FERDOUSI1997 ^{494,494}	Not PEF over/under a certain threshold versus asthma status
FERDOUSI2005 ^{494,495}	Not doctor-diagnosed asthma
FIELDER1999 ^{498,498}	Not PEF over/under a certain threshold versus asthma status
FRISCHER 1995 ^{524,526}	Wrong population: general population, not suspected asthma.
FRISCHER1993B ^{524,525}	Not PEF over/under a certain threshold versus asthma status
GIBSON1995 ^{564,564}	Case control study
GOLDSTEIN 2001 ^{585,586}	PEFv calculation includes post-BD values
HANSEN1994 ^{640,640}	Not PEF over/under a certain threshold versus asthma status
HARGREAVE1982 ^{643,643}	Not PEF over/under a certain threshold versus asthma status
HARGREAVE1986 ^{642,643}	Not PEF over/under a certain threshold versus asthma status
HART2002 ^{646,646}	Not primary study
HEDMAN1998 ^{656,656}	PEF included in the definition of asthma (i.e. in reference standard not index

Reference	Reason for exclusion
	test)
HENDERSON1989 ^{663,663}	Case control study
HETZEL1980 ^{676,676}	Not PEF over/under a certain threshold versus asthma status
HIGGINS 1992 ^{678,679}	Wrong reference standard: Physician Dx but no objective test.
HIGGINS1989 ^{679,679}	Not PEF over/under a certain threshold versus asthma status or sensitivity/specificity
HSU1997 ^{713,713}	Not PEF over/under a certain threshold versus asthma status or sensitivity/specificity
JAIN1998 ^{749,749}	No numerical data for sensitivity/specificity; not a primary study
JAMISON1993 ^{755,755}	Case control study
JINDAL2002 ^{778,778}	Not a primary study
KERCSMAR1996 ^{848,848}	Not a primary study
KHOO1984 ^{862,862}	Not PEF over/under a certain threshold versus asthma status
KOH2005 ^{897,898}	Not PEF over/under a certain threshold versus asthma status
KOLBE1996 ^{902,902}	Not PEF over/under a certain threshold versus asthma status
KUNZLI 1999 ^{943,943}	Wrong population: general population, not suspected asthma.
LAPRISE1997 ^{966,966}	Not PEF over/under a certain threshold versus asthma status
LARSSON1994 ^{969,969}	Not PEF over/under a certain threshold versus asthma status (PEF included in diagnosis)
LARSSON1995 ^{968,969}	Not PEF over/under a certain threshold versus asthma status (PEF included in diagnosis)
LAWSON2011 ^{978,978}	Not PEF over/under a certain threshold versus asthma status
LEBOWITZ1997 ^{982,982}	Not PEF over/under a certain threshold versus asthma status
LEWIS 2001 ^{1002,1005}	Wrong population: general population, not suspected asthma. Wrong reference standard: Physician Dx but no objective test.
LINDENSMITH2004 ^{1019,1019}	Not PEF over/under a certain threshold versus asthma status
LINNA1993 ^{1026,1026}	Not PEF over/under a certain threshold versus asthma status
MAGYAR1998 ^{1062,1062}	Not primary study
MATSUNAGA2008 ^{1106,1106}	Not PEF over/under a certain threshold versus asthma status

Reference	Reason for exclusion
MICHOUD1982 ^{1142,1142}	Not PEF over/under a certain threshold versus asthma status
MOORE2009 ^{1177,1177}	Function of different monitoring devices not PEF over/under a certain threshold versus asthma status or other test
MOSCATO1993 ^{1181,1181}	Occupational asthma
MOSFELDTLAURSEN1993 ¹¹⁸²	Not PEF over/under a certain threshold versus asthma status
MUERS1984 ^{1187,1187}	Not PEF over/under a certain threshold versus asthma status
PAGGIARO1993 ^{1295,1295}	Not PEF over/under a certain threshold versus asthma status or sensitivity/specificity
PARAMESWARAN1999 ^{1306,1306}	Not PEF over/under a certain threshold versus asthma status
PINO1996 ^{1365,1365}	Not PEF variability over/under a certain threshold versus asthma status; PEF during bronchodilator test versus FEV1 during bronchodilator test – included in bronchodilator response review
PODER1987 ^{1373,1373}	Not PEF over/under a certain threshold versus asthma status
POGSON2009 ^{1374,1374}	Not PEF over/under a certain threshold versus asthma status
PRIETO1998 ^{1406,1406}	Not PEF over/under a certain threshold versus asthma status
PRIETO2000 ^{1406,1407}	Not PEF over/under a certain threshold versus asthma status
SANO2004 ^{1509,1509}	Not all patients had reference standard test
SEKEREL1997 ^{1558,1558}	Not PEF over/under a certain threshold versus asthma status
SHAKERI2012 ^{1568,1568}	Mixed population of patients with asthma and COPD
SHIRAHATA2005 ^{1583,1583}	Not PEF over/under a certain threshold versus asthma status
SIERSTED 1994 ^{1590,1590}	Wrong reference standard: Physician Dx but no objective test.
SIERSTED 1996 ^{1590,1591}	Wrong reference standard: Physician Dx but no objective test. Wrong population: general population, not suspected asthma.
SINGH2012 ^{1613,1614}	Case control study
SLIEKER 2003A ^{1624,1624}	Wrong outcome measure: PEF not PEF variability.
STEIN1997 ^{1673,1673}	Not PEF over/under a certain threshold versus asthma status
TAJI2013 ^{1717,1717}	Not PEF over/under a certain threshold versus asthma status

Reference	Reason for exclusion
THIADENS 1999 ^{1746,1747}	Index test is BDR
TIMONEN1997 ^{1757,1757}	Not PEF over/under a certain threshold versus asthma status
TOKUYAMA1998 ^{1767,1768}	Not PEF over/under a certain threshold versus asthma status
TOUNGOUSSOVA2007 ^{1780,1780}	Not PEF over/under a certain threshold versus asthma status
VANSCHAYCK1996 ¹⁸³⁸	Not PEF over/under a certain threshold versus asthma status
VARGAS2005 ^{1845,1845}	Not PEF over/under a certain threshold versus asthma status
VASAR1996 ^{1847,1847}	Not PEF over/under a certain threshold versus asthma status
VENABLES1984 ^{1852,1852}	Not PEF over/under a certain threshold versus asthma status
YOO2007 ^{1959,1959}	Not PEF over/under a certain threshold versus asthma status
YURDAKUL2005 ^{1968,1968}	PEF variability included as part of reference standard as well as index test
ZILMER2011 ^{1988,1988}	Not PEF over/under a certain threshold versus asthma status
ZUREIK1995 ^{1993,1993}	Not PEF over/under a certain threshold versus asthma status with a reference standard (comparing 2, 3 or 4 measurements of PEF versus 5)

1 K.9 Diagnosis: Skin prick tests

2 Table 215: Studies excluded from the clinical review

Reference	Reason for exclusion
ALENIZI2013 ³⁵	Conference abstract – have enough fully published data already
ALMEIDA 1999 ³⁹⁴	Results for SPT not given thus cannot calculate sens/spec.
ANTOLIN2013 ⁵⁵	Conference abstract – have enough fully published data already
ANTOLINAMERIGO 2012 ⁵⁴	Conference abstract – have enough fully published data already
ARDUSSO 2009 ⁶³	Conference abstract – have enough fully published data already
ARMENTIA2007 ⁷¹	no data on SPT by/within asthma status
BARNIG 2013 ¹¹²	Correlation study – cannot

Reference	Reason for exclusion
	calculate sens/spec.
BONINI 2010 ¹⁸⁷	Conference abstract – have enough fully published data already
BRAND 1993 ²¹³	Results in mixed population of asthma/COPD (no asthma subgroup analysis).
BUSINCO1988 ²⁵²	not SPT by asthma status
CAIMMI2013A ²⁶¹	Conference abstract – have enough fully published data already
COMERT2014 ³⁶¹	No reference standard
CONNOLLY1981 ³⁶²	not SPT by asthma status
DEANE2005 ⁴⁰⁸	not SPT by asthma status
DELACOURT1994 ⁴¹⁶	control group too young (<1 year)
DERVADERICS2002 ⁴²⁸	no data on SPT by/within asthma status
DHARMAGE1998 ⁴³⁴	not SPT by asthma status
DIBEK 2007 ⁴³⁹	All asthma pts – no comparative test group thus unable to calculate sens/spec.
ESCUDERO 1993 ⁴⁸³	Wrong reference standard: allergen challenge was part of the reference standard test.
FOUCARD1973 ⁵¹²	longitudinal not cross-sectional data
FUIANO2013 ⁵³²	Conference abstract – have enough fully published data already
GARCIA1997 ⁵⁴⁷	patients selected for previous negative SPT
GARCIAGONZALEZ1999 ⁵⁴⁸	castor bean pollen not relevant to UK
GOETZ2007 ⁵⁸⁰	Asian ladybug not relevant to UK, no other SPT by asthma reported
GRADMAN2006 ⁵⁸⁹	Some children had both asthma and rhinitis; table of SPT by diagnosis double counts these children so sensitivity/specificity not calculable
GRAIF 2002 ⁵⁹⁰	Wrong comparison: data in this study are given for suspected asthma pts or control pts only and are for test vs. test rather than test vs physician Dx (which is the comparison we look for in suspected asthma pts)

Reference	Reason for exclusion
GUDELJ 2012 ⁶⁰⁸	Wrong reference standard: physician Dx includes the objective test
GUERRA1995 ⁶¹¹	Percentages given for SPT positive and negative and number with asthma but unable to calculate raw data or sensitivity/specificity etc due to rounding
HAYES2013 ⁶⁵⁴	All patients had positive SPT
HILL1994 ⁶⁸¹	not SPT by asthma status
HUERTAS2011 ⁷¹⁹	All pollen-allergic; no data on SPT by asthma status
IMBEAU1978 ⁷³⁷	not SPT by asthma status
JULIA1995 ⁷⁹³	Population is rhinitis and/or asthma (not suspected asthma)
KARAKAYA 2006 ⁸²³	Asthma/rhinitis pts – does not split results for asthma or rhinitis groups separately, thus cannot calc sens/spec for asthma.
KAUFMAN1984 ⁸³²	not SPT by asthma status
KIM 2002 ⁸⁷²	Wrong reference standard definition: Physician Dx = patient-reported in a questionnaire.
KIM2013A ⁸⁶⁷	General population
KOUTSOUPIAS2013A ⁹²⁰	Conference abstract – have enough fully published data already
KOWAL 2009 ⁹²⁴	Unable to calculate sens/spec as the number of +ve and –ve SPTs are bnit given for SPT with asthma.
KUMAR2011A ⁹³⁹	Conference abstract – have enough fully published data already
KUMARI 2006 ⁹⁴²	Wrong allergens / country for allergen: food allergies and pollen in India.
LAURENT1994 ⁹⁷⁷	SPT to diagnose winter pollinosis not asthma
LEWIS1989 ¹⁰⁰²	Case-control study including asthma and suspected asthma groups in the sensitivity/specificity analysis
LUISI 2012 ¹⁰⁴⁵	All asthma pts, but unable to calculate sens/pec of SPT vs. other tests (BDR or spirometry).
MARINOVIC2013 ¹⁰⁸⁹	Conference abstract – have enough fully published data

Reference	Reason for exclusion
	already
MASULLO1996 ¹⁰⁹⁸	All SPT positive
MIGUERES2011 ¹¹⁴⁷	selected for positive skin prick tests
MOSBECH 1987A ¹¹⁸⁰	All asthma pts but wrong comparative test: bronchial, conjunctival challenge with the same allergen as the index (SPT) test.
MURRAY1985 ¹¹⁹⁶	not SPT by asthma status
MUSKEN2002 ¹¹⁹⁸	not SPT by asthma status
NEGRINI1992 ¹²¹⁸	not SPT by asthma status
NIEDOSZYTKO2007 ¹²³⁸	not symptomatic controls
NIEMEIJER 1992A ¹²⁴⁰	All asthma pts – SPT but no comparison test, thus cannot calculate sens/spec.
NOGUEIRA1994 ¹²⁵⁴	Non-English
NOLTE 1990 ¹²⁵⁶	Suspected asthma pts recruited, but no final Physician Dx of asthma was done and the wrong comparison tests also used.
OSTERGAARD 1990 ¹²⁹⁰	All asthma pts: wrong comparison test - IgE or BPT with the allergens.
PALMACARLOS2005 ¹²⁹⁶	not SPT by asthma status
PANASZEK 2007 ¹³⁰⁰	Does not give SPT results for Dx of asthma – cannot calc sens/spec.
PANICHWATTANA2013 ¹³⁰¹	Conference abstract – have enough fully published data already
PAPA2001 ¹³⁰⁴	selected for SPT positivity
PEARLMAN 2009 ¹³²¹	Correlation study and cannot calculate sens/spec for asthma pts..
QUIRALTE2005 ¹⁴¹⁸	all SPT positive
RESANO1998 ¹⁴⁵²	Intradermal not skin prick test
RODRIGUEZ2013 ¹⁴⁷⁰	Not in English
ROTTOLI1989 ¹⁴⁸⁵	not SPT by asthma status
SASTRE 1996 ¹⁵¹³	Duplicate study – already excluded
SASTRE1996 ¹⁵¹³	not SPT by asthma status
SCHWARTZ1995 ¹⁵⁴⁶	not SPT by asthma status
SILVESTRI1996 ¹⁵⁹⁹	not SPT by asthma status
SILVESTRI1997 ¹⁵⁹⁸	not SPT by asthma status
SMITH2005 ¹⁶²⁹	not SPT by asthma status
SRITIPSUKHO 2004 ¹⁶⁶⁷	All asthma pts – no comparative

Reference	Reason for exclusion
	test group thus unable to calculate sens/spec.
STAFANGER 1986 ¹⁶⁶⁸	Wrong comparison test: BPT (contains the same allergens as the index SPT)
STELMACH 2002A ¹⁶⁷⁴	Results for SPT allergens divided by cockroach allergen – ve and +ve pts; cannot calc sens/spec of true asthma pts.
STOKES2000 ¹⁶⁸⁴	not SPT by asthma status
TASKINEN 1997 ¹⁷³²	Wrong allergen results: results for >10 moulds all pooled together. Unable to get specific results for <i>Cladosporium</i> or <i>Alternaria</i>
TAUBER 2000 ¹⁷³³	Correlation study – cannot calculate sens/spec.
TOMASSEN2013 ¹⁷⁷²	General population/no objective test
TORRESRODRIGUEZ2012 ¹⁷⁷⁹	All skin prick positive
TROISE1992 ¹⁷⁸⁶	not SPT by asthma status
TSCHOPP 1998 ¹⁷⁸⁸	Wrong reference standard definition: Physician Dx = patient-reported in a questionnaire.
VARELA2003 ¹⁸⁴⁴	SPT given for asthma group but not for control group
VENTURA2007 ¹⁸⁵⁶	Some participants had both asthma and rhinitis so sensitivity/specificity not calculable
VERVLOET1999 ¹⁸⁶⁰	All skin prick positive
VIEIRA 2009 ¹⁸⁶³	Conference abstract – have enough fully published data already
VIEIRA 2011 ¹⁸⁶⁴	Wrong reference standard definition: Physician Dx = patient-reported in a questionnaire. Validation study.
WEINTRAUB 2001 ¹⁹⁰⁴	Wrong definition of physician Dx: physician Dx was patient-reported via a questionnaire
WOODMANSEE 2009 ¹⁹³⁸	Conference abstract – have enough fully published data already
YURDAKUL 2005 ¹⁹⁶⁸	Case-control study including asthma and suspected asthma groups in the sensitivity/specificity analysis
ZETTERSTROM 1972 ¹⁹⁷⁶	Wrong country for allergen: pollen in Sweden.

1K.10 Diagnosis: IgE

2 **Table 216: Studies excluded from the clinical review**

Reference	Reason for exclusion
ABDULAMIR 2009 ^{7,7}	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
ABUT 2007 ^{14,14}	Wrong outcomes: correlations of IgE not no. of positive/negative.
ADLER 1985 ^{19,19}	Wrong outcomes: levels of IgE not no. of positive/negative.
AGATA 1993 ^{20,20}	Wrong comparisons: different IgE methods compared.
AHLSTEDT 1974 ^{22,22}	Mixed population (asthma and/or allergic rhinitis), with no separate analysis for Dx of asthma.
AHMAD 2008 ^{23,23}	Incorrect study design: case-control study
AKCAKAYA 2005 ^{27,27}	Wrong outcomes: only gives SPT results, not IgE.
ALMQVIST 2007 ^{37,37}	Wrong outcomes: predictors of subsequent development of sensitisation.
BACKER 1992 ^{87,90}	Mixed population (asthma, rhinitis and dermatitis), with no separate analysis for Dx of asthma.
BARNES 2014 ¹¹¹	Conference abstract
BEEH 2000 ^{137,137}	Cannot calculate sens/spec as only gives numbers who were positive for each test individually.
BJORNSSON 1994 ^{176,176}	Wrong outcomes: correlations of IgE not no. of positive/negative.
BRANCATO 1995 ^{208,208}	Wrong outcomes: levels of IgE not no. of positive/negative.
BRAND 1993 ^{210,213}	Mixed population (asthma and COPD), with no separate analysis for Dx of asthma
BRUCE 1976 ^{235,235}	Wrong outcomes: levels of IgE and split by HLA antigen groups, not no. of positive/negative.
BRYANT 1975 ^{240,240}	Wrong reference standard: allergen-specific BPT.
BURROWS 1991 ^{250,250}	Wrong outcomes: predictors of subsequent development of asthma.
BUTERLEVICIUTE 2013 ^{257,257}	Conference abstract
CANTANI 1990 ^{267,267}	Mixed population (asthma and/or rhinitis with others), with no separate analysis for Dx of asthma. Wrong outcomes: Dx of atopy, not asthma.
CANTANI 2005A ^{267,269}	Wrong outcomes: levels of IgE not no. of positive/negative.

CANTONI 2003 ^{267,268}	Cannot calculate sens/spec as only gives numbers who were positive for each test individually.
CARSIN 2013 ^{285,285}	Wrong outcomes: predictors of subsequent development of asthma.
CASSIMOS 2008 ^{290,290}	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
CHAKRABARTI 1993 ^{297,297}	Wrong outcomes: Dx of Aspergillus lung disease not asthma.
CHAO 2001 ^{302,302}	Incorrect study design: case-control study.
CHEN 2014 ^{308,310}	General population
CHOI 2005 ^{319,320}	Wrong outcome (Dx): Dx of early or late airway reaction, not asthma Dx.
CHOI 2005A ^{319,322}	Incorrect study design: case-control study
CHOU 2002 ^{323,323}	Cannot calculate sens/spec as only gives numbers who were positive for asthma only.
COCKCROFT 1979 ^{356,356}	Wrong outcomes: correlations/relationships of IgE not no. of positive/negative.
COOKSON 1976 ^{363,364}	Wrong outcomes: correlations of IgE not no. of positive/negative.
CRAMERI 1998 ^{375,375}	Wrong outcomes: levels of IgE not no. of positive/negative.
CULLINAN 2004 ^{384,384}	Wrong outcomes: not Dx of asthma.
CUSTOVIC 1996 ^{387,387}	Does not mention IgE.
DECLERK 1986 ³⁹⁸	Wrong comparison: methods/assay development.
DELOVIN 1994 ⁴⁰³	Wrong comparison: sens/spec of RAST vs. mite-levels in mattress.
DOEKES 1996 ^{446,446}	Wrong comparison: two different methods of IgE measurement.
DUC 1988 ^{459,459}	Mixed population (asthma and/or rhinitis with others), with no separate analysis for Dx of asthma.
EWAN 1990 ^{485,485}	Mixed population (asthma and/or rhinitis with others), with no separate analysis for Dx of asthma.
EYSINK 2001 ^{486,486}	Wrong outcomes: predictors of subsequent development of asthma.
EYSINK 2005 ^{486,487}	Cannot calculate sens/spec as only gives numbers who were positive for each test individually.
FERNANDEZ 2007 ^{497,497}	Wrong reference standard: allergen-specific BPT.
FERNANDEZ 2011 ^{496,497}	Wrong reference standard: allergen-specific BPT.
FLAHERTY 1980 ^{502,502}	Wrong study design: case-control study.

	Wrong outcomes: levels of IgE not no. of positive/negative.
FREIDHOFF 1993 ^{522,522}	Cannot calculate sens/spec as only gives numbers who were positive or negative for each test individually.
FRITH 2011 ^{527,527}	Wrong comparison: SPT
GERGEN 2009 ^{559,559}	Cannot calculate sens/spec as only gives numbers of positives for each test individually.
GODFREY 1975 ^{576,576}	Wrong outcomes: levels of IgE not no. of positive/negative.
GOLDSTEIN 2005 ^{584,585}	Wrong population: not asthma but allergy
HAATELA 1981 ^{619,619}	Mixed population (wheeze or asthma), with no separate analysis for Dx of asthma.
HEIDEN 2010 ⁶⁵⁸	Incorrect study design: case-control study. Wrong outcomes: levels and relationships of IgE, not no. of positive/negative.
HOFFMANN 2013 ⁶⁸⁶	Wrong comparison (SPT)
HOGARTH 1973 ⁶⁸⁷	Wrong comparison: SPT
IWAMOTO 1990 ^{744,744}	Incorrect study design: case-control study
JAAKKOLA 2006 ^{745,745}	Incorrect study design: case-control study
JACKOLA 2004 ^{746,746}	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
JANG 2007 ^{758,759}	Incorrect study design: case-control study
KALYONCU 1995 ^{815,815}	Incorrect study design: case-control study. Wrong outcomes: levels of IgE not no. of positive/negative.
KARADAG 2007 ^{821,821}	Wrong outcomes: not Dx of asthma but of atopic eczema (in general population).
KARTASAMITA 1994 ^{826,826}	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
KEIL 2006 ^{840,841}	Review – used as a source of references.
KELSO 1991 ^{846,846}	Mixed population (asthma and/or rhinitis), with no separate analysis for Dx of asthma.
KERKHOF 2003 ^{850,850}	Mixed population (asthma and/or allergy symptoms), with no separate analysis for Dx of asthma.
KHADADAH 2000A ^{854,855}	Wrong comparison: SPT
KING 2004 ^{876,877}	Wrong outcomes: levels of IgE and Odds, not no. of positive/negative.
KITANI 1993 ^{879,879}	Does not answer the question:

	compares drug-induced asthma vs. non-drug induced asthma, and only gives numbers who were positive for each test individually.
KJAER 2008 ^{883,883}	Wrong outcomes: results for SPT and IgE are combined.
KLINKANOVA 1995 ^{888,888}	Abstract not fully published paper.
KOIVIKKO 1991 ^{899,899}	Cannot calculate sens/spec.
KONDERAK 2013 ^{907,907}	Conference abstract
KOROL 2006 ^{912,912}	Wrong study design: case-control. Wrong outcomes: levels of IgE, not no. of positive/negative.
KOVAC 2007 ^{921,921}	Wrong outcomes: asthma severity.
KURIMOTO 1978 ^{944,944}	Wrong outcomes: agreement with IgE, not no. of positive/negative.
LAI 2002 ^{959,961}	Cannot calculate sens/spec as only gives numbers who were positive for each test individually.
LASKE 2003 ^{970,970}	Wrong outcomes: levels of IgE not no. of positive/negative.
LODRUPCARLSEN 2010A ^{1035,1035}	Wrong outcomes: predictors of subsequent development of asthma.
MASUKO 2011 ^{1097,1097}	Wrong population: healthy people only. Wrong outcomes: levels of IgE.
MATRICARDI 1990 ^{1102,1102}	Mixed population (asthma and/or oculorhinitis with others), with no separate analysis for Dx of asthma.
MATRICARDI 2009 ^{1100,1102}	Wrong outcomes: levels of IgE over time, not no. of positive/negative.
MATSUI 2010 ^{1103,1103}	Wrong outcomes: levels of IgE not no. of positive/negative.
MOGI 1977 ^{1168,1168}	Incorrect study design: case-control study. Wrong outcomes: levels of IgE not no. of positive/negative.
MOGI 1977A ^{1168,1169}	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
MOUTHUY 2011 ^{1185,1185}	Wrong outcomes: levels of IgE not no. of positive/negative.
MOVERARE 2002 ^{1186,1186}	Mixed population (asthma and/or rhinoconjunctivitis), with no separate analysis for Dx of asthma.
MUSTONEN 2013 ^{1200,1200}	Wrong outcomes: predictors of asthma over time linked to CRP.levels of IgE not no. of positive/negative.
MYGIND 1978 ^{1202,1202}	Wrong outcomes: levels of IgE not no. of positive/negative.
NAVRATIL 2009 ^{1217,1217}	Wrong outcomes: levels and relationships of IgE, not no. of positive/negative.
NIELSEN 1992 ^{1239,1239}	Results for all allergens pooled together.

NIGGEMAN 2008 ^{1242,1243}	Wrong outcomes: Dx of allergy made with symptoms and IgE, not Dx of asthma.
NOLLES 2001 ^{1255,1255}	Wrong outcomes: not Dx of asthma.
NUSSLEIN 1987 ^{1262,1262}	Wrong comparison: old RAST vs. new RAST
OKUDAIRA 1983 ^{1277,1277}	Cannot calculate sens/spec as only gives numbers for each test individually.
ORYSZCZYN 2009 ^{1285,1286}	Not IgE versus SPT status; cannot calculate sensitivity etc of test.
OSTERBALLE 1979 ^{1289,1289}	Cannot calculate sens/spec as only shows data as graphs.
PANZANI 1993 ^{1303,1303}	Not physician diagnosed asthma and no objective tests.
PARK 1997 ^{1311,1312}	Wrong outcomes: not Dx of asthma.
PASTORELLO 1995 ^{1317,1317}	Wrong outcomes; Dx of symptomatic and non-symptomatic allergy, not asthma.
PEAT 1996 ^{1324,1325}	Wrong outcomes: levels of IgE not no. of positive/negative.
PECOUD 1982 ^{1328,1328}	Wrong comparison: newer RAST test vs. older RAST test.
PEKKARINEN 2007 ^{1332,1332}	Cannot calculate sens/spec as only gives numbers who were positive for each test individually.
PELIKAN 1982 ^{1333,1333}	Results for all allergens pooled together.
PEPYS 1975 ^{1334,1334}	Mixed population (asthma and/or allergic rhinitis), with no separate analysis for Dx of asthma.
PEREIRA 2005 ^{1335,1335}	Mixed population (asthma and/or allergic rhinitis), with no separate analysis for Dx of asthma.
PERRIN 1983 ^{1338,1338}	Wrong outcomes: levels of IgE not no. of positive/negative.
PERZANOWSKI 1998 ^{1344,1344}	Report of data from several other studies.
PLASCHKE 1996 ^{1369,1369}	Wrong outcomes: not Dx of asthma but of atopy (in general population).
PLEBANI 1995 ^{1370,1370}	Not asthma versus no asthma (mixed population of asthma and rhinitis patients)
PRICE 1989 ^{1403,1403}	Wrong outcomes: % agreement of SPT and RAST, not no. of positive/negative.
PRICHARD 1985 ^{1404,1404}	Occupational asthma.
RAHERISON 2004 ^{1423,1423}	Wrong outcomes: levels of IgE not no. of positive/negative.
REIJULA 2003 ^{1446,1446}	Mixed population (asthma with others), with no separate analysis for Dx of asthma. Incorrect study design: case-control study.
ROGERS 2002 ^{1472,1472}	Not asthma versus no asthma (not Dx of

	asthma); no reference standard or other test for allergy
ROSARIO 1997 ^{1481,1481}	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
RUDZKI 1990 ^{1489,1489}	Wrong population: atopic dermatitis pts.
RYDJORD 2008 ^{1494,1494}	Wrong outcomes: not used for Dx of asthma.
SANTOSO 1998 ^{1511,1511}	Wrong comparison: SPT
SCHOEFER 2008 ^{1538,1538}	Wrong outcomes: levels of IgE not no. of positive/negative.
SCORDAMAGLIA 1992 ^{1549,1549}	Mixed population (asthma, rhinitis and conjunctivitis), with no separate analysis for Dx of asthma.
SELASSIE 2000 ^{1559,1559}	Incorrect study design: case-control study
SHARMA 2006A ^{1572,1572}	Incorrect study design: case-control study.
SHERRILLI 1999 ^{1576,1577}	Wrong outcomes: wheezing, not Dx of asthma.
SHIBASAKI 1997 ^{1578,1578}	Incorrect study design: case-control study
SIMONI 2001 ^{1605,1605}	Wrong test: PRIST test (modified RAST test) – not commonly used in current practice.
SIMPSON 2005 ^{1606,1606}	Wrong outcomes: Dx of wheeze not asthma.
SIROUX 2003 ^{1616,1616}	Correlation study in people with asthma
STAFANGER 1986 ^{1668,1668}	Cannot calculate sens/spec as only gives data in graphs.
STEVENS 1983 ^{1679,1679}	Mixed population (asthma and/or rhinitis), with no separate analysis for Dx of asthma.
STEVENS 2011 ^{1678,1679}	Incorrect study design: case-control study
SUBIRA 1976 ^{1696,1696}	Wrong outcomes: levels and correlations of IgE not no. of positive/negative.
SUMAN 2005 ^{1698,1698}	Incorrect study design: case-control study. Wrong test: for indian-specific pollen.
SUNYER 1996 ^{1701,1701}	Cannot calculate sens/spec as only gives numbers who were positive for each test individually.
SUNYER 2004 ^{316,316}	Not asthma versus no asthma (not Dx of asthma); no reference standard or other test for allergy
TAMURA 1991 ^{1723,1723}	Wrong outcomes: predicted true positives and negatives, not actual numbers.
TANG 1989 ^{1726,1726}	Wrong comparison: SPT

TANG 2010 ^{1725,1726}	Wrong outcomes: levels of IgE not no. of positive/negative.
TERZIOGLU 1998 ^{1744,1744}	IgE vs. SPT (measures of the same thing); no comparison with Physician Dx.
TOMASSEN 2013 ^{1772,1772}	General population / wrong comparison (SPT).
TORRENT 2006 ^{1776,1776}	Wrong outcomes: risk of sensitisation, not Dx of asthma.
TU 2013 ^{1796,1796}	Conference abstract
VAGIC 2008 ^{1812,1812}	Incorrect study design: case-control study. Wrong outcomes: levels of IgE not no. of positive/negative.
VALENCIA 1993 ^{1814,1814}	Mixed population (asthma or rhinitis), with no separate analysis for Dx of asthma.
VANTO 1982 ^{1843,1843}	Wrong reference standard: allergen-specific BPT.
VIANDER 1983 ^{1862,1862}	Wrong comparison: conjunctival provocation test.
VOOREN 1983 ^{1877,1877}	Wrong reference standard: allergen-specific BPT.
WAKAMORI 2009 ^{1882,1882}	Wrong population: dermatitis not asthma.
WANG 1992 ^{1892,1892}	Wrong test: MAST test – not commonly used in current practice. RAST test also used in study but results not reported.
WANG 2009 ^{1891,1892}	Wrong outcomes: levels of IgE and predictors of mortality.
WEDNER 1987 ^{1900,1900}	Wrong allergen: rare plant
WEINMAYR 2007 ^{1903,1903}	Wrong outcomes: not used for Dx of asthma.
WICKMAN 2005 ^{1913,1914}	Mixed population (asthma and/or allergic rhinitis), with no separate analysis for Dx of asthma.
WITTEMAN 1996 ^{1928,1928}	Wrong outcomes: levels of IgE not no. of positive/negative.
WOODMANSEE 2009 ^{1938,1938}	Abstract only (conference abstract, not a full paper)
YANG 2010 ^{1951,1951}	Abstract only (conference abstract, not a full paper)
YAZICIOGLU 1994 ^{1955,1955}	Incorrect study design: case-control study. Results for all allergens pooled together.
ZIMMERMAN 1988A ^{1989,1989}	Mixed population (asthma and/or rhinitis and others), with no separate analysis for Dx of asthma.

1K.11 Diagnosis: FeNO

2 **Table 217: Studies excluded from the clinical review**

Reference	Reason for exclusion
<i>ANSARIN2001</i> ⁵²	Not treatment naïve (>50% on CS treatment)
<i>ANTUS2010</i> ⁵⁶	Not treatment naïve (>50% on CS treatment)
<i>ARTLICH1996</i> ⁷⁵	N<50 for case-control study
<i>AVITAL2001</i> ⁸⁴	Reference standard objective test not widely used
<i>BACKER 2014</i> ⁹¹	Reference standard does not match protocol – sn/sp of FeNO to predict positive mannitol in suspected asthma (not physician diagnosis and objective test)
<i>BAKKEHEIM2011</i> ⁹⁴	Not treatment naïve (>50% on CS treatment)
<i>BALINOTTI2013</i> ⁹⁷	No objective test for asthma, only Asthma Predictive Index
<i>BARALDI2003</i> ¹⁰⁴	Case-control study for FeNO levels but <50 people
<i>BARALDI2003A</i> ¹⁰¹	Not treatment naïve (>50% on CS treatment)
<i>BARALDI2005</i> ¹⁰³	N<50 for case-control study
<i>BARALDI2006</i> ¹⁰²	Case-control study for FeNO levels but <50 people
<i>BARRETO2001</i> ¹¹⁴	Not treatment naïve (unclear % of patients on CS treatment)
<i>BARRETO2006</i> ¹¹⁵	N<50 for case-control study
<i>BEG2009</i> ¹⁴⁰	Index test does not match protocol – flow rate of 200ml/s
<i>BEIGELMAN2008</i> ¹⁴¹	Not treatment naïve and no objective test
<i>BERKMAN2005</i> ¹⁵⁹	Index test does not match protocol – flow rate of 250ml/s
<i>BERNSTEIN2009</i> ¹⁶²	Not treatment naïve (no restrictions on treatment)
<i>BERRY2005A</i> ¹⁶³	Not treatment naïve (>50% on CS treatment)
<i>BEVER2003</i> ¹⁶⁶	Non-English
<i>BOBOLEA2012</i>	Not full paper (letter)
<i>BOMMARITO2008</i> ¹⁸³	Not treatment naïve; no objective test
<i>BRINDICCI2007</i> ²²³	N<50 for case-control study
<i>BRODLIE2010</i> ²²⁶	Review not primary study
<i>BRUSSEE2005</i> ²³⁷	Population does not match protocol – general population.
<i>BYRNES1997</i> ²⁵⁹	Not treatment naïve (>50% on CS treatment)

Reference	Reason for exclusion
<i>CARRARO2005</i> ²⁸¹	N<50 for case-control study
<i>CARRARO2007A</i> ²⁸³	Not treatment naïve (>50% on CS treatment)
<i>CARRARO2010</i> ²⁸²	N<50 for case-control study
<i>CASTRORODRIGUEZ2013</i> ²⁹²	All people with asthma for FeNO levels but <50 people
<i>CHEROTKORNOBIS2011</i> ³¹¹	Case-control study for FeNO levels but <50 people
<i>CHO2013</i> ³¹⁷	Index test does not match protocol – incorrect flow rate
<i>CHOW2009</i> ³²⁴	Results split into obese vs. non-obese pts; if use the non-obese people with asthma it means N<50 for case-control study. Otherwise meets all inclusion criteria.
<i>CIPRANDI2010</i> ³³⁷	Reference standard does not match protocol – unclear if objective test used
<i>COLONSEMIDEY2000</i> ³⁶⁰	All people with asthma for FeNO levels but <50 people
<i>CORRADI2001</i> ³⁶⁶	N<50 for case-control study (if exclude the subgroup on CS Tx)
<i>CRANE2012</i> ³⁷⁶	Not treatment naïve; no objective test
<i>DEBLEY2010</i> ⁴¹⁰	Asthma only pts, but N<50.
<i>DEBOT2013</i> ³⁹⁷	No objective test
<i>DECIMO2011</i> ⁴¹¹	Meets all inclusion criteria, but does not report the FeNO levels.
<i>DEDIEGO2005</i> ³⁹⁹	FeNO levels but <50 people; not sensitivity/ specificity vs. other test
<i>DEGOUW2001</i> ⁴⁰⁰	N<50 for case-control study
<i>DEGROOT2012</i> ⁴⁰¹	Not treatment naïve (all on CS treatment)
<i>DELABARRA2011</i>	Cannot calculate sn/sp
<i>DELEN2000</i> ⁴¹⁸	Not treatment naïve (unclear % of patients on CS treatment)
<i>DELGIUDICE2004</i> ⁴¹⁴	All people with asthma for FeNO levels but <50 people
<i>DEMEER2005</i> ⁴⁰⁶	No relevant outcomes – cannot calculate sn/sp of FeNO for Dx of asthma
<i>DOTSCH1996</i> ⁴⁵⁰	Unclear physician Dx.
<i>DRESSEL2008</i> ⁴⁵²	Method of asthma Dx not reported.
<i>DRESSEL2010</i> ⁴⁵³	Unclear physician Dx.
<i>EKROOS2009</i> ⁴⁷¹	Index test does not match protocol – flow rate of 80-150ml/s
<i>ELHALAWANI2003</i> ⁴⁷²	Suspected EIB and exercise challenge test.
<i>ELLIOTT 2013</i> ^{475,476}	Population does not match protocol – children less than 1 year old
<i>FABBRI2003</i> ⁴⁸⁸	Case-control study for FeNO levels but

Reference	Reason for exclusion
	<50 people
<i>FITZPATRICK2006</i> ⁵⁰¹	Severe asthma and moderate asthma. If exclude the severe asthma subgroup then N<50 for case-control study.
<i>FORMANEK2002</i> ⁵⁰⁹	Index test does not match protocol – nitrite levels not FeNO
<i>FORTUNA2007</i> ⁵¹¹	Reference standard objective test does not match protocol – methacholine challenge test cut-off at 16mg/ml
<i>FOWLER2009</i> ⁵¹⁵	Not treatment naïve (>50% on CS treatment)
<i>FRANK1998</i> ⁵¹⁹	Not treatment naïve (unclear % of patients on CS treatment)
<i>FRANKLIN2003</i> ⁵²⁰	Population does not match protocol – general population, asymptomatic children
<i>FRANKLIN2004</i> ⁵²¹	Population does not match protocol – general population
<i>FUJIMURA2008</i> ⁵³⁴	FeNO levels but <50 patients
<i>GABRIELE2005</i> ⁵³⁶	All people with asthma for FeNO levels but <50 people
<i>GADE2009</i> ⁵³⁷	Asthma only pts but N<50.
<i>GAGLIARDO2009</i> ⁵³⁸	Not treatment naïve (>50% on CS treatment)
<i>GEVORGYAN2013</i> ⁵⁶⁰	Review not primary study
<i>GRONKE2002</i> ⁶⁰⁰	Population does not match protocol – all atopic and comparing FeNO levels in groups with different durations of asthma
<i>GRZELEWSKI 2014</i> ^{606,607}	Study does not report results in such a way that it is possible to calculate sensitivity and specificity.
HAHN 2007	Sn/sp of FeNO for predicting response to ICS treatment, not asthma
<i>HENRIKSEN2001</i> ⁶⁶⁸	Not treatment naïve (unclear % of patients on CS treatment)
<i>HENRIKSEN2002</i> ⁶⁷⁰	No relevant outcomes – cannot calculate sn/sp of FeNO for Dx of asthma
<i>HENRIKSEN2003</i> ⁶⁶⁹	Not treatment naïve (unclear % of patients on CS treatment)
<i>HERVAS2008</i> ⁶⁷⁴	Not treatment naïve (unclear % of patients on CS treatment)
<i>HOGMAN2001</i> ⁶⁸⁹	Not treatment naïve (>50% on CS treatment)
<i>HOGMAN2002</i> ⁶⁸⁸	Not treatment naïve (>50% on CS treatment)
<i>HOLGUIN2011</i> ⁶⁹⁰	Not treatment naïve (>50% on CS treatment)
<i>HORVATH2004</i> ⁷¹⁰	Physician Dx with no objective tests (just

Reference	Reason for exclusion
	does SPT).
HOVI2010 ⁷¹²	Non-English
HSU2013	Sn/sp of FeNO for predicting response to ICS treatment, not asthma
HUSZAR2002 ⁷²⁶	Index test does not match protocol – flow rate of 5-6L/min
ISHIZUKA2011 ⁷⁴¹	No objective test
JATAKANON1998A ⁷⁷⁰	All asthma pts but N<50
JENTZSCH2006 ⁷⁷⁵	Not treatment naïve (>50% on CS treatment)
JERZYNSKA 2014 ^{776,776}	Study does not report results in such a way that it is possible to calculate sensitivity and specificity.
KANAZAWA2004 ⁸¹⁷	Case-control study. Phys Dx with objective test but wrong cut-off for objective test (BDR >20% - should be 12%)
KATSOULIS2013 ⁸²⁸	Reference standard does not match protocol – sn/sp of FeNO to predict positive methacholine challenge test not physician diagnosis of asthma with objective test.
KEEN2011 ⁸³⁹	Not treatment naïve (>50% on CS treatment)
KHARITONOV2003 ⁸⁵⁹	Unclear physician Dx.
KIELBASA2008 ⁸⁶⁵	Not treatment naïve (>50% on CS treatment)
KIM2013 ⁸⁷⁴	Wrong-cut off for the MCT objective test as part of Phys Dx. MCT <16mg/ml or FEV1 12% (doesn't give the % Dx by MCT or FEV1).
KLEIS2007 ⁸⁸⁶	Wrong-cut off for the MCT objective test as part of Phys Dx. MCT <16mg/ml – should be 8mg/ml.
KO2009 ⁸⁹⁴	Not treatment naïve (>50% on CS treatment)
KOMAKULA2007 ⁹⁰⁵	Not treatment naïve (>50% on CS treatment)
KONDO2003 ⁹⁰⁸	FeNO levels but <50 people
KOSKELA2008 ⁹¹⁴	Not treatment naïve (>50% on CS treatment)
KOVESI2008 ⁹²³	Not treatment naïve (unclear % on CS treatment)
KOVESI2009 ⁹²²	No objective test
LAGRUTTA2003 ⁹⁵³	Not treatment naïve (>50% on CS treatment)
LANGLEY2003 ⁹⁶⁵	Not treatment naïve (>50% on CS treatment)
LARA2008 ⁹⁶⁷	Not treatment naïve (>50% on CS

Reference	Reason for exclusion
	treatment)
<i>LEHTIMAKI2002</i> ⁹⁸⁹	FeNO levels measured but not reported in paper (only alveolar NO concentration and bronchial NO flux)
<i>LEUPPI2002</i> ⁹⁹⁹	Population does not match protocol – FeNO levels in patients with atopy, not asthma
<i>LI2006</i> ¹⁰⁰⁸	All people with asthma for FeNO levels but <50 people
<i>LI2006A</i> ¹⁰⁰⁹	Not treatment naïve (>50% on CS treatment)
<i>LIM2000A</i> ¹⁰¹⁷	Not treatment naïve (>50% on CS treatment)
<i>LINKOSALA2012</i>	Sn/sp of FeNO to predict positive exercise challenge test.
<i>LINN2009B</i> ¹⁰²³	Population does not match protocol – general population
<i>LUDVIKSDOTTIR2012</i> ¹⁰⁴⁴	Review not primary study
<i>MACLEOD2009</i> ¹⁰⁵⁵	Not treatment naïve (>50% on CS treatment)
<i>MALBYSCHOOS2012</i> ¹⁰⁶⁹	All on CS Tx.
<i>MALINOVSCHI2009</i> ¹⁰⁷²	No objective test
<i>MALINOVSCHI2012</i> ¹⁰⁷¹	Reference standard does not match protocol – not all patients had objective test (response to treatment only)
<i>MALMBERG2003</i> ¹⁰⁷⁶	Sens/spec is calculated for the wrong population: suspected asthma vs. healthy controls.
<i>MALMBERG2009</i> ¹⁰⁷⁷	Comparator test does not match protocol – outdoor running test with non-standard cut-off
<i>MANSO2011</i> ¹⁰⁸⁶	Only reports FeNO levels but is not a case-control study or case-series. Pts are suspected asthma.
<i>MARTINS2008</i> ¹⁰⁹⁵	Population does not match protocol – FeNO levels in symptomatic patients, not asthma
<i>MATSUNAGA2011</i> ¹¹⁰⁵	Unclear cut-off for objective test part of the Phys Dx.
<i>MCELDOWNEY2008</i> ¹¹¹⁶	FeNO levels but <50 people
<i>MENZIES2007A</i> ¹¹³⁴	Not treatment naïve (>50% on CS treatment)
<i>MITSUFUJI2001</i> ¹¹⁶⁵	FeNO levels after bronchoprovocation
<i>MONTUSCHI2010</i> ¹¹⁷⁵	Unclear cut-offs for objective tests as part of the Phys Dx.
<i>MUSK2011</i> ¹¹⁹⁷	Not asthma vs. no asthma
<i>NADIF2010</i> ¹²⁰⁴	Reference standard does not match protocol – no objective test
<i>NARANG2002</i> ¹²¹⁰	Not treatment naïve (>50% on CS

Reference	Reason for exclusion
	treatment)
NELSON1997 ¹²²¹	Not treatment naïve (>50% on CS treatment)
NICKELS2014 ¹²³¹	Conference abstract
NICKELS2014A ¹²³²	Conference abstract
NICOLAOU2006 ¹²³⁶	Population does not match protocol – FeNO levels in general population and patients with wheeze
NOGAMI2003 ¹²⁵³	No relevant outcomes – correlation of FeNO and FEV1
NORDVALL2005 ¹²⁵⁸	Population does not match protocol – general population
OH2008 ¹²⁷³	Population does not match protocol – only chronic cough and unclear treatment
OHKURA2009 ¹²⁷⁵	Not treatment naïve (>50% on CS treatment)
OHKURA2013 ¹²⁷⁴	Conference abstract
OJOO2005 ¹²⁷⁶	Case-control study for FeNO levels but <50 people
OLIN2006 ¹²⁸⁰	Population does not match protocol – general population
ONUR2011 ¹²⁸¹	FeNO levels but <50 people
OZAREKHANC2012 ¹²⁹³	Non-English
PARAMESWARAN2001 ¹³⁰⁵	Case-control study for FeNO levels but <50 people
PAREDI2002 ¹³⁰⁹	Case-control study for FeNO levels but <50 people
PAREDI2005 ¹³¹⁰	People with asthma only for FeNO levels but <50 people
PEDROSA2010 ¹³³⁰	Reference standard objective test does not match protocol – methacholine challenge test cut-off at 16mg/ml
PEIRSMAN 2013 ^{1331,1331}	Study included in FeNO monitoring review
PERZANOWSKI2010 ¹³⁴⁵	No objective test (only questionnaire report of wheeze)
PERZANOWSKI2010A ¹³⁴³	Population does not match protocol – general population
PETSKY 2010 ^{1350,1353}	Abstract
PETSKY 2014 ^{1353,1354}	Study included in FeNO monitoring review
PIACENTINI1999 ¹³⁵⁷	People with asthma only for FeNO levels but <50 people
PIACENTINI2000 ¹³⁵⁶	Not treatment naïve (>50% on CS treatment)
PRADO2011 ¹³⁹⁵	Non-English
PRASAD2006 ¹³⁹⁶	Population does not match protocol – general population

Reference	Reason for exclusion
PRIETO2009 ¹⁴⁰⁸	Not treatment naïve (>50% on CS treatment). Reference standard does not match protocol - ICS responsiveness.
PROFITTA2010 ¹⁴⁰⁹	Not treatment naïve (>50% on CS treatment)
RADULOVIC2010 ¹⁴²²	FeNO levels but <50 people
RAMIREZ2010 ¹⁴²⁶	FeNO versus C-reactive protein (not in protocol)
RAMSER2008 ¹⁴²⁸	Sn/sp of FeNO to predict BHR or positive exercise challenge test.
RATNAWATI2006 ¹⁴³⁷	Not treatment naïve (>50% on CS treatment)
REID2003 ¹⁴⁴⁵	N<50 pts who are ICS naïve, for a study which can only calculate FeNO levels.
RICCIONI2012 ¹⁴⁵⁵	Not treatment naïve (unclear % on CS treatment)
ROBINSON2012A ¹⁴⁶⁷	Population does not match protocol – general population
ROBROEKS2007 ¹⁴⁶⁸	Not treatment naïve (>50% on CS treatment)
ROLLA2007 ¹⁴⁷³	Not asthma vs. non-asthma
ROSA2011 ¹⁴⁸⁰	No objective test (only questionnaire report of wheeze)
ROSIAS2004 ¹⁴⁸²	Not treatment naïve (>50% on CS treatment)
ROUHOS2008 ¹⁴⁸⁷	Not asthma
SACHSOLSEN2010 ¹⁴⁹⁷	Population does not match protocol – general population
SAITO2004 ¹⁴⁹⁹	Population does not match protocol – FeNO levels in patients with and without wheeze, no Dx of asthma
SAKAI2010 ¹⁵⁰⁰	Reference standard does not match protocol – no objective test
SALOME1999 ¹⁵⁰⁴	Population does not match protocol – general population
SANDRINI2010 ¹⁵⁰⁷	Review not primary study
SARAIVA2009 ¹⁵¹²	FeNO levels but <50 people; not treatment naïve
SATOUCHI1996 ¹⁵¹⁶	Case-control study for FeNO levels but <50 people
SCHLEICH2012 ¹⁵³⁰	Reference standard objective test does not match protocol - methacholine challenge test cut-off at 16mg/ml
SCHNEIDER2009 ¹⁵³⁷	Wrong reference standard: Physician Dx with objective test, but objective test uses the wrong cut-off: methacholine at 16ug/ml (should be 8ug/ml).
SCHNEIDER2013 ¹⁵³⁶	Wrong reference standard: Physician Dx with objective test, but objective test

Reference	Reason for exclusion
	uses the wrong cut-off: methacholine at 16ug/ml (should be 8ug/ml).
SCHNEIDER2014 ¹⁵³⁴	Wrong reference standard: no objective test
SCHULZE2013 ¹⁵⁴³	Reference standard does not match protocol – no objective test
SCOLLO2000 ¹⁵⁴⁸	All people with asthma for FeNO levels but <50 people
SCOTT2010 ¹⁵⁵⁰	Population does not match protocol – general population
SEE2013 ¹⁵⁵⁵	Population does not match protocol – general population
SETHI2010 ¹⁵⁶²	All people with asthma for FeNO levels but <50 people
SHIN2006 ¹⁵⁸²	Case-control study for FeNO levels but <50 people
SHORT2011 ¹⁵⁸⁷	Not treatment naïve (>50% on CS treatment)
SILKOFF2000 ¹⁵⁹²	FeNO levels but < 50 people
SILVESTRI2000 ¹⁶⁰¹	Index test does not match protocol – incorrect flow rate
SILVESTRI2001 ¹⁶⁰²	Index test does not match protocol – incorrect flow rate
SILVESTRI2003 ¹⁶⁰³	Population does not match protocol – FeNO levels in people with atopic and non-atopic asthma
SILVESTRI2006 ¹⁵⁹⁷	Case-control study for FeNO levels but <50 people
SIMON2010 ¹⁶⁰⁴	No relevant outcomes – correlation analysis
SIMPSON2008 ¹⁶⁰⁸	Review not primary study
SINGH2007 ¹⁶¹³	Treatment study; not FeNO for diagnosis or levels in asthma/non-asthma
SIPPEL2000 ¹⁶¹⁵	No relevant outcomes – correlation analysis
SIVAN2009 ¹⁶¹⁹	Index test does not match protocol – no flow rate reported
SMITH2004 ¹⁶³⁰	Reference standard objective test does not match protocol - hypertonic saline challenge test
SMITH2005 ¹⁶²⁹	Reference standard objective test does not match protocol - ICS response only used for Dx in a proportion of patients.
SONNAPPA2010 ¹⁶³⁹	Not treatment naïve (>50% on CS treatment)
SONNAPPA2011 ¹⁶³⁸	Population does not match protocol – FeNO levels in general population and patients with wheeze
SORDILLO2011 ¹⁶⁴³	Population does not match protocol –

Reference	Reason for exclusion
	general population
SPALLAROSSA2003 ¹⁶⁵⁴	Wrong phys Dx – does not mention objective test.
SPITALE2012 ¹⁶⁶⁰	Review not primary study
STRUNK2003 ¹⁶⁹⁴	No relevant outcomes – correlation analysis
SUTHERLAND2007 ¹⁷⁰⁴	Not treatment naïve; no objective test
SVERRILD2009 ¹⁷⁰⁸	Population does not match protocol – general population
SVERRILD2010 ¹⁷⁰⁷	Population does not match protocol – general population
TAMASI2009 ¹⁷²²	Population does not match protocol – pregnancy
TERADA2001 ¹⁷⁴⁰	All people with asthma for FeNO levels but <50 people
THOMAS2005 ¹⁷⁵⁰	Population does not match protocol – general population
TILEMANN2011 ¹⁷⁵⁶	Wrong reference standard: Physician Dx with objective test, but objective test uses the wrong cut-off: methacholine at 16ug/ml (should be 8ug/ml).
TOMASIAKLOZOWSKA2012 ¹⁷⁷¹	Case-control study for FeNO levels but <50 people (excluding those on CS treatment)
TRAVERS2007 ¹⁷⁸⁴	Population does not match protocol – general population
TSUJINO2000 ¹⁷⁹¹	Unclear / insufficient Dx criteria. National heart and lung institute criteria.
TUFVESSON2007 ¹⁷⁹⁸	Case-control (rhinitis vs healthy controls: 26 of the rhinitis patients also had asthma but with the n=12 healthy controls this only makes n=38
TURKTAS2003 ¹⁸⁰²	All people with asthma for FeNO levels but <50 people
UASUF1999 ¹⁸⁰⁸	Reference standard does not match protocol – no objective test
VANAMSTERDAM2003 ¹⁸¹⁸	Population does not match protocol – general population
VANASCH2008 ¹⁸¹⁹	Population does not match protocol – general population
VANDERVALK2012 ¹⁸²⁹	Population does not match protocol – general population
VANDERVALK2012A ¹⁸²⁸	No relevant outcomes – FeNO for monitoring
VERLEDEN1999 ¹⁸⁵⁸	Population does not match protocol – smokers and non-smokers
VIEIRA2011 ¹⁸⁶⁴	Population does not match protocol – general population
VISSER2000 ¹⁸⁶⁸	Case-control study for FeNO levels but <50 people (excluding those on CS

Reference	Reason for exclusion
	treatment)
VOORENDVAN2013 ¹⁸⁷⁸	Conference abstract
WANG2012 ¹⁸⁹³	Reference standard does not match protocol – not all patients had objective test
WARKE2002 ¹⁸⁹⁶	No relevant outcomes – sn/sp is not for Dx of asthma
WELSH2007 ¹⁹⁰⁵	Population does not match protocol – general population
WILLIAMSON2010 ¹⁹²³	Not treatment naïve (>50% of asthma patients on CS treatment)
XU2011 ¹⁹⁴⁸	No objective test
YAO2011 ¹⁹⁵²	Population does not match protocol – general population
YAVUZ2012 ¹⁹⁵⁴	No relevant outcomes – FeNO for monitoring
YOON2012 ¹⁹⁶¹	Not treatment naïve; not FeNO levels in asthma vs. non-asthma or diagnostic accuracy
ZETTERQUIST2008 ¹⁹⁷⁵	Case-control study for FeNO levels but <50 people
ZHAO2013 ¹⁹⁷⁷	No objective test
ZIETKOWSKI2007 ¹⁹⁸⁶	Case-control study for FeNO levels but <50 people
ZIETKOWSKI2008 ¹⁹⁸²	Case-control study for FeNO levels but <50 people
ZIETKOWSKI2008A ¹⁹⁸¹	Case-control study for FeNO levels but <50 people
ZIETKOWSKI2008B ¹⁹⁸⁴	Case-control study for FeNO levels but <50 people
ZIETKOWSKI2009 ¹⁹⁸⁷	Case-control study for FeNO levels but <50 people
ZIETKOWSKI2010 ¹⁹⁸³	Case-control study for FeNO levels but <50 people
ZIETKOWSKI2010B ¹⁹⁸⁵	Exclude: correlations not sensitivity/specificity for FeNO; <50 treatment naïve patients + healthy controls

1K.12 Diagnosis: Eosinophils

2 **Table 218: Studies excluded from the clinical review**

Reference	Reason for exclusion
ADJAMI 2011 ¹⁸	Conference abstract. Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative
ALVAREZPUEBLA 2003 ⁴⁰	Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative

Reference	Reason for exclusion
ATTAPATTU 1991 ⁷⁸	General population. Wrong comparative test: blood eosinophils vs. SPT.
BARNES 1999 ¹¹⁰	Combinations of tests. Does not report eosinophil counts.
BJORNSSON 1994 ¹⁷⁶	Incorrect population
BOUZIGON 2012 ²⁰⁴	Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative
BRAND 1993 ²¹³	Not addressing specified population: mixed population (no asthma subgroup analysis)
BURNETT 2011 ²⁴⁷	Conference abstract. Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative.
BURROWS 1991 ²⁵⁰	Not addressing specified outcomes: predictors of future disease of asthma
CRATER 1999 ³⁷⁷	NOT addressing specified outcomes
DIFRANCO 2003 ⁴³⁵	Not addressing review question: sputum eosinophil not blood; eosinophil blood levels given at baseline but N<50.
DILORENZO 2007 ⁴³⁶	Incorrect study design
FRANKLIN 2003 ⁵²⁰	Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative.
FRETTE 1991 ⁵²³	Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative
FUJIMURA 2005 ⁵³³	Predictors of future asthma development and eosinophil levels, but N<50.
HALLDEN 1999 ⁶²⁹	Case-control study which reports levels of eosinophils, but N<50.
HASTIE 2013 ⁶⁴⁸	Incorrect population
HYVARINEN 2010 ⁷²⁸	Predictors of future asthma development
IMAI 1999 ⁷³⁶	Case-control study which reports levels of eosinophils, but N<50.
JANG 2003 ⁷⁵⁹	Case control: but N<50 and does not report eosinophil counts at baseline, only correlations.

Reference	Reason for exclusion
JUNG 2011 ⁷⁹⁶	NOT addressing review question: excluded asthma patients
KARTASAMITA 1994 ⁸²⁶	Not addressing specified outcomes
KOWAL 2009 ⁹²⁴	Not addressing specified outcomes/population
KUEHR 1994 ⁹³³	Mixed population of asthma and non-asthma but data not separated.
LECKIE 2000 ⁹⁸³	Wrong study: looks at effects of treatment
LIANG 2012 ¹⁰¹²	Not addressing review question
LIM 2010 ¹⁰¹⁵	Conference abstract. Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative.
MAGNAN 1998 ¹⁰⁶¹	Not addressing review question. Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative.
MAHMOUD 2011 ¹⁰⁶⁵	Incorrect study design
MAHMOUD 2013 ¹⁰⁶⁴	Meeting abstract
MALINOVSKI 2013 ¹⁰⁷³	Incorrect population & reference standard
MATSUNAGA 2011 ¹¹⁰⁵	Incorrect study design. Not addressing specified outcomes
MATSUNAGA 2012 ¹¹⁰⁴	NOT addressing specified outcomes
MEYER 2014 ¹¹⁴⁰	Incorrect population
MOHAMMADIEN 2009 ¹¹⁷⁰	Wrong study/Incorrect study design: case-control study and relationships + levels
NOGAMI 2003 ¹²⁵³	Not addressing specified outcomes: values not given
PALMER 2001 ¹²⁹⁸	Not addressing clinical/review question
PARK 2013 ¹³¹⁴	Conference abstract
POHUNEK 2005 ¹³⁷⁵	Wrong outcomes: predictors of subsequent development of asthma.
POSTMA 1995 ¹³⁸⁵	Incorrect population
PRONK 2001 ¹⁴¹⁰	Case control study, but does not report levels of blood eosinophils.

Reference	Reason for exclusion
RAZI 2010 ¹⁴³⁹	Wrong outcomes: eosinophil count as predictor of response to treatment
ROQUET 1996 ¹⁴⁷⁹	Levels: hyperactive versus hyperactive patients; N,50.
SOUMA 2011 ¹⁶⁵¹	Conference abstract. Wrong outcomes: associations of eosinophil levels.
SPALLAROSSA 1995 ¹⁶⁵³	Case-control study which reports levels of eosinophils, but N<50.
SPECTOR 2012 ¹⁶⁵⁵	Case-control study which reports levels of eosinophils, but N<50.
TSYBULKINA 2012 ¹⁷⁹³	Conference abstract. Wrong outcomes: levels and correlations of eosinophils, not no. of positive/negative.
ULRIK 2005 ¹⁸¹⁰	General population. Does not give +ve and -ve for eosinophils or eosinophil levels.
VOLBEDA 2013 ¹⁸⁷¹	Not disease but markers of control (i.e. monitoring)
YURDAKUL 2005 ¹⁹⁶⁸	Incorrect study design
ZEDAN 2010 ¹⁹⁷³	Incorrect study design

1K.13 Diagnosis: Histamine and methacholine challenge tests

2 **Table 219: Studies excluded from the clinical review**

Reference	Reason for exclusion
ALBERTS 1994 ^{32,32}	Index test and reference standard do not match protocol – sn/sp of FEF25-75% in predicting positive methacholine test
ALBORNOZ 1995 ^{33,33}	All people with confirmed asthma and no comparator test
ALVAREZPUEBLA 2003 ⁴⁰	Reference standard does not match protocol (Dx based on symptoms without objective test)
ANDERSON 2010A ^{44,46}	Conference abstract
ANDERSON 2011 ^{44,47}	Review article
ANDREGNETTE 2011 ^{49,49}	Conference abstract
ANTOLINAMERIGO 2012 ⁵⁴	Conference abstract
ANTOLINAMERIGO 2013 ⁵⁵	Conference abstract
AVITAL 1995 ^{82,82}	Population does not match protocol – mean age < 5years
AVITAL 1995A ^{82,83}	Comparator tests do not match protocol

Reference	Reason for exclusion
	(methacholine vs AMP and exercise) and sn/sp of methacholine not compared to reference standard of physician Dx with objective test (American Thoracic Soc diagnostic criteria for asthma)
BACKER 1991 ^{87,87}	Reference standard does not match protocol – questionnaire based on symptoms and physician Dx without report of objective test
BACKER 1992 ^{87,90}	No relevant outcomes and does not match review question - relationship between bronchial responsiveness and IgE
BACKER 1992B ^{87,89}	Index test does not match protocol (sn and sp of physician Dx and symptoms in relation to exercise challenge)
BACKER 1995 ^{86,87}	Population does not match protocol - prevalence of positive HCT in general population and correlation with asthma and atopy
BACKER 2014 ^{87,91}	Index test and reference standard do not match protocol – sn/sp of FeNO to predict positive mannitol in suspected asthma (not physician diagnosis and objective test)
BAILLY 2011 ^{93,93}	No relevant outcomes and does not match review question (different methods of measuring methacholine response, Pc20 used as part of reference standard for Dx)
BALLWEG 2012 ^{99,99}	Review article
BARBEN 2011 ^{106,106}	Index test does not match protocol – mannitol and exercise challenge test
BASIR 1995 ^{123,123}	Index test does not match protocol – methacholine challenge test. No reference standard of physician diagnosis with objective test
BENNETT 1987 ^{152,152}	No relevant outcomes and does not match review question (different methods of measuring methacholine and histamine response; all people with confirmed asthma and comparator does not match protocol)
BERKMAN 2005 ^{159,159}	Reference standard does not match protocol – physician Dx without objective test in a proportion of patients and no data on the percentage of patients who were Dx with an objective test.
BEYDON 2008 ^{167,167}	No relevant outcomes and does not match review question – correlation between BDR and methacholine response
BIBI 1991 ^{171,171}	Reference standard does not match protocol – physician Dx without objective test. Cannot compare index test vs comparator test as people with suspected asthma and no suitable reference standard

Reference	Reason for exclusion
BIRNBAUM 2007 ^{174,174}	Review article
BONAVIA 1996 ^{184,184}	Comparator tests and reference standard do not match protocol (asthma group defined by symptom score not physician Dx)
BOONSAWAT 1992 ^{189,189}	Reference standard does not match protocol (physician Dx without objective test)
BOUAZIZ 1996 ^{198,198}	Comparing different methods of measuring methacholine test (all patients with asthma and no comparator test)
BRAND 1993 ^{210,213}	Index test does not match protocol – no challenge test performed
BRUSCHI 1989 ^{236,236}	Population does not match protocol - general population not suspected asthma
BUSSE 2005 ^{255,255}	Review / report from workshop
CARLSEN 1998 ^{273,275}	case-control study
CARLSTEN 2011 ^{277,278}	Reference standard does not match protocol – Dx was clinical decision made by the paediatric allergist based on symptoms of wheeze and cough, use of medications and physical findings
CHATHAM 1982 ^{305,305}	Sn/sp of histamine and methacholine vs exercise in people with asthma and controls (does not match this protocol comparator). No reference standard of physician Dx with objective test.
CHOI 2003 ^{319,319}	Index test does not match protocol (incorrect cut-off for positive test)
CHOI 2007A ^{319,321}	Population does not match protocol (all patients had positive methacholine challenge test)
CHUNG 2010 ^{329,329}	Conference abstract – sn/sp of mannitol and methacholine but reference standard not mentioned
CIPRANDI 2010 ^{331,337}	No relevant outcomes and does not match review question – correlation between FeNO and methacholine PC20 and sn/sp of FeNO to predict positive methacholine test
CIPRANDI 2011 ^{331,335}	Population does not match protocol – all Dx with allergic rhinitis and excluded if a history of asthma or referred with asthma symptoms
CIRILLO 2009 ^{340,341}	Population does not match protocol – all Dx with allergic rhinitis and excluded if a history of asthma or referred with asthma symptoms
COCKCROFT 1979 ^{356,356}	No relevant outcomes and does not match review question (correlation between allergen PC20 and histamine PC20 in people with confirmed asthma)
COCKCROFT 1992 ^{355,356}	Reference standard does not match

Reference	Reason for exclusion
	protocol – Dx based on questionnaire (previous doctor diagnosis or wheeze symptoms)
COCKCROFT 2005 ^{354,356}	No relevant outcomes and does not match review question (correlation between allergen, histamine and methacholine PC20 in people with confirmed asthma)
COCKCROFT 2009 ^{356,357}	Review article
COCKCROFT 2010 ^{356,358}	Review article
CORDEIRO 2011 ^{365,365}	Index test and reference standard do not match protocol – histamine test used as part of reference standard to Dx (index test = FeNO)
DEHAUT 1983 ^{412,412}	No relevant outcomes and does not match review question (different methods of measuring histamine response)
DELGIUDICE 2004 ⁴¹⁴	No relevant outcomes and does not match review question – correlation between FeNO and PC20 (all patients with asthma but Dx made by physician with no objective test)
DEN OTTER 1997 ⁴²²	Reference standard for asthma diagnosis included methacholine/histamine challenge test
DI LORENZO 2007 ⁴³⁶	Case control type study with 3 groups (asthma Dx by symptoms and objective test; gastro-oesophageal reflux group with asthma symptoms; healthy controls) – study gives sn/sp values for MCT but this is based on 52% of patients having asthma (includes asymptomatic healthy control group)
DREWEK 2009 ^{454,454}	Index test does not match protocol (sn and sp of FEF25-75 to measure methacholine response; diagnosis of asthma based on symptoms during challenge test)
DURAND 2011 ⁴⁵⁸	Conference abstract – reference standard not mentioned
DURZO 2012 ³⁸⁹	Conference abstract
FORASTIERE 1991 ^{507,507}	Reference standard does not match protocol (asthma defined as affirmative answer to ‘has a doctor ever said this child has asthma’ or 3 out of 4 wheezing symptoms on questionnaire)
FORTUNA 2007 ^{510,511}	Methacholine used as reference standard - sn/sp of FeNO, eos, spirometry and BDR with positive methacholine test used to diagnose asthma
FRANKLIN 2003 ^{520,520}	Population does not match protocol (all asymptomatic at time of the study)
FRUCHTER 2009 ^{530,530}	Reference standard does not match protocol - not physician diagnosis and

Reference	Reason for exclusion
	objective test
GADE 2009 ^{537,537}	Does not match review question (influence of mannitol and methacholine tests on each other)
GARCIA-RIO 2004 ⁵⁴⁹	Population does not match protocol – all had positive histamine challenge
GHODRATI 2011 ^{562,562}	Not in English
GILBERT 1990 ^{569,570}	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test)
GODFREY 1999 ^{576,577}	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test)
GOLDSTEIN 1994 ^{585,585}	Reference standard does not match protocol – based on symptoms and response to therapy (no objective test)
GOLDSTEIN 2001 ^{585,586}	Does not match review question – longitudinal follow-up to asthma diagnosis and methacholine test used as part of reference standard to Dx asthma
GRAIF 2002 ^{590,590}	Sn/sp of SPT with positive methacholine test used to diagnose asthma (no reference standard of physician Dx to calculate sn/sp of methacholine test)
GREENSPON 1992 ^{598,598}	Reference standard does not match protocol – Dx asthma group gave a history typical of asthma and had histories of acute exacerbation that were relieved by bronchodilator therapy
GRUCHALLA 2003 ^{601,601}	Reference standard does not match protocol – methacholine used as part of Dx of asthma for calculation of sn/sp of symptoms questionnaire in the Dx of asthma
HIGGINS 1992 ^{678,679}	Reference standard does not match protocol – Dx based on symptoms questionnaire or 'ever had asthma attack' (no mention of objective test)
HOPP 1984 ^{702,702}	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test).
HUNTER 2002 ^{721,721}	Methacholine challenge tests used as one of the objective tests to Dx asthma in the group with asthma
HUR 2009 ^{723,724}	Conference abstract
HUR 2010 ^{722,723}	Conference abstract – duplicate of Hur 2010
IRWIN 1997 ^{739,740}	Population does not match protocol – all symptomatic and methacholine challenge positive

Reference	Reason for exclusion
JAMES 1992 ^{751,751}	Reference standard does not match protocol (physician Dx without objective test and/or wheeze in the last 12 months)
JAMES 1997 ^{751,752}	Review article – summarises studies sn/sp of challenge tests but ref standard does not match protocol (use symptom questionnaire and diagnosis based on wheeze in last 12 months or asthma Dx by doctor)
JOHNSON 1987 ^{779,779}	Reference standard does not match protocol – association of methacholine response with symptoms not physician Dx
JOSEPH 2004 ⁷⁹¹	Reference standard does not match protocol; physician diagnosis + symptoms of wheeze in last 12 months + asthma meds in last 12 months (no objective test)
KANG 2005 ^{818,818}	No relevant outcomes and does not match review question (people with confirmed asthma with no comparator test)
KHALID 2009 ^{857,857}	Sn/sp of different measure for methacholine challenge (with PC20 positive/negative used for asthma Dx)
KIM 2002 ^{872,873}	Reference standard does not match protocol (correlation of BHR with risk factors and symptoms from questionnaire – no physician Dx)
KIM 2014A ^{871,873}	Conference abstract
KIM 2014B ^{869,873}	Case control study
KING 1989 ^{876,876}	Index test and reference standard do not match protocol – sn/sp of wheezing on max forced exhalation as predictor of positive methacholine test
KIVASTIK 2007 ^{880,880}	Population does not match protocol (age range 3-6 years)
KNOX 1989 ^{893,893}	No relevant outcomes and does not match review question (different methods of measuring methacholine response)
KOLNAAR 1995 ^{904,904}	Reference standard does not match protocol - comparison of histamine test to presence of asthma symptoms (not to physician Dx)
LAU 2002 ^{972,974}	Population does not match protocol – general population
LEE 2011 ^{984,985}	Conference abstract
LEVIN 2011 ^{1001,1001}	Reference standard does not match protocol - self-reported symptoms of asthma in the last 12 months
LEWIS 2001 ^{1002,1005}	Reference standard does not match protocol - self reported doctor-Dx asthma and no mention of objective test
LIEM 2008 ^{1013,1014}	No relevant outcomes and does not match

Reference	Reason for exclusion
	review question (healthy controls and people with confirmed asthma with no comparator test)
LINNA 1998 ^{1025,1026}	All patients with asthma and no comparator test (comparing different methods of measuring methacholine challenge)
LUMELLI 2010 ^{1047,1047}	Conference abstract
MADSEN 1985 ^{1057,1057}	Reference standard does not match protocol – some patients were Dx without objective test on basis of answer to 2 questions on attacks of shortness of breath
MADSEN 1986 ^{1056,1057}	Reference standard does not match protocol – some patients were Dx without objective test on basis of answer to 2 questions on attacks of shortness of breath
MALMBERG 2001 ^{1075,1075}	No relevant outcomes and does not match review question (people with confirmed asthma with no comparator test)
MANNINO 1996 ^{1085,1085}	Methacholine challenge test but no comparator or reference standard test
MANSO 2011 ^{1086,1086}	Reference standard does not match protocol – methacholine test used as reference standard to Dx asthma in some patients
MCCLEAN 2010 ^{1111,1111}	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test). Physician diagnosis without objective test
MCGARVEY 1998 ^{1118,1118}	No relevant outcomes and does not match review question - histamine challenge in comparison to treatment response for various respiratory diseases
METSO 1996 ^{1138,1138}	Reference standard does not match protocol
MIEDINGER 2010 ^{1145,1146}	Reference standard does not match protocol – not all patients Dx with asthma had an objective test (some physician Dx only)
MULLER 1993 ^{1188,1188}	Case control study
NADASKIC 2010 ^{1203,1203}	Conference abstract
NICKELS 2014 ^{1231,1231}	Conference abstract
NIGGEMANN 2001 ^{1242,1242}	Reference standard does not match protocol - sn/sp if histamine challenge to predict asthma symptoms (not diagnosis of asthma)
NISH 1992 ^{1249,1249}	Reference standard does not match protocol – physician Dx with objective test not reported and histamine challenge used as part of reference standard to Dx
OCONNOR 1994 ¹²⁶⁴	Reference standard does not match

Reference	Reason for exclusion
	protocol - affirmative response to 'have you ever had asthma?'
OHKURA 2013 ^{1274,1275}	Conference abstract
OKUPA 2012 ^{1278,1278}	Conference abstract
PALMEIRO 1992 ^{1297,1297}	Reference standard does not match protocol – asthma Dx based on questionnaire responses
PARAMESWARAN 1999 ^{1306,1306}	Reference standard does not match protocol - physician Dx without objective test
PARK 2009 ^{1311,1313}	Conference abstract
PARKER 2004 ^{1315,1315}	Population does not match protocol (all patients had positive methacholine challenge test and looking at factors which influence the PC20)
PARKERSON 2011 ^{1316,1316}	Review article
PATTEMORE 1990 ^{1320,1320}	Reference standard does not match protocol (asthma diagnosis by previous report of a diagnosis but no objective test)
PEDROSA 2009 ^{1329,1329}	Index test and reference standard do not match protocol – methacholine test used as reference standard to Dx asthma and assess sn/sp of AMP challenge
PEDROSA 2010 ^{1329,1330}	Index test and reference standard do not match protocol – methacholine test used as reference standard to Dx asthma and assess sn/sp of FeNO
PERPINA 1993 ^{1336,1336}	Case control type study with 4 groups (asthma; rhinitis; chronic bronchitis; healthy controls) – study gives sn/sp values for MCT but this is based on all patients (includes asymptomatic healthy control group)
POPA 1988 ^{1380,1380}	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test).
PORSBJERG 2007 ^{1382,1383}	Population does not match protocol – relationship between the response to methacholine and mannitol in asymptomatic subjects who do not have asthma
PORSBJERG 2009 ^{1383,1384}	Review article
PRATTER 1983 ^{1398,1398}	Index test and reference standard do not match protocol – sn/sp of wheeze symptoms vs reference standard of physician Dx with methacholine test
PRIETO 1998 ^{1406,1406}	Index test and reference standard do not match protocol – methacholine test used as reference standard to Dx asthma and assess sn/sp of PEFV
PRIETO 1998A ^{1405,1406}	No relevant outcomes and does not match review question (differences in dose-

Reference	Reason for exclusion
	response curve to methacholine in asthma, rhinitis and controls)
PUOLIJOKI 1992 ^{1415,1415}	Population does not match protocol – all methacholine challenge test negative patients
PUROKIVI 2007 ^{1416,1416}	Index test does not match protocol – hypertonic histamine challenge
REMES 2002 ^{1447,1448}	Methacholine challenge tests used as one of the objective tests to Dx asthma
RENWICK 1996 ^{1451,1451}	Chronic airway obstruction prevalence and BDR
RIJCKEN 1989 ^{1462,1462}	Reference standard does not match protocol (sensitivity and specificity of histamine challenge test to detect self-reported symptoms (symptomatic or asymptomatic)
ROQUET 1996 ^{1479,1479}	No relevant outcomes and does not match review question –sn/sp of Eos to predict positive challenge test
SACHOLSEN 2010 ¹⁴⁹⁷	Population does not match protocol - general population not all people with asthma or suspected asthma
SCHLEICH 2012 ^{1530,1530}	Methacholine challenge test used as part of the reference standard to Dx asthma in suspected asthma patients without airway obstruction or BDR
SCHMIDT 1992 ^{1532,1532}	All patients with asthma and no comparator test (comparing different methods of histamine challenge). Physician Dx only, no objective test
SCHNEIDER 2009A ^{1535,1537}	Methacholine challenge test used as part of the reference standard to Dx asthma and assess the sn/sp of spirometry in GP
SCHULZE 2013 ^{1543,1543}	No relevant outcomes and does not match review question – sn/sp of methacholine challenge to detect a positive allergen response
SHAPIRO 1982 ^{1571,1571}	Reference standard does not match protocol – methacholine test used as reference standard to Dx asthma
SIERSTED 1994 ^{1590,1590}	Reference standard does not match protocol – asthma Dx based on questionnaire responses to doctor diagnosed asthma and symptoms (no mention of objective test)
SIERSTED 1994 ^{1590,1590}	Duplicate – ordered twice, already excluded for this review
SIERSTED 1996 ^{1590,1591}	Reference standard does not match protocol – methacholine test used as part of reference standard to Dx asthma
SISTEK 2006 ^{1617,1618}	Reference standard does not match protocol – asthma Dx based on

Reference	Reason for exclusion
	questionnaire responses to doctor diagnosed asthma and attack in the last 12 months (no mention of objective test)
SORIANO 1999 ^{1644,1646}	Reference standard does not match protocol - positive methacholine test used to Dx asthma
SOVIJARVI 1986 ^{1652,1652}	No relevant outcomes and does not match review question – different methods of measuring methacholine test
SPIROPOULOS 1986 ^{1659,1659}	No relevant outcomes and does not match review question – sn/sp of methacholine test in predicting hyper-reactive airway symptoms not physician Dx of asthma
SPOSATO 2014 ^{1661,1662}	Index test and reference standard do not match protocol
SPRINGER 2000 ^{1663,1663}	Population does not match protocol (aged 2-8 years). All people with confirmed asthma and no comparator test
STAHL 2009 ^{1669,1670}	Conference abstract
SUN 2007 ^{319,321}	Duplicate of CHOI 2007A – already excluded in this review
SVERRILD 2009 ^{1708,1708}	Same data used for Sverrild 2010 paper already excluded from this review.
SVERRILD 2010 ^{1707,1708}	Reference standard does not match protocol - physician Dx without objective test (physician Dx made on the basis of symptoms in the last 12 months in combination with either a eNO level of greater than 30 ppb, a history of allergic rhinoconjunctivitis, dermatitis, a positive skin prick test response, a familial predisposition to atopic disease, nonallergic rhinoconjunctivitis, or an FEV1/forced vital capacity ratio of less than 75%).
SVERRILD 2012 ^{1706,1708}	Review article
SVERRILD 2013 ^{1705,1708}	Sn/sp of FeNO in predicting positive mannitol response. Reference standard does not match protocol - physician Dx with no mention of objective test
TAKAMI 2013 ^{1718,1718}	No relevant outcomes and does not match review question (correlation study)
TERNESTEN 2002 ¹⁷⁴²	Methacholine challenge test used as part of the reference standard to Dx asthma
TIE 2012 ^{1755,1755}	Reference standard does not match protocol
TODD 2004 ^{1764,1764}	Not relevant outcomes and does not answer review question - all people with asthma with positive methacholine challenge (comparing methods of performing methacholine test)
TOELLE 1992 ^{1765,1765}	Methacholine challenge test used as part of the reference standard to Dx asthma

Reference	Reason for exclusion
TOWNLEY 1975 ^{1782,1782}	Reference standard does not match protocol – no objective test
TOWNLEY 1990 ^{1781,1782}	Can only calculate sensitivity (methacholine challenge in suspected asthma and asymptomatic controls – all suspected group were Dx based on reference standard and no Dx of control group reported)
VILOZNI 2009 ^{1866,1867}	Population does not match protocol (aged 3-6 years)
WONGTIM 1997 ^{1936,1936}	Methacholine challenge test used as part of the reference standard to Dx asthma
WOO 2012 ^{1937,1937}	Methacholine challenge test used as part of the reference standard to Dx asthma – Dx based on symptoms and BDR and/or positive methacholine challenge
WOOLCOCK 1984 ^{1943,1943}	Histamine challenge test but no comparator or reference standard test (looking at dose-response curve to histamine in people with asthma and controls)
WU 2011 ^{1946,1946}	Conference abstract
XU 2001 ^{1949,1949}	Reference standard does not match protocol - asthma was defined as a history of physician-diagnosed asthma at any time in the past (no mention of objective test)
YURDAKUL 2005 ^{1968,1968}	Reference standard does not match protocol – methacholine test used as part of reference standard to Dx asthma
ZAGHLOUL 2009 ^{1970,1970}	Conference abstract

1K.14 Diagnosis: Mannitol challenge test

2 **Table 220: Studies excluded from the clinical review**

Reference	Reason for exclusion
ALBERTS 1994 ^{32,32}	Index test and reference standard do not match protocol – sn/sp of FEF25-75% in predicting positive methacholine test
ALBORNOZ 1995 ^{33,33}	All people with confirmed asthma and no comparator test
ALVAREZPUEBLA 2003 ⁴⁰	Reference standard does not match protocol (Dx based on symptoms without objective test)
ANDERSON 2010A ^{44,46}	Conference abstract
ANDERSON 2011 ^{44,47}	Review article
ANDREGNETTE 2011 ^{49,49}	Conference abstract
ANTOLINAMERIGO 2012 ⁵⁴	Conference abstract
ANTOLINAMERIGO 2013 ⁵⁵	Conference abstract
AVITAL 1995 ^{82,82}	Population does not match protocol – mean age < 5years

Reference	Reason for exclusion
AVITAL 1995A ^{82,83}	Comparator tests do not match protocol (methacholine vs AMP and exercise) and sn/sp of methacholine not compared to reference standard of physician Dx with objective test (American Thoracic Soc diagnostic criteria for asthma)
BACKER 1991 ^{87,87}	Reference standard does not match protocol – questionnaire based on symptoms and physician Dx without report of objective test
BACKER 1992 ^{87,90}	No relevant outcomes and does not match review question - relationship between bronchial responsiveness and IgE
BACKER 1992B ^{87,89}	Index test does not match protocol (sn and sp of physician Dx and symptoms in relation to exercise challenge)
BACKER 1995 ^{86,87}	Population does not match protocol - prevalence of positive HCT in general population and correlation with asthma and atopy
BACKER 2014 ^{87,91}	Index test and reference standard do not match protocol – sn/sp of FeNO to predict positive mannitol in suspected asthma (not physician diagnosis and objective test)
BAILLY 2011 ^{93,93}	No relevant outcomes and does not match review question (different methods of measuring methacholine response, Pc20 used as part of reference standard for Dx)
BALLWEG 2012 ^{99,99}	Review article
BARBEN 2011 ^{106,106}	Reference standard does not match protocol – sn/sp for Mannitol test only calculated taking into account index test result. Can calculated sn/sp of mannitol vs exercise test in children but this is only in suspected asthma (cannot do calculation for those children Dx according to the RS)
BASIR 1995 ^{123,123}	No reference standard of physician diagnosis with objective test
BENNETT 1987 ^{152,152}	No relevant outcomes and does not match review question (different methods of measuring methacholine and histamine response; all people with confirmed asthma and comparator does not match protocol)
BERKMAN 2005 ^{159,159}	Reference standard does not match protocol – physician Dx without objective test in a proportion of patients and no data on the percentage of patients who were Dx with an objective test.
BEYDON 2008 ^{167,167}	No relevant outcomes and does not match review question – correlation between BDR and methacholine response
BIBI 1991 ^{171,171}	Index test does not match protocol –

Reference	Reason for exclusion
	methacholine challenge test
BIRNBAUM 2007 ^{174,174}	Review article
BONAVIA 1996 ^{184,184}	Comparator tests and reference standard do not match protocol (asthma group defined by symptom score not physician Dx)
BOONSAWAT 1992 ^{189,189}	Reference standard does not match protocol (physician Dx without objective test)
BOUAZIZ 1996 ^{198,198}	Comparing different methods of measuring methacholine test (all patients with asthma and no comparator test)
BRAND 1993 ^{210,213}	Index test does not match protocol – no challenge test performed
BRUSCHI 1989 ^{236,236}	Population does not match protocol - general population not suspected asthma
BUSSE 2005 ^{255,255}	Review / report from workshop
CARLSEN 1998 ^{273,275}	case-control study
CARLSTEN 2011 ^{277,278}	Reference standard does not match protocol – Dx was clinical decision made by the paediatric allergist based on symptoms of wheeze and cough, use of medications and physical findings
CHATHAM 1982 ^{305,305}	Sn/sp of histamine and methacholine vs exercise in people with asthma and controls (does not match this protocol comparator). No reference standard of physician Dx with objective test.
CHOI 2003 ^{319,319}	Index test does not match protocol – methacholine challenge test
CHOI 2007A ^{319,321}	Population does not match protocol (all patients had positive methacholine challenge test)
CHUNG 2010 ^{329,329}	Conference abstract – sn/sp of mannitol and methacholine but reference standard not mentioned
CIPRANDI 2010 ^{331,337}	No relevant outcomes and does not match review question – correlation between FeNO and methacholine PC20 and sn/sp of FeNO to predict positive methacholine test
CIPRANDI 2011 ^{331,335}	Population does not match protocol – all Dx with allergic rhinitis and excluded if a history of asthma or referred with asthma symptoms
CIRILLO 2009 ^{340,341}	Population does not match protocol – all Dx with allergic rhinitis and excluded if a history of asthma or referred with asthma symptoms
COCKCROFT 1979 ^{356,356}	No relevant outcomes and does not match review question (correlation between allergen PC20 and histamine PC20 in people with confirmed asthma)

Reference	Reason for exclusion
COCKCROFT 1992 ^{355,356}	Reference standard does not match protocol – Dx based on questionnaire (previous doctor diagnosis or wheeze symptoms)
COCKCROFT 2005 ^{354,356}	No relevant outcomes and does not match review question (correlation between allergen, histamine and methacholine PC20 in people with confirmed asthma)
COCKCROFT 2009 ^{356,357}	Review article
COCKCROFT 2010 ^{356,358}	Review article check for refs
CORDEIRO 2011 ^{365,365}	Index test and reference standard do not match protocol – histamine test used as part of reference standard to Dx (index test = FeNO)
DEHAUT 1983 ^{412,412}	No relevant outcomes and does not match review question (different methods of measuring histamine response)
DELGIUDICE 2004 ⁴¹⁴	No relevant outcomes and does not match review question – correlation between FeNO and PC20 (all patients with asthma but Dx made by physician with no objective test)
DI LORENZO 2007 ⁴³⁶	Case control type study with 3 groups (asthma Dx by symptoms and objective test; gastro-oesophageal reflux group with asthma symptoms; healthy controls) – study gives sn/sp values for MCT but this is based on 52% of patients having asthma (includes asymptomatic healthy control group)
DREWEK 2009 ^{454,454}	Index test does not match protocol (sn and sp of FEF25-75 to measure methacholine response; diagnosis of asthma based on symptoms during challenge test)
DURAND 2011 ⁴⁵⁸	Conference abstract – reference standard not mentioned
DURZO 2012 ³⁸⁹	Conference abstract
FORASTIERE 1991 ^{507,507}	Reference standard does not match protocol (asthma defined as affirmative answer to ‘has a doctor ever said this child has asthma’ or 3 out of 4 wheezing symptoms on questionnaire)
FORTUNA 2007 ^{510,511}	Methacholine used as reference standard - sn/sp of FeNO, eos, spirometry and BDR with positive methacholine test used to diagnose asthma
FRANKLIN 2003 ^{520,520}	Population does not match protocol (all asymptomatic at time of the study)
FRUCHTER 2009 ^{530,530}	Index test and reference standard do not match protocol – sn/sp of BDR to predict positive methacholine in suspected asthma (not physician diagnosis and objective test)
GADE 2009 ^{537,537}	Does not match review question (influence

Reference	Reason for exclusion
	of mannitol and methacholine tests on each other)
GARCIA-RIO 2004 ⁵⁴⁹	Population does not match protocol – all had positive histamine challenge
GHODRATI 2011 ^{562,562}	Not in English
GILBERT 1990 ^{569,570}	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test)
GODFREY 1999 ^{576,577}	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test)
GOLDSTEIN 1994 ^{585,585}	Index test does not match protocol – methacholine challenge test
GOLDSTEIN 2001 ^{585,586}	Does not match review question – longitudinal follow-up to asthma diagnosis and methacholine test used as part of reference standard to Dx asthma
GRAIF 2002 ^{590,590}	Sn/sp of SPT with positive methacholine test used to diagnose asthma (no reference standard of physician Dx to calculate sn/sp of methacholine test)
GREENSPON 1992 ^{598,598}	Reference standard does not match protocol – Dx asthma group gave a history typical of asthma and had histories of acute exacerbation that were relieved by bronchodilator therapy
GRUCHALLA 2003 ^{601,601}	Reference standard does not match protocol – methacholine used as part of Dx of asthma for calculation of sn/sp of symptoms questionnaire in the Dx of asthma
HEDMAN 1998 ^{656,656}	Index test does not match protocol – methacholine challenge test
HIGGINS 1992 ^{678,679}	Reference standard does not match protocol – Dx based on symptoms questionnaire or 'ever had asthma attack' (no mention of objective test)
HOPP 1984 ^{702,702}	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test).
HUNTER 2002 ^{721,721}	Methacholine challenge tests used as one of the objective tests to Dx asthma in the group with asthma
HUR 2009 ^{723,724}	Conference abstract
HUR 2010 ^{722,723}	Conference abstract – duplicate of Hur 2010
IRWIN 1997 ^{739,740}	Population does not match protocol – all symptomatic and methacholine challenge positive

Reference	Reason for exclusion
JAMES 1992 ^{751,751}	Reference standard does not match protocol (physician Dx without objective test and/or wheeze in the last 12 months)
JAMES 1997 ^{751,752}	Review article – summarises studies sn/sp of challenge tests but ref standard does not match protocol (use symptom questionnaire and diagnosis based on wheeze in last 12 months or asthma Dx by doctor)
JOHNSON 1987 ^{779,779}	Reference standard does not match protocol – association of methacholine response with symptoms not physician Dx
JOSEPH 2004 ⁷⁹¹	Reference standard does not match protocol; physician diagnosis + symptoms of wheeze in last 12 months + asthma meds in last 12 months (no objective test)
KANG 2005 ^{818,818}	No relevant outcomes and does not match review question (people with confirmed asthma with no comparator test)
KHALID 2009 ^{857,857}	Sn/sp of different measure for methacholine challenge (with PC20 positive/negative used for asthma Dx)
KIM 2002 ^{872,873}	Reference standard does not match protocol (correlation of BHR with risk factors and symptoms from questionnaire – no physician Dx)
KIM 2014 ^{869,873}	Case control study
KIM 2014A ^{871,873}	Conference abstract
KING 1989 ^{876,876}	Index test and reference standard do not match protocol – sn/sp of wheezing on max forced exhalation as predictor of positive methacholine test
KIVASTIK 2007 ^{880,880}	Population does not match protocol (age range 3-6 years)
KNOX 1989 ^{893,893}	No relevant outcomes and does not match review question (different methods of measuring methacholine response)
KOLNAAR 1995 ^{904,904}	Reference standard does not match protocol - comparison of histamine test to presence of asthma symptoms (not to physician Dx)
KOSKELA 2003 ^{915,915}	All patients with asthma and comparator test does not match protocol (comparators histamine and cold air challenge tests)
KOWAL 2009 ^{924,924}	Index test does not match protocol – histamine challenge test
LEE 2011 ^{984,985}	Conference abstract
LEVIN 2011 ^{1001,1001}	Reference standard does not match protocol - self-reported symptoms of asthma in the last 12 months
LEWIS 2001 ^{1002,1005}	Reference standard does not match

Reference	Reason for exclusion
	protocol - self reported doctor-Dx asthma and no mention of objective test
LIEM 2008 ^{1013,1014}	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test)
LINNA 1998 ^{1025,1026}	All patients with asthma and no comparator test (comparing different methods of measuring methacholine challenge)
LUMELLI 2010 ^{1047,1047}	Conference abstract
MADSEN 1985 ^{1057,1057}	Reference standard does not match protocol – some patients were Dx without objective test on basis of answer to 2 questions on attacks of shortness of breath
MADSEN 1986 ^{1056,1057}	Reference standard does not match protocol – some patients were Dx without objective test on basis of answer to 2 questions on attacks of shortness of breath
MALMBERG 2001 ^{1075,1075}	No relevant outcomes and does not match review question (people with confirmed asthma with no comparator test)
MANNINO 1996 ^{1085,1085}	Methacholine challenge test but no comparator or reference standard test
MANSO 2011 ^{1086,1086}	Reference standard does not match protocol – methacholine test used as reference standard to Dx asthma in some patients
MCCLEAN 2010 ^{1111,1111}	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test). Physician diagnosis without objective test
MCGARVEY 1998 ^{1118,1118}	No relevant outcomes and does not match review question - histamine challenge in comparison to treatment response for various respiratory diseases
METSO 1996 ^{1138,1138}	Reference standard does not match protocol
MIEDINGER 2010 ^{1145,1146}	Reference standard does not match protocol – not all patients Dx with asthma had an objective test (some physician Dx only)
MULLER 1993 ^{1188,1188}	Case control study
NADASKIC 2010 ^{1203,1203}	Conference abstract
NICKELS 2014 ^{1231,1231}	Conference abstract
NIEMINEN 1992 ^{1241,1241}	Index test does not match protocol – methacholine challenge test
NIGGEMANN 2001 ^{1242,1242}	Reference standard does not match protocol - sn/sp if histamine challenge to predict asthma symptoms (not diagnosis of asthma)

Reference	Reason for exclusion
NISH 1992 ^{1249,1249}	Reference standard does not match protocol – physician Dx with objective test not reported and histamine challenge used as part of reference standard to Dx
OCONNOR 1994 ¹²⁶⁴	Reference standard does not match protocol - affirmative response to 'have you ever had asthma?'
OHKURA 2013 ^{1274,1275}	Conference abstract
OKUPA 2012 ^{1278,1278}	Conference abstract
OTTER 1997 ⁴²²	Index test does not match protocol – histamine challenge test
PALMEIRO 1992 ^{1297,1297}	Reference standard does not match protocol – asthma Dx based on questionnaire reponses
PARAMESWARAN 1999 ^{1306,1306}	Reference standard does not match protocol - physian Dx without objective test
PARK 2009 ^{1311,1313}	Conference abstract
PARKER 2004 ^{1315,1315}	Population does not match protocol (all patients had positive methacholine challenge test and looking at factors which influence the PC20)
PARKERSON 2011 ^{1316,1316}	Review article
PATTEMORE 1990 ^{1320,1320}	Reference standard does not match protocol (asthma diagnosis by previous report of a diagnosis but no objective test)
PEDROSA 2009 ^{1329,1329}	Index test and reference standard do not match protocol – methacholine test used as reference standard to Dx asthma and assess sn/sp of AMP challenge
PEDROSA 2010 ^{1329,1330}	Index test and reference standard do not match protocol – methacholine test used as reference standard to Dx asthma and assess sn/sp of FeNO
PERPINA 1993 ^{1336,1336}	Case control type study with 4 groups (asthma; rhinitis; chronic bronchitis; healthy controls) – study gives sn/sp values for MCT but this is basedall patients (includes asymptomatic healthy control group)
POPA 1988 ^{1380,1380}	No relevant outcomes and does not match review question (healthy controls and people with confirmed asthma with no comparator test).
PORSBJERG 2007 ^{1382,1383}	Population does not match protocol – relationship between the response to methacholine and mannitol in asymptomatic subjects who do not have asthma
PORSBJERG 2009 ^{1383,1384}	Review article
PRATTER 1983 ^{1398,1398}	Index test and reference standard do not match protocol – sn/sp of wheeze symptoms vs reference standard of

Reference	Reason for exclusion
	physician Dx with methacholine test
PRIETO 1998 ^{1406,1406}	Index test and reference standard do not match protocol – methacholine test used as reference standard to Dx asthma and assess sn/sp of PEFV
PRIETO 1998A ^{1405,1406}	No relevant outcomes and does not match review question (differences in dose-response curve to methacholine in asthma, rhinitis and controls)
PUOLIJOKI 1992 ^{1415,1415}	Population does not match protocol – all methacholine challenge test negative patients
PUROKIVI 2007 ^{1416,1416}	Index test does not match protocol – histamine challenge test
REMES 2002 ^{1447,1448}	Methacholine challenge tests used as one of the objective tests to Dx asthma
RENWICK 1996 ^{1451,1451}	Chronic airway obstruction prevalence and BDR
RIJCKEN 1989 ^{1462,1462}	Reference standard does not match protocol (sensitivity and specificity of histamine challenge test to detect self-reported symptoms (symptomatic or asymptomatic))
ROQUET 1996 ^{1479,1479}	No relevant outcomes and does not match review question –sn/sp of Eos to predict positive challenge test
SACHOLSEN 2010 ¹⁴⁹⁷	Population does not match protocol - general population not all with asthma or suspected asthma
SCHLEICH 2012 ^{1530,1530}	Methacholine challenge test used as part of the reference standard to Dx asthma in suspected asthma patients without airway obstruction or BDR
SCHMIDT 1992 ^{1532,1532}	All patients with asthma and no comparator test (comparing different methods of histamine challenge). Physician Dx only, no objective test
SCHNEIDER 2009A ^{1535,1537}	Methacholine challenge test used as part of the reference standard to Dx asthma and assess the sn/sp of spirometry in GP
SCHULZE 2013 ^{1543,1543}	No relevant outcomes and does not match review question – sn/sp of methacholine challenge to detect a positive allergen response
SHAPIRO 1982 ^{1571,1571}	Reference standard does not match protocol – methacholine test used as reference standard to Dx asthma
SIERSTED 1994 ^{1590,1590}	Reference standard does not match protocol – asthma Dx based on questionnaire responses to doctor diagnosed asthma and symptoms (no mention of objective test)

Reference	Reason for exclusion
SIERSTED 1994 ^{1590,1590}	Duplicate – ordered twice, already excluded for this review
SIERSTED 1996 ^{1590,1591}	Reference standard does not match protocol – methacholine test used as part of reference standard to Dx asthma
SISTEK 2006 ^{1617,1618}	Reference standard does not match protocol – asthma Dx based on questionnaire responses to doctor diagnosed asthma and attack in the last 12 months (no mention of objective test)
SORIANO 1999 ^{1644,1646}	Reference standard does not match protocol - positive methacholine test used to Dx asthma
SOVIJARVI 1986 ^{1652,1652}	No relevant outcomes and does not match review question – different methods of measuring methacholine test
SPIROPOULOS 1986 ^{1659,1659}	No relevant outcomes and does not match review question – sn/sp of methacholine test in predicting hyper-reactive airway symptoms not physician Dx of asthma
SPOSATO 2014 ^{1661,1662}	Index test and reference standard do not match protocol
SPRINGER 2000 ^{1663,1663}	Population does not match protocol (aged 2-8 years). All people with confirmed asthma and no comparator test
STAHL 2009 ^{1669,1670}	Conference abstract
SUN 2007 ^{319,321}	Duplicate of CHOI 2007A – already excluded in this review
SVERRILD 2009 ^{1708,1708}	Same data used for Sverrild 2010 paper already excluded from this review.
SVERRILD 2010 ^{1707,1708}	Reference standard does not match protocol - physician Dx without objective test (physician Dx made on the basis of symptoms in the last 12 months in combination with either a eNO level of greater than 30 ppb, a history of allergic rhinoconjunctivitis, dermatitis, a positive skin prick test response, a familial predisposition to atopic disease, nonallergic rhinoconjunctivitis, or an FEV1/forced vital capacity ratio of less than 75%).
SVERRILD 2012 ^{1706,1708}	Review article
SVERRILD 2013 ^{1705,1708}	sn/sp of FeNO in predicting positive mannitol response. Reference standard does not match protocol - physician Dx with no mention of objective test
TAKAMI 2013 ^{1718,1718}	No relevant outcomes and does not match review question (correlation study)
TERNESTEN 2002 ¹⁷⁴²	Methacholine challenge test used as part of the reference standard to Dx asthma
TIE 2012 ^{1755,1755}	Reference standard does not match

Reference	Reason for exclusion
	protocol
TODD 2004 ^{1764,1764}	Not relevant outcomes and does not answer review question - all people with asthma with positive methacholine challenge (comparing methods of performing methacholine test)
TOELLE 1992 ^{1765,1765}	Methacholine challenge test used as part of the reference standard to Dx asthma
TOWNLEY 1975 ^{1782,1782}	Reference standard does not match protocol – no objective test
TOWNLEY 1990 ^{1781,1782}	Can only calculate sensitivity (methacholine challenge in suspected asthma and asymptomatic controls – all suspected group were Dx based on reference standard and no Dx of control group reported)
VILOZNI 2009 ^{1866,1867}	Population does not match protocol (aged 3-6 years)
WONGTIM 1997 ^{1936,1936}	Methacholine challenge test used as part of the reference standard to Dx asthma
WOO 2012 ^{1937,1937}	Methacholine challenge test used as part of the reference standard to Dx asthma – Dx based on symptoms and BDR and/or positive methacholine challenge
WOOLCOCK 1984 ^{1943,1943}	Histamine challenge test but no comparator or reference standard test (looking at dose-response curve to histamine in people with asthma and controls)
WU 2011 ^{1946,1946}	Conference abstract
XU 2001 ^{1949,1949}	Reference standard does not match protocol - asthma was defined as a history of physician-diagnosed asthma at any time in the past (no mention of objective test)
YURDAKUL 2005 ^{1968,1968}	Reference standard does not match protocol – methacholine test used as part of reference standard to Dx asthma
ZAGHLOUL 2009 ^{1970,1970}	Conference abstract

1K.15 Diagnosis: Exercise challenge test

2 **Table 221: Studies excluded from the clinical review**

Reference	Reason for exclusion
ALBERTS1994 ^{32,32}	Not exercise test
ANDERSON2009 ^{44,48}	Exercise test as gold standard not index test
ANDERSON2010A ^{44,46}	Exercise test as gold standard not index test
ANDERSON2011 ^{44,47}	Not primary study
ANSLEY2012	Not exercise test

Reference	Reason for exclusion
53,53	
ARIASIRIGOYEN1999 ^{65,65}	Case control study
AVITAL 1995A ^{82,83}	Wrong cut-off value: Change in FEV1 of 5% is very low.
AVITAL1995 ^{82,82}	Mean age <5 years
BACKER 1992 ^{87,89}	Wrong population: general population, not suspected asthma.
BACKER1991 ^{87,87}	Not exercise test +/- versus histamine challenge +/- or diagnosis of asthma
BAILLY2011 ^{93,93}	Not exercise
BARBEN2011 ^{106,106}	Exercise test as gold standard not index test
BELCHER1987 ^{143,143}	Not exercise test to diagnose asthma (refractoriness to second test)
BENARB 2011 ¹⁴⁹	Wrong reference standard: ISAAC questionnaire but no objective test.
BENNETT1987 ^{152,152}	Not exercise
BERKMAN 2005 ^{159,159}	Wrong reference standard: physician Dx but no objective test.
BEYDON2008 ^{167,167}	Not exercise
BHAGAT1984 ^{168,168}	Not exercise test over/under threshold versus comparator
BLACKIE1990 ^{178,178}	Review not primary study
BOCCACCINO2007 ^{181,181}	No comparator test of diagnosis of asthma/no asthma
BORGES2011 ^{190,190}	Review not primary study
BOUGAULT2010 ^{200,200}	Not exercise test
BRANNAN2012 ^{216,217}	Review not primary study
BROZEK2009 ^{234,234}	Case control study
BUCHVALD2005 ^{241,241}	Exercise test as gold standard not index test
CALVERT2005 ^{265,265}	Case control study
CAREY2010 ^{271,272}	Not diagnosis of asthma (healthy subjects)
CARLSEN 1998 ^{273,275}	Wrong reference standard: physician Dx but no objective test.
CARLSEN2002 ^{273,276}	Not primary study
CARLSTEN2011 ^{277,278}	Not exercise test
CHATHAM1982 ^{305,305}	Unclear cut-offs. Case-control study
CHEN2014 ^{308,310}	Population does not match protocol – general population
CHOI2005 319,320	EIB as outcome not index test
CLEARIE2010 ^{343,343}	Elite athletes
COCKCROFT1992 ^{355,356}	Not exercise test
COCKCROFT2009 ^{356,357}	SR not primary study - no data presented

Reference	Reason for exclusion
COCKCROFT2009A ^{353,356}	Review not primary study
COCKCROFT2010 ^{356,358}	Not a primary study – no data presented
DEMISSIE 1998 ^{421,421}	Wrong reference standard: physician Dx but no objective test.
DICKINSON2006 ^{440,442}	Elite athletes
DICKINSON2006A ^{440,441}	Elite athletes
DOR1999 ^{448,448}	Non-English
DRYDEN2010 ^{457,457}	Exercise test as gold standard not index test
ELHALAWANI2003 ^{472,472}	Exercise test as gold standard not index test
ELIASSON1992 ^{473,473}	Case control study
FEITOSA2012 ^{493,493}	Exercise test as gold standard not index test
FUENTES2011 ^{531,531}	Case control study
GARCIADLARUBIA1998 ⁵⁴⁶	Case control study
GARCIARIO2004 ⁵⁴⁹	Not exercise test
GERALD2002 ^{557,557}	Information on subjects with positive exercise test only, not those with negative test
GIFT1994 ^{567,567}	Commentary not primary study
GODFREY1999 ^{576,577}	Compares outcome of exercise test in subjects with asthma against previously published studies in normal populations; data for test results comparing exercise with methacholine challenge within asthma group not shown
GRUCHALLA2003 ^{601,601}	Case control study and not all participants had exercise test
GRUCHALLA2009 ^{601,602}	Not exercise test
GRZELEWSKI2012 ^{605,606}	Exercise test as gold standard not index test
HOLZER2002 ^{696,696}	Not exercise test as index test
HOLZER2003 ^{695,696}	Not exercise test as index test
HOPP1984 ^{702,702}	Not exercise test
HORIE1983 ^{709,709}	Not exercise positive/negative versus asthma diagnosis or other test positive/negative
JOHNSON1987 ^{779,779}	Not exercise test
JONES1994 ^{782,782}	Case control study with longitudinal follow up
JONES1994A ^{782,783}	Case control study
JOOS2003 ^{786,786}	Review not primary study
KANAZAWA2002 ^{816,816}	Not exercise test +/- versus asthma diagnosis or other test
KANNISTO2000 ^{819,819}	No data on exercise +/- versus comparator

Reference	Reason for exclusion
KING1989 ^{876,876}	Not exercise test
KIVILOOG 1975 ^{881,881}	Wrong outcome measure: not a standard measure (change in PEFR $\geq 15\%$)
KNOX1989 ^{893,893}	Not exercise test
KOH1996 ^{897,897}	Not exercise +/- versus comparator +/-`
KOH1998 ^{896,897}	Not exercise +/- versus comparator +/-`
KOTANIEMISYRJANEN2002 ⁹¹⁷	Exercise test part of gold standard not index test
LAZOVELASQUEZ2005 ⁹⁷⁹	Case control study
LEX2007 ^{1006,1007}	Exercise test as gold standard not index test
LIEM2008 ^{1013,1014}	Not exercise test
LUNTSOV2012 ^{1048,1048}	Not exercise +/- versus comparator +/-`
MADSEN1985 ^{1057,1057}	Not exercise test
MADSEN1986 ^{1056,1057}	Not exercise test
MALMBERG2009 ^{1075,1077}	Exercise test as gold standard not index test
MANSO2011 ^{1086,1086}	Not exercise test
MIEDINGER2010 ^{1145,1146}	Case control study
MODL 1995 ^{1166,1166}	Wrong population: symptom-free and medication-free people with asthma
MULLER 1993 ^{1188,1188}	Not exercise test
MUSSAFFI1986 ^{1199,1199}	Not exercise +/- versus comparator +/-`
NEIJENS1983 ^{1219,1219}	Review not primary study
NISH1992 ^{1249,1249}	Exercise test as part of gold standard not index test
NISHIO2007 ^{1250,1250}	Exercise test as gold standard not index test
OBATA1994 ^{1265,1265}	Case control study
PEDROSA2009 ^{1329,1329}	Not exercise test
PONSONBY 1996 ^{1377,1377}	Wrong reference standard: ISAAC questionnaire but no objective test.
PORSBJERG2009 ^{1383,1384}	Not primary study
PRATTER1989 ^{1397,1398}	Not all patients had exercise test and exercise test part of gold standard not index
PUOLIJOKI1992 ^{1415,1415}	Not exercise test
RAMSER2008 ^{1428,1428}	Exercise test as gold standard not index test
RANDOLPH2011 ^{1430,1431}	Review not primary study
RANDOLPH2011A ^{1431,1432}	Unclear what is the gold standard
REMES 2002 ^{1447,1448}	Wrong reference standard: physician Dx but no objective test.
RIEDLER1992A ^{1458,1458}	Non-English
RIEDLER1994 ^{1458,1459}	Case control study

Reference	Reason for exclusion
RIEDLER1997 ^{1457,1458}	Review, not primary study.
ROMBERG2011 ^{1474,1474}	Elite athletes
ROMBERG2012 ^{1474,1475}	Elite athletes
ROUHOS2010 ^{1486,1487}	Exercise test mentioned but results not reported
RUNDELL2004 ^{1491,1491}	Exercise = index test but also part of gold standard
SACHSOLSEN2010 ¹⁴⁹⁷	Exercise test as part of gold standard not index test
SACHSOLSEN2013 ¹⁴⁹⁸	Case control study
SCOLLO2000 ^{1548,1548}	Exercise test as gold standard not index test
SHAPIRO1982 ^{1571,1571}	Not exercise test
SIERSTED 1996 ^{1590,1591}	Wrong population: general population, not suspected asthma.
SIN2009 ^{1610,1611}	Data versus methacholine test was not all in asthma patients; data versus diagnosis not calculable
SINCLAIR1995 ^{1612,1612}	Exercise test as both index and comparison test
SMITH1990 ^{1627,1631}	Exercise test as gold standard not index test
SOTORAMOS2013 ¹⁶⁵⁰	Comparator test is FeNO – not on list in protocol
SOVIJARVI1986 1652,1652	Not exercise test
SPIERING2004 1658,1658	Exercise test as gold standard not index test
SPIROPOULOS1986 ^{1659,1659}	Not exercise test
STICKLAND2011 ^{1680,1680}	Review, not primary study. Exercise test as gold standard not index test
TAL1984 ^{1720,1720}	Cold air and exercise tests are both index tests – no comparator from protocol list
TERBLANCHE 1990 ^{1741,1741}	Wrong population: general population, not suspected asthma.
TOWNLEY1975 ^{1782,1782}	Not exercise test
TSYBULKINA2008 ^{1794,1794}	No comparator
TSYBULKINA2011 ^{1792,1794}	Not exercise +/- versus comparator +/-`
VILOZNI2007 ^{1866,1866}	Children aged 3 to 6 years (mean <5 years); not exercise test positive/negative versus diagnosis or other test
VILOZNI2009 ^{1866,1867}	Not exercise test
WEST1996 ^{1907,1907}	Case control study
WOJNAROWSKI1996 ^{1932,1932}	Not exercise test

1K.16 Monitoring: Questionnaires

2 **Table 222: Studies excluded from the clinical review**

Reference	Reason for exclusion
ADAMS 2000 ¹⁶	Validation of AQLQ-M.
APFELBACHER 2011 ⁵⁷	Review article
APFELBACHER 2012 ⁵⁸	Validation study of mini AQLQ-J and AQLQ-S and correlation with symptoms, control and patient characteristics.
ALMOAMARY 2012 ²⁸	Intervention does not match protocol – asthma control questionnaire score to guide initial therapy not ongoing management.
BARLEY 1999 ¹⁰⁹	Correlation of diary cards with questionnaires and lung function.
BATEMAN 2001 ¹²⁵	Review article
BATEMAN 2006 ¹²⁶	Intervention does not match protocol – step down of treatment according to monitoring using GINA guidelines.
BAYLISS 2000 ¹³²	Validation of ITG-ASF QOL questionnaire.
BHOGAL 2006 ¹⁷⁰	Systematic review - intervention and comparison do not match protocol – monitoring symptoms vs PEF
BIME 2012 ¹⁷²	Validation study of ASUI
BRAIDO 2012 ²⁰⁶	Validation of RhinAsthma Patient Perspective QOL questionnaire.
BUIST 2006 ²⁴³	Intervention does not match protocol – monitoring using a peak flow monitor.
CARRANZAROSENZWEIG 2007 ²⁸⁰	Conference abstract
CARROLL 2013 ²⁸⁴	Review article
DESOUZA 2011 ⁴⁰⁷	Not in English
EHRIS 2006 ⁴⁶⁹	Validation of mini AQLQ
ERKOCOGLU 2012 ⁴⁸²	Comparison of control determined by C-ACT or GINA
EVERHART 2009 ⁴⁸⁴	Validation of a pictorial version of the AQLQ
GALANT 1999 ⁵⁴⁰	Conference abstract
GARRATT 2000 ⁵⁵²	Validation of AQLQ
GRAINGER-ROUSSEAU 1996 ⁵⁹¹	Article not available
GREEN 2007 ⁵⁹⁴	No relevant outcomes - results of phase 2 (ACT completed for physician visits) not reported in this paper.
GREEN 2013 ⁵⁹⁶	Comparison of level of control between measures (FeNO, spirometry, cACT and clinical assessment).
GUENDELMAN 2002 ⁶⁰⁹	Intervention does not match protocol – interactive self-management and education programme, includes questions about symptoms, PEF, use of medications and health services and functional status (not symptoms alone)

Reference	Reason for exclusion
GUENDELMAN 2004 ⁶¹⁰	Intervention does not match protocol – interactive self-management and education programme, includes questions about symptoms, PEF, use of medications and health services and functional status (not symptoms alone)
HALBERT 2009 ⁶²⁷	Systematic review of validation studies.
HOLT 2010A ⁶⁹⁴	Review of ACT
JAN 2007 ⁷⁵⁷	Intervention does not match protocol – monitoring of symptoms and PEF (comparison of diaries and electronic diaries)
JIA 2013 ⁷⁷⁷	Systematic review of validation studies of ACT and ACQ
JUNIPER 1993 ⁸⁰²	Validation of AQLQ.
JUNIPER 1996 ⁸⁰⁰	Validation of PAQLQ
JUNIPER 1997 ⁸⁰¹	Validation of the PAQLQ
JUNIPER 1999 ⁷⁹⁹	Validation of the mini AQLQ
JUNIPER 1999A ⁷⁹⁷	Validation of the AQLQ-S
JUNIPER 1999C ⁸⁰⁵	Validation of the ACQ
JUNIPER 2000 ⁸⁰⁴	No relevant outcomes. Comparison of daily control diary and clinician assessment of control.
JUNIPER 2001 ⁸⁰³	Validation of 4 QOL instruments
JUNIPER 2001A ⁸⁰⁶	Validation of the ACQ
JUNIPER 2005 ⁸⁰⁸	Validation of the AQLQ 12+
JUNIPER 2005A ⁸⁰⁷	Validation of 3 shortened versions of the ACQ
JUNIPER 2010 ⁷⁹⁸	Validation of ACQ in children.
KATZ 1999 ⁸²⁹	Validation of AQLQ-M
KAVUT 2010 ⁸³⁴	Intervention does not match protocol – asthma awareness session, ACT is an outcome.
KHEIR 2008 ⁸⁶¹	Intervention does not match protocol – pharmaceutical care service including assessment of adherence and PEF monitoring to guide care plan.
KWON 2008A ⁹⁵²	Conference abstract
LEUNG 2013 ⁹⁹⁸	Review article
LIU 2007 ¹⁰³¹	Development and validation of cACT
LOBO 2007 ¹⁰³⁴	Conference abstract. Validation of PAQLQ in severe asthma.
MAGNAN 2004 ¹⁰⁶⁰	Review article
MARKS 1993 ¹⁰⁹⁰	Validation study of AQLQ-M and correlation with symptoms, lung function and BHR.
MCDONALD 2009 ¹¹¹⁵	Conference abstract. Validation of ACQ in children.

Reference	Reason for exclusion
NATHAN 2004 ¹²¹²	Validation of the ACT
NGUYEN 2014 ¹²²⁸	Validation of ACQ in children.
PINNOCK 2012 ¹³⁶⁴	Validation of the RCP-3
PRABHAKARAN 2010A ¹³⁹³	Intervention does not match protocol - monitoring using SMS service based on symptoms and medication use.
THOMAS 2009 ¹⁷⁴⁸	Validation of the RCP-3 and cross-sectional correlation analysis with control, QOL, BD use, lung function and FeNO.
TURNER 1998 ¹⁸⁰³	Intervention does not match protocol – PEF monitoring vs symptom monitoring (symptoms monitoring does not focus on symptom scores or diaries to monitor control)
VANGAALEN 2013 ¹⁸³³	Same study as MEER 2009 (included in this review). Long term follow-up at 30 months but monitoring intervention ended at 12 months. Already using outcomes at 12 months (use of 30 months would be double counting for >6months).
WING 2012 ¹⁹²⁴	Validation of PAQLQ and mini PAQLQ.
YOOS 2002 ¹⁹⁶³	Intervention and comparison do not match protocol – monitoring symptoms vs symptoms + PEF
ZEMEK 2008 ¹⁹⁷⁴	Systematic review - intervention and comparison do not match protocol – monitoring symptoms vs PEF

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1K.17 Monitoring: Lung function tests

2 **Table 223: Studies excluded from the clinical review**

Study	Exclusion reason
Abramson 2010 ¹³	Not guideline condition. Asthma or COPD patients are included and the results are not shown separately
Abramson 2012 ¹¹	Incorrect interventions. Spirometry intervention versus usual care (abstract only)
Anon 2004 ⁴	Commentary not primary study
Armour 2007 ⁷²	Incorrect interventions. Intervention is not monitoring with spirometry or PEF
Ayres 1996 ⁸⁵	Both groups monitored PEF
Berg 1997 ¹⁵⁵	Incorrect interventions. No self-management in control group
Bheekie 2001 ¹⁶⁹	Alternate allocation (not randomized). Inadequate allocation concealment. No relevant outcomes.
Boath 1998 ¹⁸⁰	Conference abstract not freely available
Bramson 1996 ²⁰⁷	Not full paper. Commentary on a study already excluded from this review (LAHDESUO 1996)
Brouwer 2008 ²³¹	Not SR or RCT
Charlton 1994 ³⁰³	Incorrect interventions. Both groups monitored PEF
De asis 2004 ³⁹⁵	No clinical outcomes. Cost-effectiveness paper based on clinical data from a paper already included in this review (COWIE 1997)
Deschildre 2012 ⁴³¹	Severe asthma. Severe allergic asthma according to the Third Paediatric Asthma Consensus (i. e. frequent acute episodes requiring oral corticosteroid therapy, associated with moderate episodes (exercise-induced asthma, chronic cough, sleep disturbances, treatment with short-acting beta 2-agonists >3 times per week) and airflow limitation). Incorrect intervention. Incorrect interventions
Drummond 1994 ⁴⁵⁶	Incorrect interventions. No self-management in control group
Gibson 2002 ⁵⁶⁶	SR: self-management (PEF or symptoms) versus usual care
Gibson 2004 ⁵⁶⁵	SR: all RCTs checked
Huang 2009 ⁷¹⁷	Not self-management in the control group
Ignacio 1993 ⁷²⁹	Not in English
Ignacio-garcia 1995 ⁷³⁰	Incorrect interventions. Intervention group received education and self-management plan. Control group were monitored by their physician according to symptoms but did not receive education or a self-mangement plan.
Jan 2007 ⁷⁵⁷	Incorrect interventions. Both groups used PEF monitoring
Janson 2010 ⁷⁶³	Not self-monitoring peak flow. Not self-monitoring peak flow . Not self-monitoring peak flow versus not (intervention = monthly trend PEF data given to GPs; control allowed to use PEF)
Janson-bjerklie 1988 ⁷⁶⁴	Not self-management
Jones 1995 ⁷⁸⁴	Incorrect interventions. Control group did not have self-management
Kelso 2005 ⁸⁴⁵	Commentary not primary study
Kemple 2003 ⁸⁴⁷	Action plans but not PEF monitoring versus not (not all intervention group had a peak flow monitor)

Klein 2001 ⁸⁸⁵	Control group also given peak flow meter. Incorrect interventions
Kotses 1996 ⁹¹⁸	2 groups both self-managed with PEF, the third group did not self-manage. Incorrect interventions
Kotses 2007 ⁹¹⁹	Conference abstract not freely available
Lahdensuo 1996 ⁹⁵⁸	Incorrect interventions. No self-management in control group
Lahdensuo 1998 ⁹⁵⁷	Incorrect interventions. Control group did not have self-management
Lefevre 2002 ⁹⁸⁷	SR: RCTs checked, all already in separately
Löwhagen 2002 ¹⁰⁴³	Incorrect interventions. Wrong comparator (ECP)
Magar 2005 ¹⁰⁵⁸	No self-management in control group
Malo 1993 ¹⁰⁸⁰	Crossover study
Mcgrath 2001 ¹¹¹⁹	SR: RCTs checked
Mcmullen 2002 ¹¹²⁴	Not our outcomes (qualitative data from Yoos 2002 trial)
Milenkovic 2007 ¹¹⁴⁹	Incorrect interventions. No self-management in control group
Nhlbi 2005 ¹²²⁹	Protocol only, no results
Osman 2002 ¹²⁸⁷	Incorrect interventions. No self-monitoring in control group
Persaud 1996 ¹³³⁹	No self-management in control group
Powell 2002 ¹³⁹⁰	SR: RCTs checked
Reddel 2006 ¹⁴⁴¹	Review article
Ross 2012 ¹⁴⁸⁴	No self-management in control group (abstract only)
Sangha 2004 ¹⁵⁰⁸	Not review population. Not persistent asthma (seasonal symptoms)
Schermer 2002 ¹⁵²⁷	Incorrect interventions. Control group did not self-manage
Slader 2006 ¹⁶²²	Incorrect interventions. Not randomised comparison of PEF monitoring versus other self-monitoring
Slader 2007 ¹⁶²³	Incorrect interventions. Not randomised comparison of PEF versus symptoms monitoring
Stahlman 2006 ¹⁶⁷¹	Crossover study. Crossover
Tagaya 2005 ¹⁷¹³	Incorrect interventions. No self management in control group
Tapp 2007 ¹⁷²⁷	Incorrect interventions. Education (could be self-management with PEF or symptoms or both) versus no education, not self-management with PEF versus no PEF
Thoonen 2003 ¹⁷⁵²	Incorrect interventions. No self management in control group
Thurber 2006 ¹⁷⁵⁴	Conference abstract not freely available
Toelle 2011 ¹⁷⁶⁶	Withdrawn by Cochrane Library
Van der palen 1998 ¹⁸²⁶	SR: RCTs checked
Van der palen 2001 ¹⁸²⁷	Control group did not self-treat exacerbations
Vazquez 1993 ¹⁸⁴⁹	Not PEF self-management versus other self-management. Incorrect interventions
Walders 2006 ¹⁸⁸⁵	Incorrect interventions. All participants had self-management based on PEF and symptoms
Weinberger 2002 ¹⁹⁰¹	Incorrect interventions. No self-monitoring in control group
Yoon 1993 ¹⁹⁶²	Incorrect interventions. All participants had peak flow meter; randomised comparison was of an education session
Zemek 2008 ¹⁹⁷⁴	SR: all included studies already on our list individually

1K.18 Monitoring: FeNO

2 **Table 224: Studies excluded from the clinical review**

Reference	Reason for exclusion
⁹¹ BACKER 2014	Population does not match protocol. Not monitoring FeNO.
HASHIMOTO 2011 ^{647,647}	Population does not match protocol – severe asthma
HONKOOP 2011 ^{701,701}	Published trial protocol
HONKOOP 2013 ^{699,701}	Conference abstract
KATSOULIS 2013 ^{828,828}	Population does not match protocol. Not monitoring FeNO
LURA 2010 ^{1049,1049}	Conference abstract
MALERBA 2008 ^{1070,1070}	Intervention does not match protocol – monitoring FeNO and sputum eosinophils combined.
NICKELS 2014 ^{1231,1231}	Conference abstract
NICKELS 2014A ^{1231,1232}	Conference abstract
OHKURA 2013 ^{1274,1275}	Conference abstract
PETSKY 2010 ^{1351,1353}	Conference abstract
PETSKY 2010 ^{1350,1353}	Conference abstract (duplicate)
PETSKY 2010 ^{1350,1353}	Conference abstract (duplicate)
POWELL 2011 ^{1387,1389}	Population does not match protocol – pregnant women.
SCHNEIDER 2014 ^{1534,1537}	Population does not match protocol. Not FeNO monitoring.
SYK 2012 ^{1709,1709}	Conference abstract
SYK 2012A ^{1709,1710}	Conference abstract
VOORENDVAN 2013 ¹⁸⁷⁸	Conference abstract
VOUTILAINEN 2013 ^{1879,1879}	Population does not match protocol. Not FeNO monitoring.
WANICH 2009 ^{1894,1894}	Commentary

3K.19 Monitoring: Peripheral blood eosinophils

4 **Table 225: Studies excluded from the clinical review**

Reference	Reason for exclusion
ALMOSAWI 2008 ^{36,36}	Study design does not match protocol – observational case control study comparing eosinophil levels.
BASYIGIT 2004A ^{124,124}	Intervention does not match protocol – not monitoring blood eosinophils.
BELDA 2001 ^{144,144}	Study design does not match protocol – observational prognostic study of eosinophil levels as a risk factor for exacerbation.
BRUSSELLE 2013 ^{238,238}	Review article
BUSH 2005 ^{251,251}	Clinical trial protocol only. Population does not match protocol – severe asthma.

Reference	Reason for exclusion
	Intervention does not match protocol – monitoring using sputum not blood eosinophils.
BUSSE 2013 ^{255,256}	Intervention does not match protocol – not monitoring.
DEYKIN 2005 ^{432,433}	Intervention does not match protocol – not monitoring.
GREEN 2002A ^{595,597}	Intervention does not match protocol (monitoring sputum eosinophils).
LOWHAGEN 2002 ^{1043,1043}	Intervention and comparison do not match protocol – monitoring serum eosinophil cationic protein vs monitoring PEF (as % best, not PEFv).
MALERBA 2008 ^{1070,1070}	Study design does not match protocol – observational case series (all patients monitored, no control group). Intervention does not match protocol (monitoring sputum eosinophils).
NIIMI 1999 ^{1244,1244}	Review article
PARAMESWARAN2000A ^{1306,1307}	Conference abstract
PETSKY 2007 ^{1353,1353}	Systematic review - intervention does not match protocol (monitoring sputum eosinophils).
PETSKY 2012 ^{1352,1353}	Systematic review - intervention does not match protocol (monitoring sputum eosinophils).
PREHN 2000 ^{1399,1399}	Pilot study. Study design does not match protocol – observational case series (all patients monitored using serum eosinophil protein levels, no control group).
ZACHARASIEWICZ 2006 ^{1969,1969}	Review article

1K.20 Monitoring: Challenge tests

2 **Table 226: Studies excluded from the clinical review**

Reference	Reason for exclusion
ARKINS 1968 ^{70,70}	Not relevant to review question
BELDA 2006 ^{144,145}	Intervention does not match protocol – Step-down treatment strategy, BHR as an outcome.
BRAND 1992A ^{209,210}	Population and intervention do not match protocol
FORESI 2005 ^{508,508}	Intervention does not match protocol – RCT of 2 step-down treatment strategies, BHR as an outcome.
HAYES 2012 ^{652,653}	Intervention does not match protocol - Health Technology assessment of Mannitol challenge test for diagnosis not monitoring.
JOOS 2003A ^{786,787}	Review article

Reference	Reason for exclusion
MCKINLAY 2011 ^{1122,1122}	Conference abstract. Relevant for mannitol
NUIJSINK 2013 ^{1260,1261}	Same study as NUIJSINK 2007 – long term follow up after intervention had finished.
PADOVANO 2000 ^{1294,1294}	Conference abstract
PROSPERINI 2002 ^{1411,1411}	Intervention does not match protocol – Step-down treatment strategy, BHR as an outcome.
RENSEN 1998 ^{1450,1450}	Conference abstract
SCHERR 2012 ^{1529,1529}	Conference abstract – intervention does not match protocol
SHORT 2011A ^{1586,1587}	Conference abstract. Relevant for mannitol
THOONEN 2003 ^{1752,1752}	Intervention does not match protocol

1

2

1K.21 Monitoring: Adherence to treatment

2 **Table 227: Studies excluded from the clinical review**

Reference	Reason for exclusion
APTER 2005 ^{59,60}	Not full paper (clinical trial protocol only). Intervention does not match protocol.
ARMOUR 2007 ^{72,72}	Intervention does not match protocol – asthma management plan including counselling/education, review of inhaler technique, review of adherence and referral to GP.
BALDWIN 1991 ^{95,95}	Intervention and comparison do not match protocol – new portable system vs conventional system for monitoring theophylline levels.
BENDER 2014 ^{150,151}	Conference abstract
BLACK 2008 ^{177,177}	Not full paper (conference abstract only).
BOZEK 2010 ^{205,205}	No relevant outcomes and does not match review question. Correlation between cognitive status and compliance in elderly people with asthma.
BRANDT 1994 ^{215,215}	Intervention does not match protocol - intervention included monitoring of inhaler technique, monitoring theophylline levels and counselling. Population does not match protocol – moderate to severe asthma.
BROERS 2002 ^{228,229}	Not full paper (conference abstract only).
BURGESS 2009 ^{245,245}	Not full paper (conference abstract only) – full text assessed BURGESS 2010
CHIA 2008 ^{314,314}	Intervention does not match protocol – education on asthma and inhaler technique.
GIBSON 2009 ^{563,564}	Intervention and comparison does not match protocol – systematic review of FeNO vs symptom monitoring.
JANSON 2005 ^{762,764}	Not full paper (clinical trial protocol only). Intervention does not match protocol.
KRISHNAN 2012 ^{929,929}	No relevant outcomes and does not match review question – comparison between subjective and objective measures of adherence.
LAUFENBERGHORSTMANN 2006 ⁹⁷⁶	Intervention does not match protocol - community pharmacist initiated intervention included monitoring of inhaler technique and adherence.
MATUI 2014 ^{1107,1107}	Systematic review. Intervention does not match protocol.
MCCLURE 2008 ^{1112,1112}	Intervention does not match protocol - supervision of medication administration in children to improve adherence (not based on feedback as a result of monitoring adherence).

Reference	Reason for exclusion
MEHUYS 2008 ^{1128,1128}	No relevant outcomes and does not match review question. Monitoring level of asthma control to guide therapy
MITCHELL 2005 ^{1161,1162}	Intervention does not match protocol – asthma clinical pathway.
MOULLEC 2012 ^{1184,1184}	Intervention does not match protocol – systematic review of interventions to improve adherence (eg self-management and decision support).
MUNDY 2007 ^{1190,1190}	Review article
NIDES 1993 ^{1237,1237}	Population does not match protocol – not people with asthma.
PERTSEVA 2004 ^{1341,1341}	Not full paper (conference abstract only).
PETITTO 2012 ^{1348,1348}	Not full paper – full text assessed KRISHNAN 2012. No relevant outcomes and does not match review question – comparison between subjective and objective measures of adherence.
RAND 1994 ^{1429,1429}	Review article
SANTOS 2010 ^{1510,1510}	Intervention does not match protocol – counselling intervention to improve adherence.
STRANDBYGAARD 2010 ^{1692,1692}	Intervention does not match protocol – daily SMS reminder to take medication (adherence is an outcome, intervention is not monitoring adherence).
TRAN 2014 ^{1783,1783}	Systematic review. Intervention does not match protocol.
VASBINDER 2013 ^{1848,1848}	Intervention does not match protocol – text reminder 15 minutes following missed dose to improve adherence (not based on monitoring the individual patient's adherence)
VRIES 2010 ^{1880,1880}	Not in English.
VOLLMER 2011 ^{1873,1874}	Intervention does not match protocol – refill reminder call to improve adherence both before and after missed prescription fill (not based on monitoring the individual patient's adherence)

1K.22 Monitoring: Inhaler technique

2 **Table 228: Studies excluded from the clinical review**

Reference	Reason for exclusion
BASHETI 2005 ^{121,121}	No relevant outcomes – primary outcome is inhaler technique score.
BASHETI 2006 ^{120,121}	Conference abstract
BOSNIC 2010 ¹⁹⁵	No relevant outcomes – primary outcome is inhaler

Reference	Reason for exclusion
	technique score.
BRAND 2005 ^{210,214}	Review article.
BYNUM 2001 ^{258,258}	No relevant outcomes – primary outcome is inhaler technique score.
CICUTTO 2013 ^{330,330}	Intervention does not match protocol – asthma education.
FARBER 2009 ^{491,491}	Review article
GOEMAN 2013 ^{579,579}	Intervention does not match protocol – asthma education.
KUETHE 2013 ^{935,935}	Systematic review. Intervention does not match protocol – nurse led care vs physician led care.
KUMAR 2009 ^{937,938}	Intervention does not match protocol – asthma education.
LAUFENBERGHORSTMANN 2006 ⁹⁷⁶	Study design does not match protocol – observational study.
MCELNAY 1989 ^{1117,1117}	Study design does not match protocol – observational study.
MULLOY 1996 ^{1189,1189}	Intervention does not match protocol – asthma education.
NIDES 1993 ^{1237,1237}	Population does not match protocol – not people with asthma.
NIMMO 1993 ^{1246,1246}	Population does not match protocol – asthma and COPD. Crossover study of 2 types of inhaler.
PRESS 2012 ^{1400,1400}	Population does not match protocol – mixed asthma and COPD (33% asthma)
ROOTMENSEN 2008 ^{1478,1478}	Intervention does not match protocol – asthma education.
RYDMAN 1999 ^{1495,1495}	No relevant outcomes – primary outcome is inhaler technique score.
SAVAGE 2003 ^{1518,1518}	No relevant outcomes – inhaler technique score. Immediately before and after intervention, not long-term follow-up of patient outcomes.
SKAER 1996 ^{1620,1620}	Study design does not

Reference	Reason for exclusion
	match protocol – observational study.
TURGEON 1996 ^{1801,1801}	No relevant outcomes – inhaler technique score. UHU and missed school days assessed but not reported.
VAN DER PALAN 1997 ¹⁸²⁵	Population does not match protocol – COPD.
VERVER 1996 ^{1859,1859}	No relevant outcomes – inhaler technique score and self-reported symptoms.

1K.23 Monitoring: Tele-healthcare

2 **Table 229: Studies excluded from the clinical review**

Reference	Reason for exclusion
ACTRN12606000400561 ⁸⁰	Abstract only (protocol or conference abstract, not a full paper)
Ahmed 2011 ²⁴	Study protocol
Apter 2000 ⁵⁹	Intervention does not match the protocol (not tele-healthcare)
Araujo 2012 ⁶¹	Study design does not match protocol (crossover design)
Arguel 2013 ⁶⁴	Ongoing study
Bendeer NCT00958932 ¹⁵¹	Abstract only (protocol or conference abstract, not a full paper)
Burbank 2012 ²⁴⁴	Abstract only (protocol or conference abstract, not a full paper)
Bynum 2001 ²⁵⁸	Intervention does not match the protocol (not monitoring)
Chen 2013 ³⁰⁹	Intervention does not match the protocol (not tele-healthcare)
Clark 2007 ³⁴²	Intervention does not match the protocol (not monitoring)
Clover N0702196597 ⁵	Abstract only (protocol or conference abstract, not a full paper)
Cruz-Correia 2007 ³⁸¹	Study design does not match protocol (crossover design)
De Jongste 2009 ⁴⁰²	Intervention does not match the protocol (FeNO monitoring)
DRKS00000584 ⁴⁶⁵	Population does not match protocol (mixed diagnoses)
Eakin 2012 ⁴⁶⁷	Intervention does not match the protocol (not tele-healthcare)

Reference	Reason for exclusion
eMATIC NTR2583 ¹⁸⁴⁸	Ongoing study
Finkelstein CRISP ⁴⁹⁹	Abstract only (protocol or conference abstract, not a full paper)
Fonseca 2006 ⁵⁰⁵	Not outcome of RCT.
Friedman CRISP ²	Abstract only (protocol or conference abstract, not a full paper)
Garbutt 2010 ⁵⁴⁴	Intervention does not match the protocol (not monitoring)
Garbutt 2012 ⁵⁴⁵	Ongoing study
Gustafson NCT00993590 ³⁵¹	Study terminated
Hashimoto 2011 ⁶⁴⁷	Population (severe asthma and monitoring to taper OCS dose)
Huang 2013 ⁷¹⁶	Abstract only (protocol or conference abstract, not a full paper)
Ilo 2014 ⁷³¹	Non-English language publication (Japanese). Education not monitoring.
Kokubu 1999 ⁹⁰¹	Non-English language publication (Japanese)
Kokubu 2000 ⁹⁰⁰	Non-English language publication (Japanese)
Lam 2011 ⁹⁶²	Abstract only (protocol or conference abstract, not a full paper)
Mayers NCT00562081 ³⁴⁷	Abstract only (protocol or conference abstract, not a full paper)
Merchant 2013 ¹¹³⁵	Abstract only (protocol or conference abstract, not a full paper)
Moldrup NCT00917410 ³⁴⁹	Study design does not match protocol (no control group)
Murphy 2001 ¹¹⁹⁵	Abstract only (protocol or conference abstract, not a full paper)
NCT00149474 ³⁴⁴	Abstract only (protocol or conference abstract, not a full paper)
NCT00964301 ³⁵⁰	Ongoing study
NCT01117805 ³⁵²	Ongoing study
Osman N0411013273 ¹	Abstract only (protocol or conference abstract, not a full paper)
Partridge N0016132017 ³	Abstract only (protocol or conference abstract, not a full paper)

Reference	Reason for exclusion
Petrie 2012 ¹³⁴⁹	No relevant outcomes (primary outcome – adherence).
Razi 2012 ^{1439,1440}	No relevant outcomes
Ricci 2001 ¹⁴⁵⁴	Unclear methodology (could not locate any information)
Rikkers 2012 ¹⁴⁶⁴	Included in monitoring questionnaires review: self-management based on monitoring online ACQ scores (no monitoring of ACQ scores in the control group)
Rikkers-Mutsaert 2010 ¹⁴⁶³	Abstract only (protocol or conference abstract, not a full paper)
Schatz 2010 ¹⁵²⁵	Study design does not match protocol (letter)
Sciamanna 2013 ¹⁵⁴⁷	Abstract only (protocol or conference abstract, not a full paper)
Searing 2012 ¹⁵⁵³	Abstract only (protocol or conference abstract, not a full paper)
Shanovich 2009 ¹⁵⁷⁰	Abstract only (protocol or conference abstract, not a full paper)
Sparrow NCT00232557 ³⁴⁵	Abstract only (protocol or conference abstract, not a full paper)
Stout 2012 ¹⁶⁸⁶	Study design does not match protocol (cluster randomised feasibility trial)
Strandbygeerd 2010 ¹⁶⁹²	No uploading of patient information.
Strunk NCT00910585 ³⁴⁸	Abstract only (protocol or conference abstract, not a full paper)
Taitel 2014 ¹⁷¹⁶	Not monitoring (only one telephone call)
Uysal 2013 ¹⁸¹¹	Experimental study looking at the feasibility of using the ACT via text
van Gaalen 2012 ¹⁸³²	Abstract only (protocol or conference abstract, not a full paper).
VANGAALEN 2013 ¹⁸³³	Included in monitoring questionnaires review: self-management based on monitoring online ACQ scores (no monitoring of ACQ scores in the control group).
Vollmer 2011 ¹⁸⁷⁴	No relevant outcomes (primary outcome – adherence).

Reference	Reason for exclusion
VOOREND-VAN 2013 ¹⁸⁷⁸	Abstract only (protocol or conference abstract, not a full paper)
Wouters NCT00411346 ³⁴⁶	Abstract only (protocol or conference abstract, not a full paper)
Yun 2013 ¹⁹⁶⁶	No relevant outcomes (QOL reported incompletely, cannot combine in meta-analysis).

1

1 Appendix L: Excluded economic studies

2 L.1 Diagnosis: FeNO

3 **Table 230: Studies excluded from the economic review**

Reference	Reason for exclusion
BERG2008 ¹⁵⁶	Price 2009 ¹⁴⁰² is an update of this analysis
Harnan 2013 ⁶⁴⁴	This study only assessed diagnostic tests in isolation rather than as part of a diagnostic pathway.
PRICE2009 ¹⁴⁰²	This study only assessed diagnostic tests in isolation rather than as part of a diagnostic pathway.

4 L.2 Monitoring: Lung function tests

5 **Table 231: Studies excluded from the economic review**

Reference	Reason for exclusion
De Asis ³⁹⁵	This study was assessed as partially applicable with very serious limitations.

6 L.3 Monitoring: FeNO

7 **Table 232: Studies excluded from the economic review**

Reference	Reason for exclusion
Price 2009 ¹⁴⁰²	This study was assessed as partially applicable with very serious limitations. Harnan et al. 2013 ⁶⁴⁴ is more recent and more applicable.
Berg 2008 ¹⁵⁶	This study was assessed as partially applicable with very serious limitations. Price et al. 2009 ¹⁴⁰² updated this analysis using a UK NHS perspective and is hence more applicable.

8 L.4 Monitoring: Tele-healthcare

9 **Table 233: Studies excluded from the economic review**

Reference	Reason for exclusion
Pinnock 2007 ^{1361,1362}	Only includes cost to the service rather than cost to the NHS. Including these additional costs could change the results of the study as cost differences are very small.
Pinnock 2005 ^{1362,1363}	Only uses proportion of patients reviewed as an outcome. Excluding quality of life from the analysis could change the results as face to face reviews may improve health outcomes.

10

Appendix M: Cost-effectiveness analysis: Diagnosis of asthma in adults and young people aged over 16

M.1 Introduction

There are a variety of tests that can be used to diagnose asthma, and no clear gold standard. Available tests have different costs and different levels of accuracy, therefore it is important to identify which combination of tests represents a cost-effective use of NHS resources. Currently it is believed that asthma is over-diagnosed with a large portion of individuals with asthma currently being in-correctly diagnosed. This concern has been confirmed in a recent study by Aaron et al^{6,6} which found that nearly a third of individuals with an asthma diagnosis did not have asthma. Misdiagnosis of asthma represents a large waste of NHS resources as a significant portion of patients will be receiving treatment that does not improve their condition. For these reasons the GDG prioritised original economic analysis to be conducted to compare different combinations of diagnostic tests for the diagnosis of asthma. This analysis will weigh up the cost of providing additional tests against the cost savings from reducing unnecessary asthma treatment and improved health outcomes from providing the correct treatment.

The economic review found no studies that assessed the cost-effectiveness of diagnostic pathways. However two studies were found which assessed the cost-effectiveness of asthma diagnostic tests as standalone tests. Although the results from these studies give little indication of how cost-effective a test will be as part of a pathway they do give insight into the methods used to build an economic model for asthma diagnosis. These methods are compared to the following analysis in M.4.4.

M.2 Methods

M.2.1 Model overview

M.2.1.1 Comparators

Six diagnostic strategies were created using combinations of the following tests:

- spirometry
- bronchodilator reversibility
- FeNO
- peak expiratory flow variability
- challenge tests.

The GDG agreed that only one challenge test would ever be conducted per patient meaning that challenge testing would only appear once in a diagnostic strategy. Therefore once the diagnostic strategies were developed it was proposed to duplicate each strategy which used challenge testing using the diagnostic accuracies and costs of histamine/methacholine, mannitol or exercise challenge test. However once the costs of an exercise challenge test and a methacholine challenge test had been established it was apparent that the exercise challenge test was the more expensive test (see M.2.3.7). The clinical review also found that exercise challenge tests had a lower sensitivity and specificity when compared to a methacholine challenge test. Therefore exercise challenge tests were not modelled as they would always be dominated (more costly and provide lower health outcomes) when compared to methacholine challenge tests. Mannitol was also not modelled as the clinical

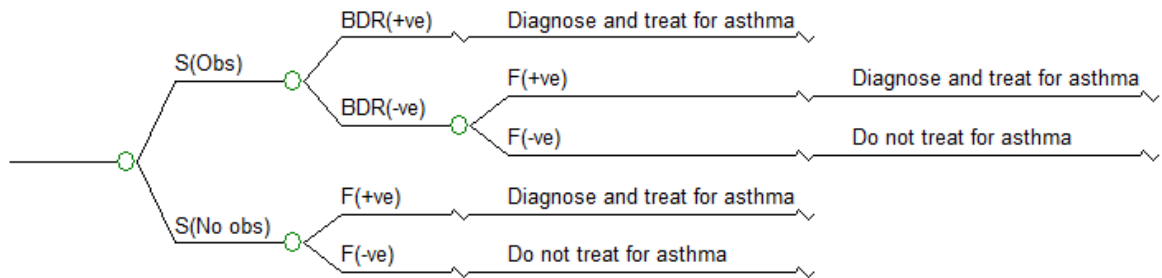
1 review found it had a low sensitivity and specificity. Adding mannitol to the diagnostic pathway
 2 would in fact decrease the overall diagnostic accuracy of the pathway making it dominated by
 3 strategies that did not use challenge tests.

4 All the pathways were constructed using clinical judgement and taking into account the evidence
 5 produced in the clinical review.

6 **Strategy 1**

7 Strategy 1 involves the fewest number of tests. The exact point that each test appears in the
 8 diagnostic pathway and at which point patients are diagnosed with asthma is shown in Figure 301.
 9 For example in Figure 301 spirometry (S) is used as the initial test, followed by bronchodilator
 10 reversibility (BDR) if S detects obstruction (Obs) or FeNO (F) if S does not detect obstruction (No obs).
 11 BDR is not performed after a non-obstructive spirometry as there is no obstructive airway to reverse.
 12 If BDR is negative this is followed by F. A diagnosis of asthma is made with either a positive BDR or F,
 13 while asthma is excluded only with a negative F.

14 **Figure 301: Strategy 1**

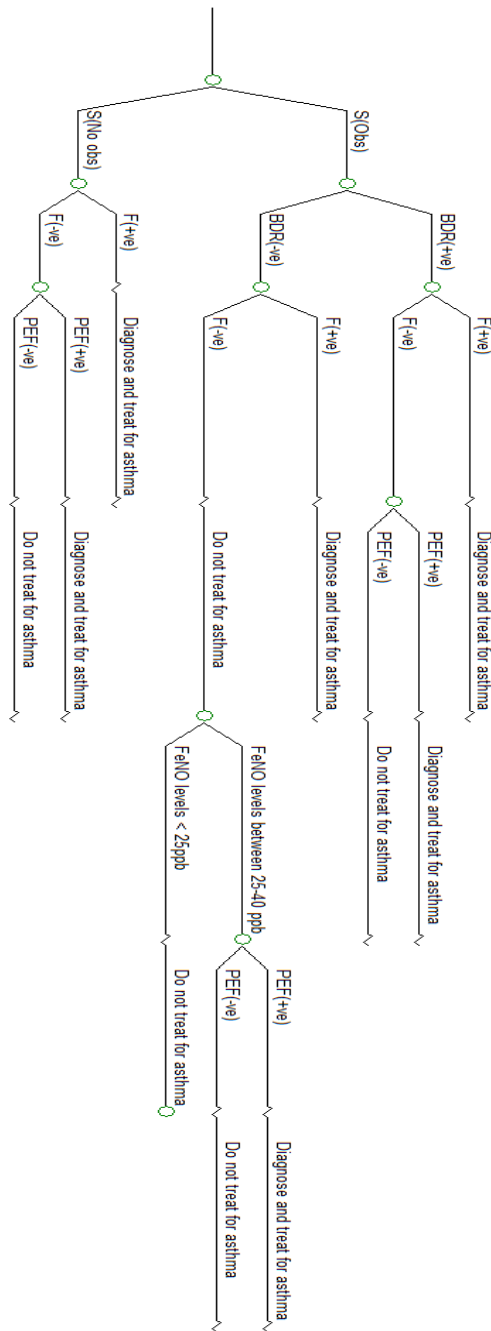


15
 16 *(-ve): negative; (+ve): positive; BDR: bronchodilator reversibility test; F: FeNO; S: spirometry; (Obs): obstruction*

17 **Strategy 2**

18 The second strategy involves spirometry, bronchodilator reversibility, FeNO and PEF variability (PEF).
 19 The diagnostic pathway is shown in Figure 302. As more tests can be conducted after a FeNO test, if a
 20 patient receives a negative FeNO test, the FeNO level that was measured in the patient is also taken
 21 into account when deciding what to do next. This test is considered negative when the FeNO level is
 22 below 40 parts per billion (ppb), however the confidence in excluding a diagnosis of asthma depends
 23 on how close to this cut off the result is. If the FeNO level is below 25 parts per billion (ppb), along
 24 with an obstructive spirometry and a negative BDR, asthma is ruled out. If the FeNO level is between
 25 25 – 40ppb then the diagnosis of asthma still cannot be ruled out and further tests are conducted. In
 26 strategy 2 below the patient goes on to have a PEFv test.

1 **Figure 302: Strategy 2**

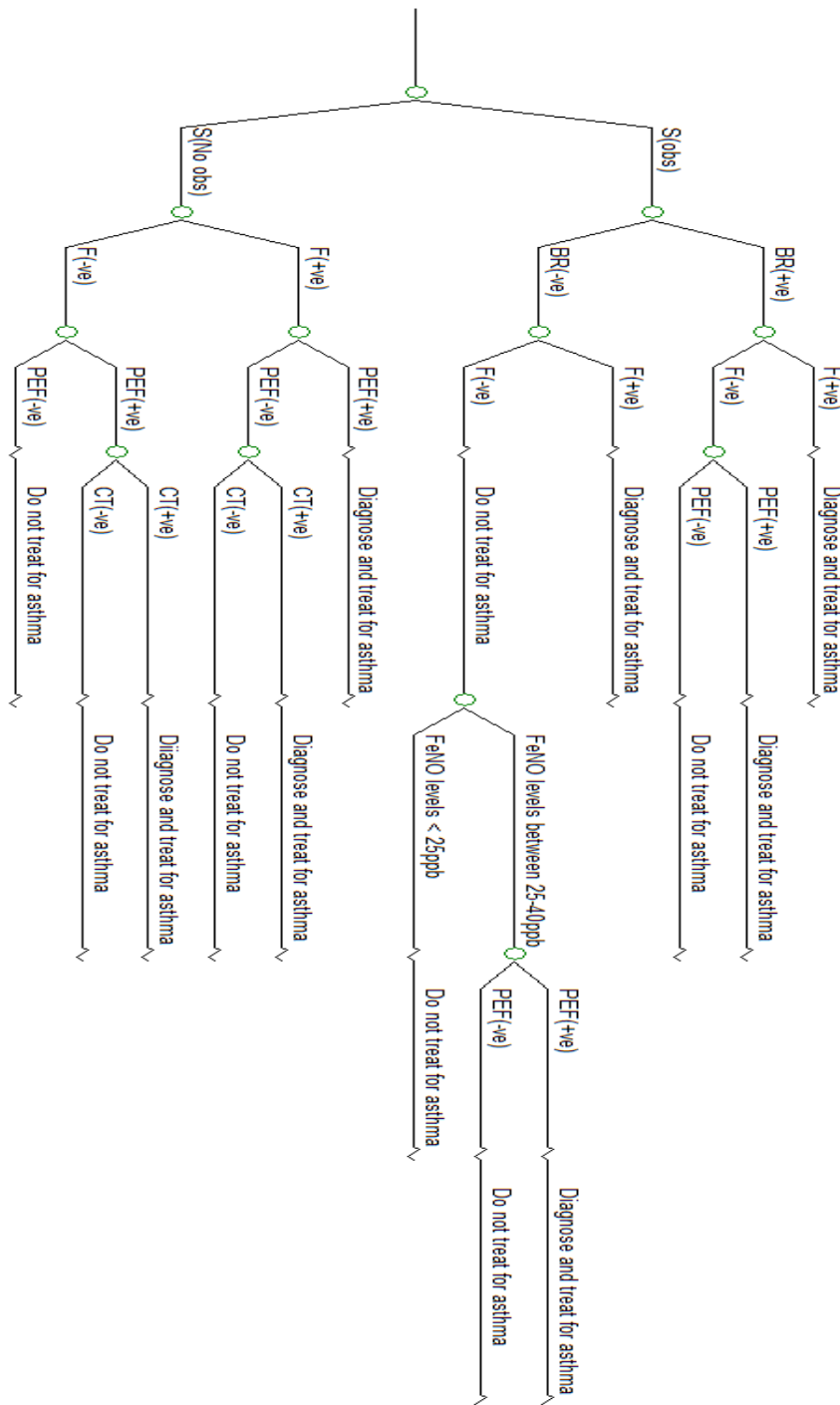


2
 3 *(-ve): negative; (+ve): positive; BDR: bronchodilator reversibility test; F: FeNO; S: spirometry; (Obs): obstruction;*
 4 *PEF: peak expiratory flow variability*

5 **Strategy 3**

6 The third strategy uses spirometry, bronchodilator reversibility, FeNO, PEF variability and a
 7 methacholine challenge test (CT). The diagnostic pathway is shown in Figure 303. Note in this
 8 pathway challenge tests are only used on patients who have a non-obstructive spirometry.

1 **Figure 303: Strategy 3**

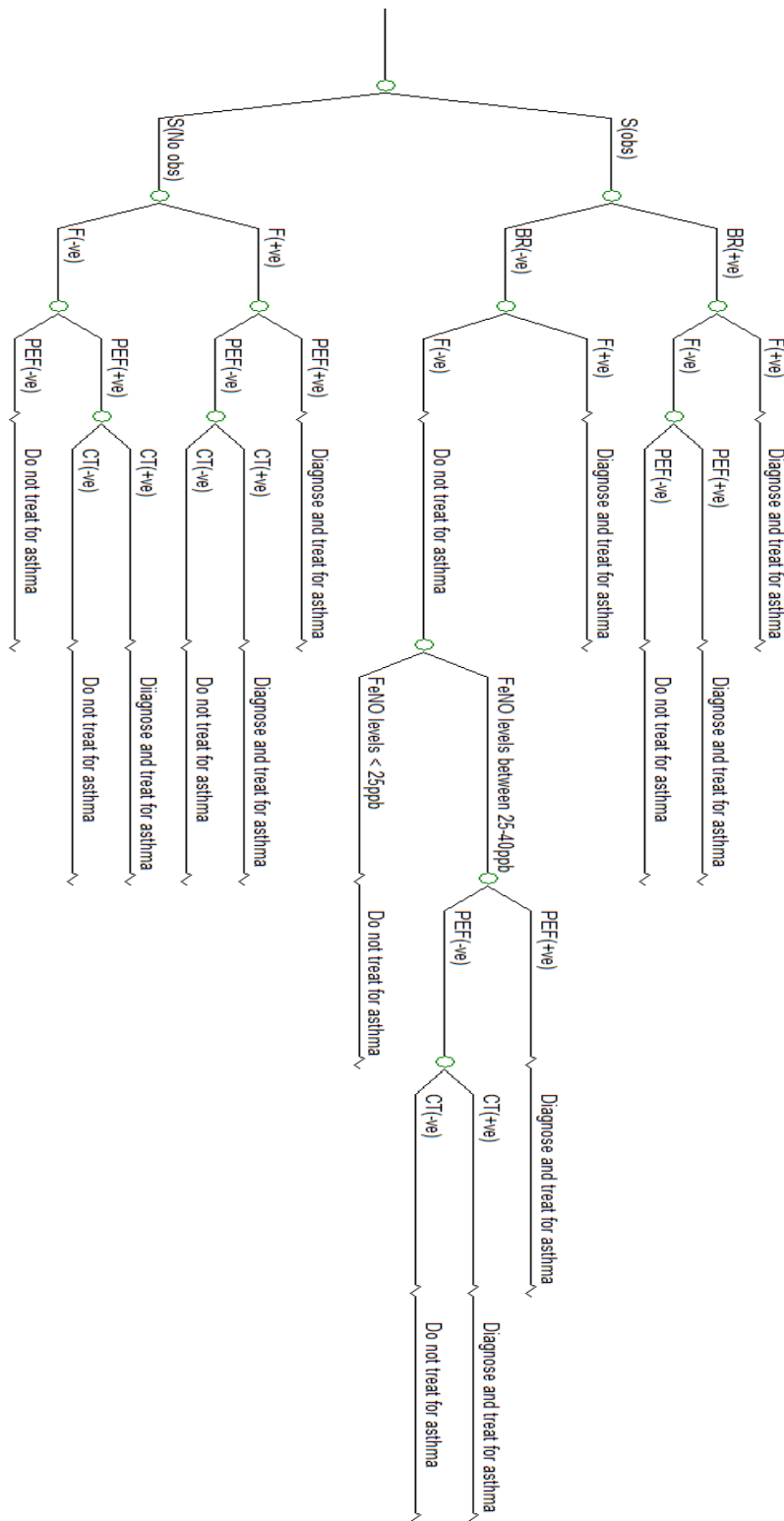


2
3 (-ve): negative; (+ve): positive; BDR: bronchodilator reversibility test; CT: challenge test; F: FeNO; S: spirometry;
4 (Obs): obstruction; PEF: peak expiratory flow variability

5 **Strategy 4**

6 The fourth strategy shown in Figure 304 expands the use of challenge tests as seen in strategy 3. Now
7 a CT is also conducted on patients with a positive BDR, negative FeNO and a negative PEFv result. The
8 use of FeNO levels is also taken into account, whereby a CT is only conducted in this arm when FeNO
9 levels are between 25-40ppb.

1 **Figure 304: Strategy 4**

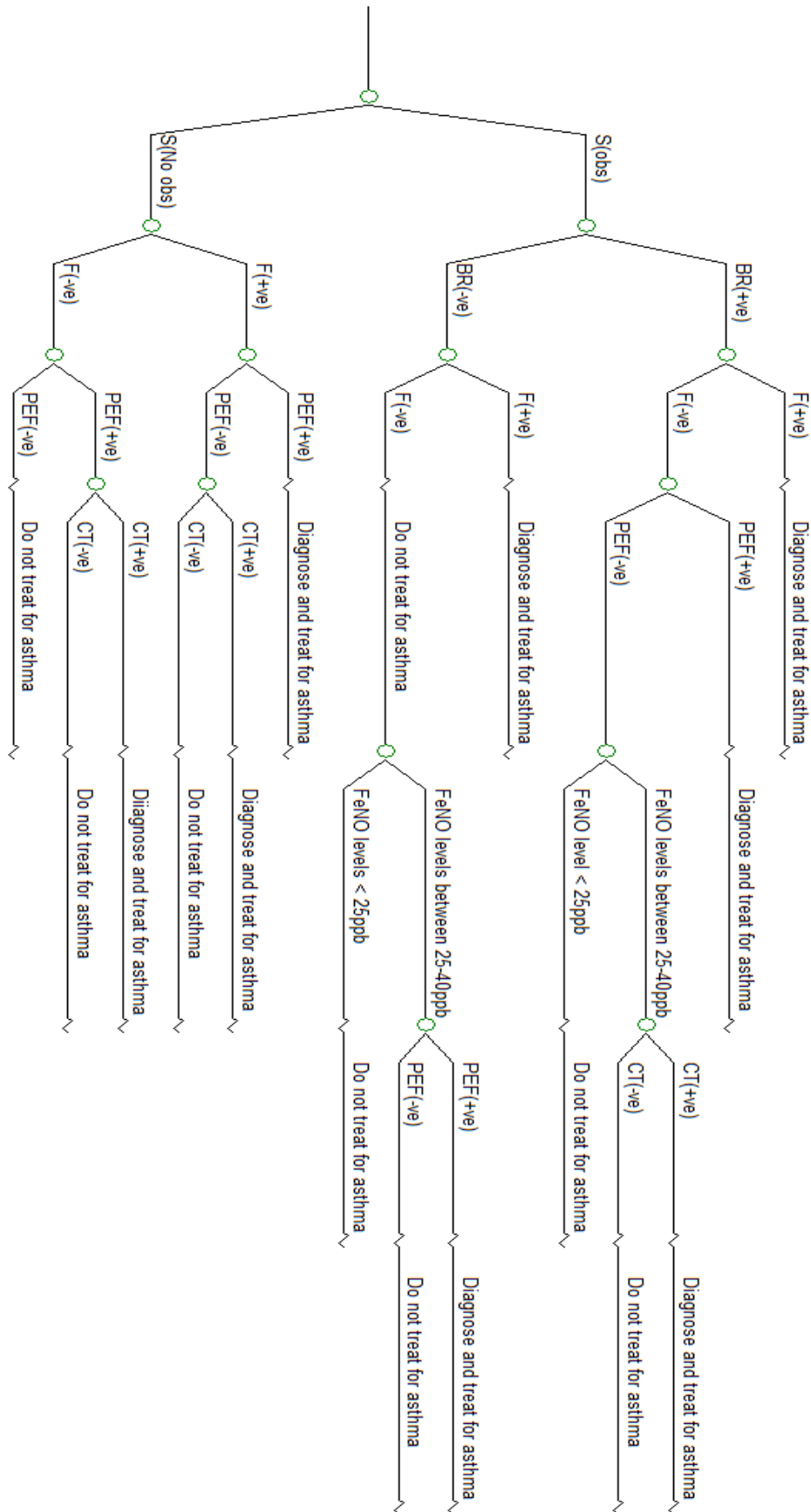


- 2
- 3 *(-ve): negative; (+ve): positive; BDR: bronchodilator reversibility test; CT: challenge test; F: FeNO; S: spirometry;*
- 4 *(Obs): obstruction; PEF: peak expiratory flow variability*

1 **Strategy 5**

2 The fifth strategy, shown below in Figure **305**, also expands the use of challenge tests, as seen in
3 strategy 3, however places the additional CT at a different point in the pathway. Now a CT is also
4 conducted on patients with a negative BDR, negative FeNO (between 25-40ppb) and a negative PEFv
5 test result.

1 **Figure 305: Strategy 5**



2

1 Strategy 7

2 A final strategy considered involves not giving the patient any tests and diagnosing without the use of
 3 objective tests. To make this strategy more reflective of current practice it is assumed that some of
 4 the non-asthmatics will be correctly diagnosed as not having asthma. One prevailing thought is that
 5 one third of people currently diagnosed with asthma are misdiagnosed, ie they do not have asthma
 6 (False positive) according to a study by Aaron et al^{6,6}. Therefore the proportion of false positives
 7 calculated in this strategy will be a third of the total number of positive diagnoses made:

$$\frac{\text{False positives}}{\text{False positives} + \text{True positives}} = \frac{1}{3}$$

8 As no tests are conducted the only costs that are incurred in this strategy are those that occur after
 9 the diagnosis is made (e.g. the cost of asthma treatment). An assumption was made that all people
 10 with asthma are correctly diagnosed giving this strategy a sensitivity of 100%.

11 M.2.1.2 Population

12 The model considers patients over 16 years of age who present symptoms of asthma to their GP.
 13 Patients who present symptoms in a secondary care setting are not considered.

14 A separate analysis was considered for children between 5 – 16 years of age. However there were no
 15 included studies in the clinical review which identified the diagnostic accuracy of bronchodilator
 16 reversibility in this age group. As this test would appear in all diagnostic pathways its diagnostic
 17 accuracy would highly influence which pathway is cost-effective. On top of this, the evidence found
 18 for the diagnostic accuracies of other tests on children was weak.

19 M.2.1.3 Time horizon, perspective, discount rates used

20 The analysis follows the standard assumptions of the reference case including discounting at 3.5% for
 21 costs and health effects, and incremental analysis is conducted. A sensitivity analysis using a
 22 discount rate of 1.5% for costs and 1.5% for health benefits is conducted. A lifetime horizon has been
 23 chosen to fully capture the long-term adverse outcome derived from incorrect diagnosis.

24 M.2.2 Approach to modelling

25 The model is based on two parts:

- 26 • **Decision tree** - Using the sensitivity and specificity, combined with data on the prevalence of
 27 asthma in the defined population, the model identifies the proportion of patients that receive a
 28 true positive (TP), true negative (TN), false positive (FP) or false negative (FN) diagnosis.
- 29 • **Markov model** - Once the diagnosis is made the patient moves on to the second part of the
 30 model which involves a Markov model to fully evaluate the patients' health and cost outcomes.

31 Further information and technical details are provided below.

32 M.2.2.1 Model structure

33 Diagnostic pathways (decision tree)

34 First of all patients go through a decision tree to calculate the proportion that will receive either a
 35 FN, FP, TN or TP diagnosis. The way this is calculated is shown below in Figure 304. Here strategy 1 is
 36 used as an example (detailed in **Figure 301** above).

37 In Figure 304 below the circles represent chance nodes. This means that the outcome is determined
 38 by a probability, rather than a decision. When the patient enters the model, they have a probability

1 of having asthma or not, depending on the asthma prevalence in the defined population. If the
2 patient has asthma then the probability of a test result being positive is determined by the sensitivity
3 of that test. If the patient does not have asthma then the probability of the test result being negative
4 is determined by the specificity of that test. Using these probabilities the decision tree can calculate
5 the proportion of patients that will end up at each arm. For example the probability of an asthmatic
6 patient having an obstructive spirometry and a positive result from a bronchodilator reversibility test
7 is:

$$\begin{aligned} & \textit{Probability}(\textit{Asthma} \cap \textit{S}(\textit{Obs}) \cap \textit{BDR}(+ve)) \\ & = (\textit{Probability of having asthma}) * (\textit{Sensitivity of spirometry}) \\ & \quad * (\textit{Sensitivity of bronchodilator reversibility}) \end{aligned}$$

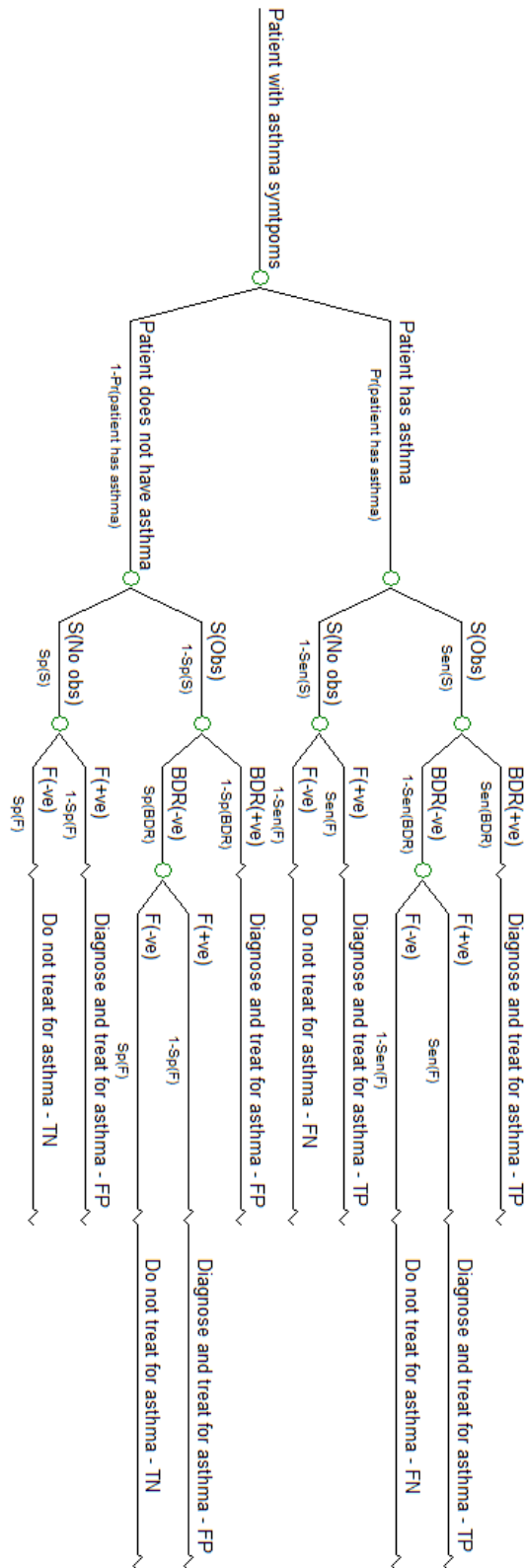
8 In this case the patient will receive a true positive diagnosis. Likewise the probability of a non-
9 asthmatic having an obstructive spirometry and a positive BDR result is:

$$\begin{aligned} & \textit{Probability}(\textit{No Asthma} \cap \textit{S}(\textit{Obs}) \cap \textit{BDR}(+ve)) \\ & = (\textit{Probability of not having asthma}) * (1 - \textit{Specificity of spirometry}) * (1 \\ & \quad - \textit{specificity of bronchodilator reversibility}) \end{aligned}$$

10 In this case the patient will receive a false positive diagnosis.

11 Once the proportion of patients that will receive either a TP, TN, FP or FN diagnosis is calculated, final
12 health and cost outcomes are determined by a Markov model which is discussed below.

1 **Figure 307: Calculating patient movement through the model**



2
3 (-ve): negative; (+ve): positive; BDR: bronchodilator reversibility test;; F: FeNO; S: spirometry; (Obs): obstruction;
4 Sen: sensitivity; Sp: specificity; TP: True positive; FP: false positive; FN: False negative; TN: True negative.

5

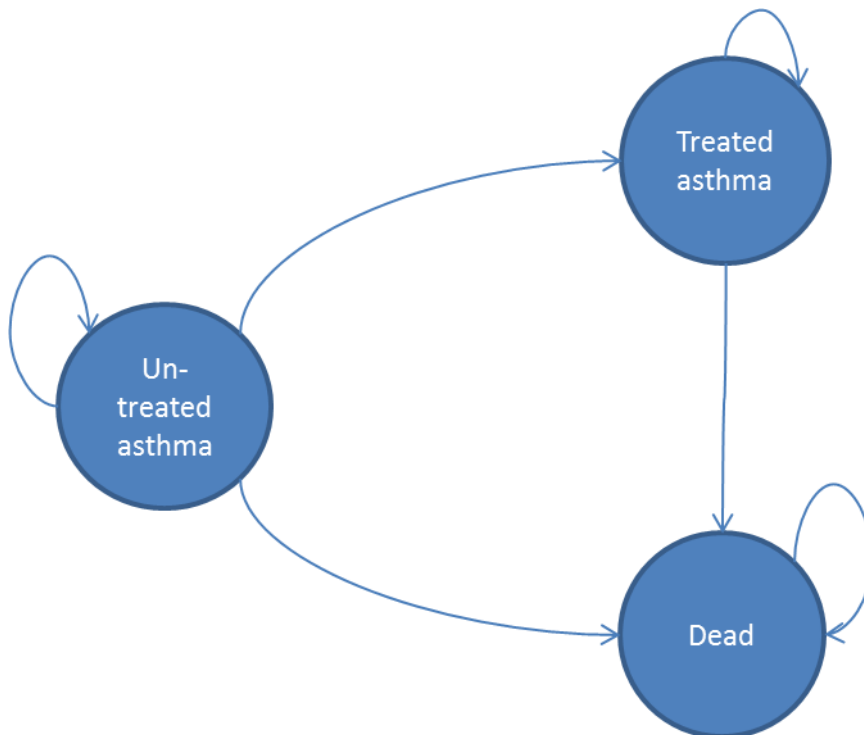
1 **Calculating health and cost outcomes after diagnosis for patients who have asthma (Markov model)**
2

3 The decision tree will determine the proportion of people with asthma that receive a correct
4 diagnosis (true positive) and that receive an incorrect diagnosis (false negative).

5 *False negatives*

6 After a false negative diagnosis is made the patient enters the Markov model depicted in Figure 308.

7 **Figure 308: Markov model for false negative diagnoses**



8
9 The patient starts in the state 'un-treated asthma'. After a cycle length of six months there is a
10 probability that the false negative diagnosis will be rectified and the patient will be treated for
11 asthma. This probability is determined by whether or not the patient has an exacerbation. It is
12 assumed that after an exacerbation the patient will be correctly re-diagnosed as having asthma. In
13 this case the patient is treated and moves from 'un-treated asthma' to 'treated asthma'. After one
14 year has passed the patient will move to treated asthma, regardless of whether they have had an
15 exacerbation, and a re-diagnosis cost is added. This is to reflect that a patient with un-treated asthma
16 will have persisting symptoms and an assumption was imposed that a methacholine challenge test
17 along with a respiratory outpatient visit and persisting asthmatic symptoms would guarantee a
18 correct diagnosis at this point. The probability of the patient entering the dead state is contingent on
19 an all-cause mortality rate plus an added mortality risk associated with an exacerbation. As the
20 patient is more likely to exacerbate if they are untreated, the mortality risk is slightly higher for un-
21 treated asthmatics.

22 The costs associated with each state are discussed in section M.2.3.7. The quality of life (QoL)
23 associated with each state is discussed in section M.2.3.6.

24 *True positives*

25 After a true positive diagnosis is made the patient enters the Markov model depicted in Figure 309.

1 **Figure 309: Markov model for true positive**



2

3

4 The patient starts in the 'treated asthma' state and remains there until they die. The QoL,
5 exacerbations, and costs associated with this state are the same as those in the 'treated asthma'
6 state in Figure 308.

7

8 **Calculating health and cost outcomes after diagnosis for patients that do not have asthma (Markov**
9 **model)**

10 The decision tree will determine the proportion of non-asthmatic patients that receive a correct
11 diagnosis (true negative) and the proportion that receive an incorrect diagnosis (false positive).

12 An important aspect of the model was to consider the condition the individual is likely to have if they
13 present asthma symptoms but don't have asthma. The true underlying condition the patient has will
14 determine the length and severity of misdiagnosis. The GDG identified four sub-groups of patients
15 that would have asthmatic symptoms but not have asthma:

16 The first two subgroups of patients would have an illness that would go un-treated if an asthma
17 diagnosis were made, as the physician would believe the patient was being correctly treated. As
18 these patients would forego correct treatment then during this period of incorrect diagnosis they
19 would receive a lower quality of life, relative to what they could achieve with optimal treatment. The
20 NHS would also incur unnecessary asthma treatment costs. The GDG felt the two main groups this
21 would affect are patients with COPD or chronic heart failure. As these patients will remain
22 symptomatic after asthma treatment the probability of re-diagnosis will be high and increase over
23 time as it becomes clearer that asthma treatment is not helping the patients. It is worth noting that
24 once these patients are being correctly treated the NHS will now incur the cost of the respective
25 treatment meaning that re-diagnosis is not necessarily cost-saving.

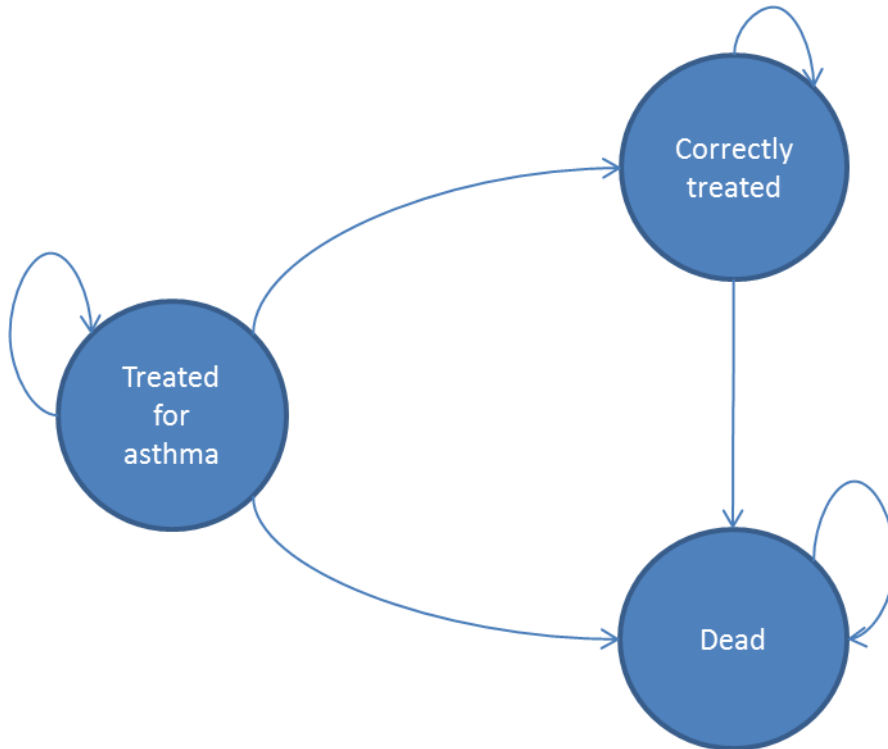
26 The third and fourth subgroups of patients would not forego any treatment because they are labelled
27 as having asthma. Therefore for these patients there is no disutility from being labelled as asthmatic;
28 instead the only disadvantage of incorrect diagnosis is that the NHS has to incur unnecessary asthma
29 treatment costs. The GDG felt the two main groups this would affect are patients with physical de-
30 conditioning or short-lived acute symptoms. Patients with short-lived acute symptoms, such as those
31 recovering from an infection, would not be on asthma medication long as they would quickly become
32 asymptomatic, naturally rather than due to medication, and stop taking asthma medication.
33 Individuals with physical de-conditioning however could remain on asthma medication for a long
34 time as they remain symptomatic but symptoms would rise and fall over time.

35 The GDG recognised that there would be other conditions that the patient could have however the
36 four outlined above would cover the majority and those not covered would produce similar
37 outcomes to those outlined above. As there is no data in the literature on the distribution of diseases
38 amongst the misdiagnosed asthmatics an assumption was made that the probability of a patient
39 having one of the above conditions was equal. This assumption, along with all data inputs used for
40 these patients, are extensively tested in the sensitivity analysis, detailed in section M.2.5.

1 **False positives**

2 After a false positive diagnosis is made the patient enters the Markov model depicted below in Figure
3 310.

4 **Figure 310: Markov model for false positives**



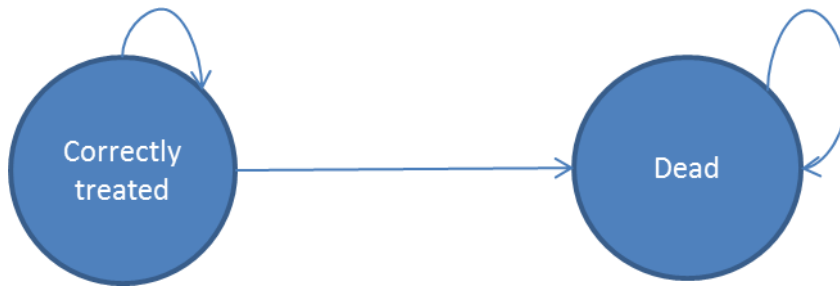
5
6 The individual starts in the state 'treated for asthma', as the individual does not have asthma this can
7 be classed as 'incorrect treatment'. After a cycle length of six months there is a probability that the
8 individual will be correctly diagnosed as not having asthma. This probability is contingent on the
9 under-lying condition the individual has. After each cycle the probability of correct diagnosis
10 increases, the extent to which also depends on the patient's underlying condition. This is to reflect
11 the fact that the longer un-treated symptoms reside the more likely the physician is to make a re-
12 diagnosis. If the individual is correctly re-diagnosed then they move to the state 'correctly treated',
13 which means they are receiving the treatment for the condition they actually have (if a treatment is
14 required), where they remain until they die. The model assumes that once asthma is excluded, the
15 real condition is diagnosed correctly. To enter the state 'correctly treated' it is assumed that a
16 patient has a respiratory outpatient visit and under-goes a methacholine challenge test to rule-out
17 the diagnosis of asthma, as this test was identified as having the highest sensitivity and specificity in
18 the clinical review. A sensitivity analysis was conducted around re-diagnosis costs as detailed in
19 section M.2.5.

20 The costs associated with each state are discussed in section M.2.3.7. The quality of life (QoL)
21 associated with each state is discussed in section M.2.3.6.

22 **True negatives**

23 After a true negative diagnosis is made the patient enters the Markov model in Figure 311.

1 **Figure 311: Markov model for true negative**



2
3
4 It is assumed that by ruling out asthma as a potential cause of symptoms the individual will start in
5 the state 'correctly treated', which means they are receiving the treatment for the condition they
6 actually have (if a treatment is required) and remain there until they die. The QoL and costs
7 associated with this state are the same as those in Figure 310.

8 **M.2.2.2 Key assumptions**

9 The key assumptions of the model are summarised in **Table 234** below:

10 **Table 234: Summary of key assumptions**

Assumption	Comment
A patient with a false negative diagnosis will always be correctly re-diagnosed after an exacerbation.	
A patient with a false negative diagnosis will remain misdiagnosed for a maximum of one year, even if an exacerbation does not occur.	
Adults correctly identified as not having asthma will either have, with equal probability: acute symptoms, physical de-conditioning, chronic heart failure or COPD.	This assumption was built into the model to address the concern that those identified as not having asthma are likely to have something else. This ensures the model gives a better reflection of the true costs and health losses incurred through misdiagnosis.
After a true negative diagnosis patients are assumed to be correctly treated for their true underlying condition.	This assumption is built on the fact that ruling out asthma as a potential cause of symptoms will help rule in the true diagnosis after further tests. The costs of these tests (such as an echocardiogram) have been excluded from the model as they will be incurred for both true negatives and false positives and therefore there will be no incremental cost.
Uncontrolled asthma was used as a proxy for untreated asthma when calculating QoL	
FeNO is conditionally independent with other tests	As FeNO is the only test in the model that measures inflammation of the airways a patient's FeNO count is unlikely to be dependent on the results of other tests. Likewise other lung function test results are unlikely to be dependent on a patient's FeNO count. Therefore this test was considered to be conditionally independent with all other tests. Further details regarding conditional independence are provided in section M.2.2.3 below.

1 M.2.2.3 Conditional dependence

2 In the clinical review, the sensitivity and specificity of each test was calculated across the whole
 3 population of interest. However, if a test is only conducted after a certain test result (for example if
 4 test 2 is only conducted following a positive result from test 1 then ideally we would use accuracy
 5 data for the second test on this sub-group of the original population. The sensitivity and specificity of
 6 a test will be different in this sub-group if the two tests (T1 and T2 in example below) are
 7 conditionally dependent. **Table 235** below shows how conditional dependence affects the probability
 8 of obtaining two test results.

9 **Table 235: Probability of obtaining two test results**

Event	Probability
Patients who have the disease	
T1(+ve) AND T2(-ve)	$Se(T1) \times (1 - Se(T2)) - \gamma_{se}$
T1(+ve) AND T2(+ve)	$Se(T1) \times Se(T2) + \gamma_{se}$
T1(-ve) AND T2(+ve)	$(1 - Se(T1)) \times Se(T2) - \gamma_{se}$
T1(-ve) AND T2(-ve)	$(1 - Se(T1)) \times (1 - Se(T2)) + \gamma_{se}$
Patients who do not have the disease	
T1(+ve) AND T2(-ve)	$(1 - Sp(T1)) \times Sp(T2) - \gamma_{sp}$
T1(+ve) AND T2(+ve)	$(1 - Sp(T1)) \times (1 - Sp(T2)) + \gamma_{sp}$
T1(-ve) AND T2(+ve)	$Sp(T1) \times (1 - Sp(T2)) - \gamma_{sp}$
T1(-ve) AND T2(-ve)	$Sp(T1) \times Sp(T2) + \gamma_{sp}$

10 *Abbreviations: Se = sensitivity; Sp = specificity; T1 = test 1; T2 = test 2; γ_{se} = sensitivity covariance; γ_{sp} = specificity covariance*

11 From **Table 235** shows that the probability of obtaining any one result is dependent on the
 12 covariance between the two sensitivities γ_{se} or specificities γ_{sp} . Assuming that tests 1 and 2 are
 13 positively correlated, the upper-limit of these co-variances can be calculated as follows:

$$\gamma_{se} = \text{MIN}(Se_1(1 - Se_2); Se_2(1 - Se_1))$$

$$\gamma_{sp} = \text{MIN}(Sp_1(1 - Sp_2); Sp_2(1 - Sp_1))$$

14 where MIN is a function which selects the minimum value between those listed.

15 This limit ensures the probability of obtaining two test results is bounded between zero and one.
 16 Therefore the covariance must fall between zero and this upper limit. If a test result is highly
 17 dependent on a previous test result then the covariance is likely to fall closer to the upper limit. If the
 18 result of the second test is fairly independent from the result of the first test then the covariance will
 19 be closer to zero. This method is outlined in full in Gardener et al^{551,551}.

20 For the model the GDG were asked to give their opinion on how strongly they believed the
 21 conditional dependence between two tests were. Tests that were weakly dependent were given a
 22 covariance value closer to zero; tests that were moderately dependent were given a value midway
 23 between zero and the upper limit. The results are shown in **Table 236**. Some points to note:

- 24 • FeNO does not appear as it was assumed to be conditionally independent with the other tests.
- 25 • The diagnostic review on bronchodilator reversibility was assessed in patients that had an
 26 obstructive spirometry therefore conditional dependence will have already been taken into
 27 account between those two tests.
- 28 • The conditional dependence between spirometry and other tests has not been considered as the
 29 GDG agreed that other test results are unlikely to be dependent on the results from a single
 30 spirometry.

- 1 • Finally it is assumed that the dependence between tests will be the same for individuals with and
 2 without asthma. Therefore the strength of dependence applies equally to specificities and
 3 sensitivities.

4 **Table 236: Strength of dependence between tests**

Test 1	Test 2	Strength of dependence (value given between 0 and 1)	Source
Bronchodilator reversibility	PEFv	Weak (0.1)	GDG opinion
PEFv	Histamine/Methacholine	Moderate (0.5)	GDG opinion
Bronchodilator reversibility	Histamine/Methacholine	Moderate (0.5)	GDG opinion

5 *Abbreviations: PEFv= Peak expiratory flow variability*

6 Using this information and the formulas in **Table 235** the sensitivity and specificity of tests which
 7 occur further down the pathway can be re-calculated to account for conditional dependence. For
 8 example the specificity of test 2 for patients without asthma who test positive for test 1 is:

$$Sp_2 = \frac{\text{Probability}(T1_{+ve} \cap T2_{-ve})}{Sp_1}$$

9 Using the formula for $\text{Probability}(T1_{+ve} \cap T2_{-ve})$ from **Table 235** and results from **Table 236** we
 10 know:

$$\text{Probability}(T1_{+ve} \cap T2_{-ve}) = (1 - Sp_1)(Sp_2) - \{(\gamma_{sp}) * (\text{Strength of dependence})\}$$

11 Here 'strength of dependence' lies between zero and one.

12 Although conditional dependence has been incorporated into the model not every dependency has
 13 been accounted for. As challenge tests are incorporated last in the diagnostic pathway they will have
 14 the most dependencies between tests. In the model conditional dependence has not been fully
 15 incorporated for challenge test results that are dependent on more than one test result. In some
 16 circumstances a challenge test will be dependent on the results from a PEFv test and a BDR test. An
 17 assumption was made that if a challenge test proceeds a BDR and PEFv test then the conditional
 18 dependence will only be taken into account between the BDR test and the challenge test. Rather
 19 than formally model three way dependencies, this issue has been examined in a sensitivity analysis
 20 detailed in section M.2.5.

21 M.2.2.4 Uncertainty

22 The model was built probabilistically to take account of the uncertainty around input parameter
 23 point estimates. A probability distribution was defined for each model input parameter. When the
 24 model was run, a value for each input was randomly selected simultaneously from its respective
 25 probability distribution; mean costs and mean QALYs were calculated using these values. The model
 26 was run 5,000 times for the base case.

27 **Table 237: Description of the type and properties of distributions used in the probabilistic**
 28 **sensitivity analysis**

Parameter	Type of distribution	Properties of distribution
Specificity	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified r and n values were calculated as follows:

Parameter	Type of distribution	Properties of distribution
		$r = (\text{True negatives})$ $n = (\text{Number of patients}) - (\text{True negatives})$
Diagnostic Odds ratio (DOR) ^a	Normal	Derived from: Mean = $\ln(\text{DOR})$ Standard error = $\text{Se}(\ln(\text{DOR}))$
Exacerbation rate	Log-normal	Derived from the mean and standard deviation
Utility, asthma prevalence, transition probabilities, covariance strength	Beta	Bounded between 0 and 1. Derived from mean of a domain and its standard error, using the method of moments. Alpha and beta values were calculated as follows: $\text{Alpha} = \text{mean}^2 * [(1 - \text{mean}) / \text{SE}^2] - \text{mean}$ $\text{Beta} = \text{Alpha} * [(1 - \text{mean}) / \text{mean}]$
NHS Reference Costs, test costs	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and lambda values were calculated as follows: $\text{Alpha} = (\text{mean} / \text{SE})^2$ $\text{Lambda} = \text{SE}^2 / \text{Mean}$

1 Note: When the standard error (SE) is not given an assumption was imposed that the SE is 20% of the mean.

2 a) The use of the diagnostic odds ratio is discussed in section M.2.3.3

3 In addition, various deterministic sensitivity analyses were undertaken to test the robustness of
 4 model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate
 5 the impact on results and whether conclusions on which intervention should be recommended
 6 would change.

7 As sensitivities were estimated as functions of other variables, no distributions were attached to
 8 these parameters.

9 M.2.3 Model inputs

10 M.2.3.1 Summary table of model inputs

11 Model inputs were based on clinical evidence identified in the systematic review undertaken for the
 12 guideline, supplemented by additional data sources as required. Model inputs were validated with
 13 clinical members of the GDG. A summary of the model inputs used in the base-case (primary)
 14 analysis is provided in Table 238 below. More details about sources, calculations and rationale for
 15 selection can be found in the sections following this summary table.

16 **Table 238: Summary of base-case model inputs**

Input	Input	Source
Probability patient is male (adult)	0.40	Weighted average from the diagnostic studies identified in the clinical review
Patient age at diagnosis (adult)	43	Weighted average from the diagnostic studies identified in the clinical review
Time horizon	Lifetime	
Discount rate	Costs = 3.5%; effects = 3.5%	

1

Table 239: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Decision tree probabilities				
Prevalence of asthma	0.406	Beta	$\alpha = 606, \beta = 887$	<i>Taken from a meta-analysis of the diagnostic studies identified in the clinical review, see section (A.2.3.2)</i>
Sensitivity of spirometry	0.465	-	-	Pino 1996 ^{1365,1365}
Specificity of spirometry	0.415	Beta	$r = 17, n = 41$	Pino 1996 ^{1365,1365}
Ln(Diagnostic odds ratio for spirometry)	-0.485	Normal	$\mu = -0.485, \sigma = 0.44$	<i>Derived from sensitivity and specificity, see section M.2.3.3</i>
Sensitivity of BDR used in model	0.409	<i>Distributions were fitted directly on the parameters</i>	-	Pooled average from Kim 2012 ^{870,873} and Chhabra 2012 ^{313,313} below
Specificity of BDR used in model	0.713	<i>derived from each of the two studies and in each iteration the pooled average was calculated from the individual parameters.</i>	-	Pooled average from Kim 2012 and Chhabra 2012 ^{313,313} - see below
Sensitivity of BDR (Chhabra 2012)	0.65	-	-	Chhabra 2012 ^{313,313}
Specificity of BDR (Chhabra 2012)	0.811	Beta	$r = 125, n = 154$	Chhabra 2012 ^{313,313}
Ln(Diagnostic odds ratio for BDR) (Chhabra 2012)	2.08	Normal	$\mu = 2.08, \sigma = 0.25$	<i>Derived from sensitivity and specificity, section M.2.3.3</i>
Sensitivity of BDR (Kim 2012)	0.168	-	-	Kim 2012 ^{870,873}
Specificity of BDR (Kim 2012)	0.614	Beta	$r = 89, n = 145$	Kim 2012 ^{870,873}
Ln(Diagnostic odds ratio for BDR) (Kim 2012)	-1.14	Normal	$\mu = -1.14, \sigma = 0.22$	<i>Derived from sensitivity and specificity, section M.2.3.3</i>
Sensitivity of FeNO	0.88	-	-	Kowal 2009 ^{924,924}
Specificity of FeNO	0.83	Beta	$R = 299, n = 362$	Kowal 2009 ^{924,924}
Ln(Diagnostic odds ratio for FeNO)	3.57	Normal	$\mu = 3.57, \sigma = 0.27$	<i>Derived from sensitivity and specificity, section M.2.3.3</i>
Sensitivity of PEFv	0.116	-	-	Thiadens 1998 ^{1746,1746}
Specificity of PEFv	0.99	Beta	$R = 100, n = 101$	Thiadens 1998 ^{1746,1746}
Ln(Diagnostic odds ratio for PEFv)	2.57	Normal	$\mu = 2.57, \sigma = 1.07$	<i>Derived from sensitivity and specificity, section M.2.3.3</i>
Sensitivity of histamine challenge test	0.933	-	-	Kowal 2009 ^{924,924}

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Specificity of histamine challenge test	0.99 ^(a)	Beta ^(a)	R = 358, n =362	Kowal 2009 ^{924,924}
Ln(Diagnostic odds ratio for histamine challenge test)	8.52	Normal	$\mu = 8.52, \sigma = 1.05$	<i>Derived from sensitivity and specificity, section M.2.3.3</i>
Mean FeNO level for an asthmatic	96	Lognormal	$\mu = 4.32, \sigma = 0.52$	<i>See section M.2.3.3 for derivation</i>
Probability that FeNO level < 25ppb for a patient with asthma and a FeNO below 40ppb	0.142	-	-	<i>Derived from the distribution around the mean FeNO level for patients with asthma</i>
Mean FeNO level for a non-asthmatic	25	Lognormal	$\mu = 2.77, \sigma = 0.94$	<i>See section M.2.3.3 for derivation</i>
Probability that FeNO level < 25ppb for a patient without asthma and a FeNO level below 40ppb	0.823	-	-	<i>Derived from the distribution around the mean FeNO level for patients without asthma</i>
Strength of dependence between BDR and PEFv	0.1	Beta	$\alpha = 6.11, \beta = 54.96$	GDG opinion
Strength of dependence between PEFv and histamine/methacholine	0.5	Beta	$\alpha = 85.7, \beta = 85.7$	GDG opinion
Strength of dependence between BDR and histamine/methacholine	0.5	Beta	$\alpha = 85.7, \beta = 85.7$	GDG opinion
Proportion of non-asthmatic patients that have acute symptoms	0.25	Beta ^(c)	$\alpha = 78.16, \beta = 233.8$	GDG opinion
Proportion of non-asthmatic patients that have physical de-conditioning	0.25	Beta ^(c)	$\alpha = 78.16, \beta = 233.8$	GDG opinion
Proportion of non-asthmatic patients that have heart failure	0.25	Beta ^(c)	$\alpha = 78.16, \beta = 233.8$	GDG opinion
Proportion of non-asthmatic patients that have COPD	0.25	Beta ^(c)	$\alpha = 78.16, \beta = 233.8$	GDG opinion
Utility weights				
QoL increase from asthma treatment	0.0443	Beta	$\alpha = 23.86, \beta = 518.33$	McTaggart et al ¹¹²⁵
Disutility from severe exacerbation	0.56	Beta	$\alpha = 0.91, \beta = 71$	Lloyd et al ^{1033,1033}
Duration of severe exacerbation (in years)	0.08	Gamma	$\alpha = 19.26, \lambda = 246.34$	Harnan 2014 ⁶⁴⁴
Disutility from non-severe exacerbation	0.32	Beta	$\alpha = 0.537, \beta = 1.14$	Lloyd et al ^{1033,1033}
Duration of non-severe exacerbation (years)	0.01	Gamma	$\alpha = 82.9, \lambda = 8259$	Harnan 2014 ⁶⁴⁴
QoL increase for a mild severity COPD patient being correctly treated for COPD as	0.045	Beta	$\alpha = 23.83, \beta = 505.73$	Spencer et al ^{1657,1657}

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
opposed to asthma.				
QoL increase for a moderate severity COPD patient being correctly treated for COPD as opposed to asthma.	0.025	Beta	$\alpha = 24.35, \beta = 949.65$	Spencer et al ^{1657,1657}
QoL increase for a heart failure patient being correctly treated for heart failure as opposed to asthma.	0.098	Beta	$\alpha = 22.45, \beta = 206.65$	Gohler et al ^{581,581}
Cost (£)^(b)				
Cost of hospitalised exacerbation	£873.75	Gamma	$\alpha = 25, \lambda = 0.028$	NHS reference costs ⁴²⁵ (weighted average of HRG codes DZ15H, DZ15J, DZ15K, DZ15L)
Cost of non-hospitalised exacerbation	£38.33	Gamma	$\alpha = 25, \lambda = 0.65$	PSSRU ^{386,386} , NHS drug tariff ¹²³⁰
Cost of spirometry	£16.86	Gamma	$\alpha = 100, \lambda = 5.93$	GDG opinion, PSSRU ^{386,386} , NHS supply catalogue ⁴²⁶
Cost of BDR	£26.16	Gamma	$\alpha = 100, \lambda = 3.82$	GDG opinion, PSSRU ^{386,386} , NHS supply catalogue ⁴²⁶
Cost of FeNO	£13.66	Gamma	$\alpha = 100, \lambda = 4.23$	GDG opinion, PSSRU ^{386,386} , NHS supply catalogue ⁴²⁶
Cost of PEF	£21.08	Gamma	$\alpha = 100, \lambda = 4.74$	GDG opinion, PSSRU ^{386,386} , NHS supply catalogue ⁴²⁶
Cost of histamine/methacholine challenge test	£162.50	-	-	GDG opinion, NHS reference costs ⁴²⁵
Cost of Bronchial Challenge Studies, HRG code: DZ36Z	£102	Lognormal	$\alpha = 25, \lambda = 0.2451$	NHS reference costs ⁴²⁵
Cost of respiratory outpatient visit	£150.22	Gamma	$\alpha = 100, \lambda = 0.6657$	NHS reference costs ⁴²⁵
Cost of GP appointment	£37	-	-	PSSRU ^{386,386}
Cost of annual asthma management	£290.00	Gamma	See Table 253	Price et al ^{1401,1403}
Cost of annual asthma management for patients without asthma but who have acute symptoms	£180.00	Gamma	See Table 253	Price et al ^{1401,1403}
Cost of annual asthma management for patients without asthma but who have chronic symptoms	£248.91	Gamma	See Table 253	Price et al ^{1401,1403}
Annual cost of COPD management for moderate severity	£307.74	Gamma	$\alpha = 25, \lambda = 0.08$	NICE 2010 COPD guideline ¹²¹³
Annual cost of COPD	£149.68	Gamma	$\alpha = 25, \lambda = 0.17$	NICE 2010 COPD

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
management for mild severity				guideline (CG101) ¹²¹³
Cost of heart failure treatment	£135	Gamma	$\alpha = 25, \lambda = 0.19$	NICE 2014 Acute heart failure guideline (CG187) ¹²¹⁴
Transition probabilities for Markov model and mortality adjustments				
Annual exacerbation rate for un-treated asthmatics	1.02	Lognormal	$\mu = 0.02, \sigma = 0.1$	Harnan 2014 ⁶⁴⁴
Annual exacerbation rate for treated asthmatics	0.42	Lognormal	$\mu = -0.87, \sigma = 0.2$	Shaw et al ^{1574,1574}
Probability of exacerbation for un-treated asthmatic per cycle	40%	-	-	<i>Derived from the exacerbation rate for un-treated asthmatics. See section (M.2.4)</i>
Probability of exacerbation for un-treated asthmatic per cycle	19%	-	-	<i>Derived from the exacerbation rate for un-treated asthmatics. See section (M.2.4)</i>
Proportion of exacerbations that are hospitalised	2.7%	Beta	$R = 40,243, n = 1474698$	See section (M.2.3.6) for derivation and source input
Probability of death after hospitalisation	0.41%	Beta	$R = 165, n = 40,243$	National review of asthma deaths 2014 ¹⁴⁸⁸
Probability of correct re-diagnosis for patients with acute symptoms in 6 months	20%	Beta	$\alpha = 21.87, \beta = 87.47$	GDG opinion, see section M.2.3.5 for further details.
Probability of correct re-diagnosis for patients with physical de-conditioning in 6 months	1%	Beta	$\alpha = 0.06, \beta = 5.77$	GDG opinion, see section M.2.3.5 for further details.
Probability of correct re-diagnosis for patients with moderate COPD in 6 months	20%	Beta	$\alpha = 21.87, \beta = 87.47$	GDG opinion, see section M.2.3.5 for further details.
Probability of correct re-diagnosis for patients with mild COPD in 6 months	10%	Beta	$\alpha = 6.11, \beta = 55$	GDG opinion, see section M.2.3.5 for further details.
Probability of correct re-diagnosis for patients with heart failure in 6 months	30%	Beta	$\alpha = 21.87, \beta = 87.47$	GDG opinion, see section M.2.3.5 for further details.
Absolute probability increase of correct re-diagnosis after each 6-month cycle for patients with acute symptoms	20%	Beta	$\alpha = 21.87, \beta = 87.47$	GDG opinion, see section M.2.3.5 for further details.
Absolute probability increase of correct re-diagnosis after each 6-month cycle for patients with physical de-conditioning	0.5%	Beta	$\alpha = 0.01, \beta = 2.42$	GDG opinion, see section M.2.3.5 for further details.
Absolute probability increase of correct re-diagnosis after	20%	Beta	$\alpha = 21.87, \beta = 87.47$	GDG opinion, see section M.2.3.5 for

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
each 6-month cycle for patients with moderate COPD				further details.
Absolute probability increase of correct re-diagnosis after each 6-month cycle for patients with mild COPD	5%	Beta	$\alpha = 1.59, \beta = 30.17$	GDG opinion, see section M.2.3.5 for further details.
Absolute probability increase of correct re-diagnosis after each 6-month cycle for patients with heart failure	20%	Beta	$\alpha = 21.87, \beta = 87.47$	GDG opinion, see section M.2.3.5 for further details.
Hazard ratio of mortality for COPD patient	1.28	Lognormal	$\mu = 0.247, \sigma = 0.064$	Diaz-Guzman et al ⁴³⁸
Hazard ratio of mortality for patient with physical de-conditioning	1.18	Lognormal	$\mu = 0.166, \sigma = 0.028$	Flegal 2013 ^{503,503}
Hazard ratio of mortality for patient with chronic heart failure	2.1	Lognormal	$\mu = 0.742, \sigma = 0.103$	Mosterd 2001 ^{1183,1183}

Abbreviations: BDR: bronchodilator reversibility; FeNO: fractional exhaled nitric oxide; PEF: peak expiratory flow variability

(a) This study found that the specificity of histamine and methacholine challenge tests were 100%. However the GDG agreed that there is no perfect test so this value was reduced to 99% to reflect the high specificity but allowing some scope for error. This assumption was also incorporated into the beta distribution by changing the number of true negatives to achieve a specificity of 99%.

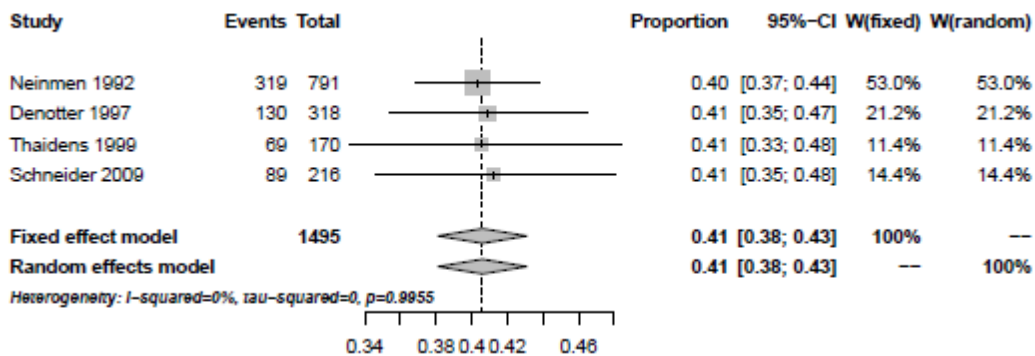
(b) These are costs of the tests as they appear in the pathway rather than the cost of conducting the test independently

(c) To ensure these values sum to one once a value has been chosen from each distribution the probability of having a particular disease becomes: $Prob(disease A) = Prob(disease A) / \sum Prob(disease_n)$ where each probability is taken from its respective beta distribution.

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11 M.2.3.2 Initial cohort settings

12 The initial cohort settings were derived from information given in the studies included in our clinical
13 review of diagnostic accuracy studies. The prevalence of asthma was obtained from a meta-analysis
14 of all the included diagnostic studies which looked at the model's defined population. Ideally
15 prevalence would be based only on UK studies, however no UK studies were included in the clinical
16 reviews. To obtain a prevalence estimate applicable to the population in the model a few exclusion
17 criteria were imposed. Firstly studies were excluded which only looked at children or looked at both
18 adults and children and did not separate out the results. The prevalence of asthma is likely to deviate
19 significantly between adults and children and therefore including child studies could bias the
20 prevalence, most likely upwards. Secondly studies were included only if the inclusion criteria for
21 patient entry into the study were patients presenting symptoms of asthma. For example if only
22 patients with a normal spirometry were allowed to enter the study then the prevalence of asthma
23 would fall as a significant portion of asthmatics have an obstructive spirometry. Finally as no study
24 was conducted in the UK the GDG felt that studies which were conducted in Northern Europe, North
25 America, Australia and New Zealand would give a better indication of asthma prevalence in the UK.
26 Therefore studies outside of these areas were excluded when calculating asthma prevalence. The
27 resulting meta-analysis is shown below in Figure 312 was based on four studies^{422,1535,1747}.

1 **Figure 312: Meta-analysis for asthma prevalence**

2

3 The majority of excluded studies had a lower prevalence rate ranging from 20% to 37%. Three
 4 studies had a prevalence of approximately 70% however they were all in Asian countries (Japan and
 5 S. Korea). It is worth noting a paper by Morice et al found asthma prevalence to be on average 25%
 6 across 13 studies in patients with chronic cough. This paper was not used in the base case as it is not
 7 clear what the exact recruitment methods were for patients into the studies, secondly patients
 8 entering the model are likely to exhibit other asthma symptoms rather than just a chronic cough.
 9 However this study suggests that the 41% estimate produced above is unlikely to be an
 10 underestimate of asthma prevalence in the defined population.

11 This value was also tested in the sensitivity analysis detailed in section M.2.5.

12 **M.2.3.3 Diagnostic accuracies**13 *Using diagnostic odds ratios to conduct probabilistic sensitivity analysis*

14 The clinical review did not identify enough diagnostic studies to conduct meaningful diagnostic meta-
 15 analyses. Therefore, for each test included in the model the most relevant study used for the base
 16 case was identified as that which had: the correct cut-off, most relevant population and best
 17 reference standard. As there is no universally agreed reference standard for the diagnosis of asthma,
 18 the GDG agreed that an appropriate reference standard would be an objective test alongside a
 19 physician diagnosis. The bronchodilator reversibility test was the only exception where an average
 20 was taken from the two studies identified in the clinical review. The reason was that the GDG could
 21 not identify one study being more appropriate than the other, therefore an average was used in the
 22 base case and each separate set of diagnostic accuracies was used in a sensitivity analysis.

23 To account for uncertainty around diagnostic accuracies and correlation between sensitivity and
 24 specificity a joint distribution was used when making diagnostic accuracies probabilistic. The
 25 following method is outlined in Genders et al.^{554,554} First of all the diagnostic odds ratio (DOR) was
 26 calculated for the diagnostic test:

$$DOR = \frac{sensitivity}{1 - sensitivity} * \frac{specificity}{1 - specificity}$$

27 The standard error of the log DOR was calculated using the absolute values for the number of TP, TN,
 28 FP and FN:

$$SE(\ln(DOR)) = \sqrt{\frac{1}{TP} + \frac{1}{FN} + \frac{1}{TN} + \frac{1}{FP}}$$

1 Using these equations a normal distribution was fitted using the log of the DOR and the standard
 2 error of $\ln(\text{DOR})$. Once the DOR is calculated, the sensitivity can become a function of the DOR and
 3 the specificity:

$$\text{sensitivity} = 1 - \frac{\text{specificity}}{\text{specificity} + (1 - \text{specificity}) * \text{DOR}}$$

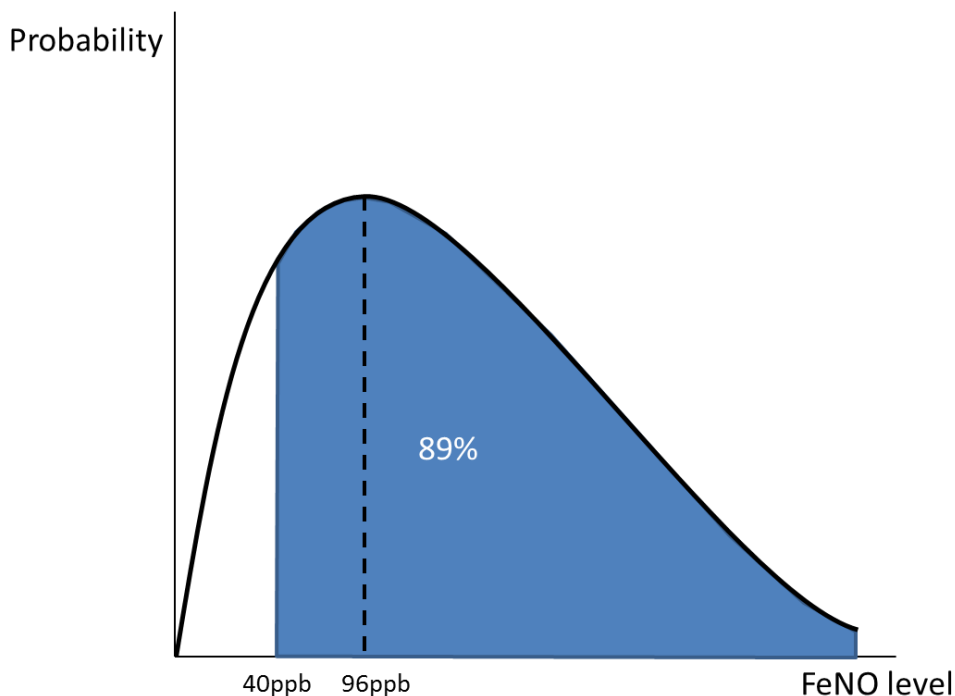
4 Finally a beta distribution was fitted around the specificity of the test, therefore when probabilistic
 5 sensitivity analysis is conducted the specificity will change in accordance to the overall diagnostic
 6 uncertainty and its relationship with the test sensitivity.

7 *Using additional cut-offs for negative FeNO results*

8 In some diagnostic strategies we had to take into account the probability of a FeNO level below
 9 25ppb together with the probability of receiving a negative FeNO result (FeNO level < 40 ppb). The
 10 GDG recognised that the lower an individual's FeNO level was the lower the probability the individual
 11 has asthma. Current guidelines¹⁵⁵² recommend that an individual with a FeNO level below 25ppb is
 12 highly unlikely to have asthma. None of the studies identified in the clinical review gave a sensitivity
 13 and specificity at 25ppb cut-off. Therefore to calculate the probability of a patient with asthma
 14 producing a FeNO level below 25ppb two pieces of information were used:

- 15 • The mean FeNO level for an asthmatic.
- 16 • The sensitivity of FeNO at a 40ppb cut-off.

17 **Figure 313: Probability distribution of FeNO levels in individuals with asthma**

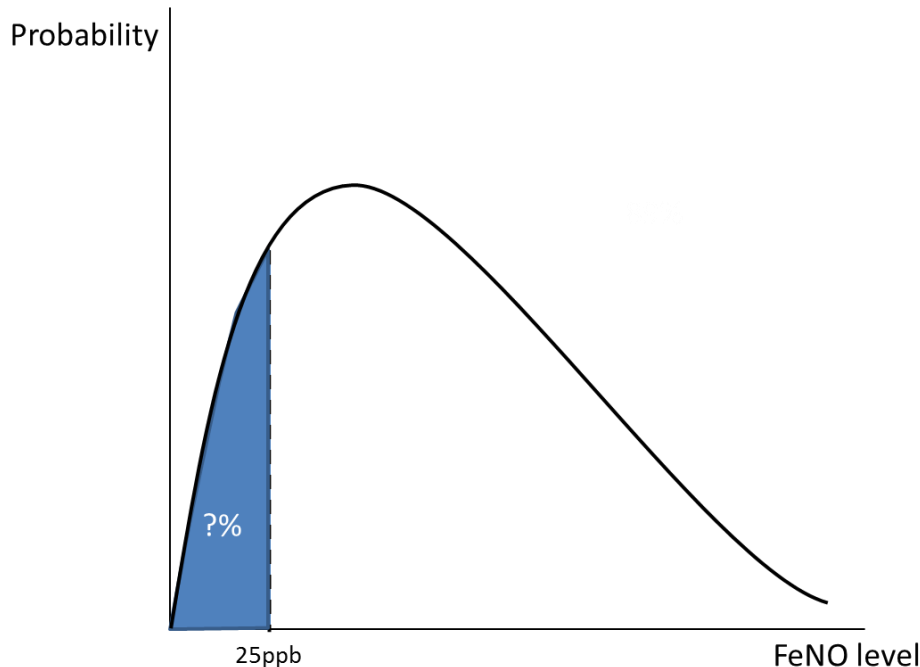


18
 19 As shown in Figure 313 above, using these two pieces of information a distribution was fitted around
 20 what FeNO level would be achieved by asthmatics. At 40ppb the sensitivity used for FeNO in the
 21 model was 89%. This means that the area under the curve highlighted in blue should equate to 89%.
 22 The mean FeNO level calculated for asthmatics in that study was 96ppb. As FeNO levels cannot go
 23 below zero a gamma and lognormal distribution were fitted to see which was more appropriate. A
 24 lognormal distribution was chosen as the gamma distribution gave a much higher probability to
 25 values close to zero whereas the lognormal gave a more even distribution amongst lower values.

1 After this distribution was fitted, the final step was to calculate the proportion of patients with
 2 asthma that would produce a FeNO level below 25ppb.

3 **Figure 314: Probability distribution of FeNO levels in individuals with asthma**

4



5

6 As shown in Figure 314 above this was done by calculating the area under the distribution that fell to
 7 the left of 25ppb.

8 The same process was then completed for patients without asthma except this time the mean FeNO
 9 level for non-asthmatics and the specificity at a 40ppb cut-off (instead of the sensitivity) were used.

10 M.2.3.4 Mortality

11 For all patients at any point in the model the probability of death is determined by an age specific all-
 12 cause mortality rate. For patients with asthma the probability of death is also dependent on the
 13 probability of having a hospitalised exacerbation and the probability of death after hospitalisation. As
 14 exacerbation rates are higher in un-treated asthmatics, the overall probability of death calculated by
 15 the model is slightly higher for un-treated asthmatics compared to treated asthmatics. For non-
 16 asthmatics correct or incorrect treatment has no differential impact on mortality. Age-specific all-
 17 cause mortality, weighted for the gender split of the cohort population, was based on the most
 18 recent available life tables for England and Wales (2012-2013)¹²⁷². For non-asthmatic conditions
 19 hazard ratios were identified in the literature for patients with: COPD, chronic heart failure and de-
 20 conditioning. In the model the hazard ratio in people with obesity is used as a proxy for physical de-
 21 conditioning.

22 M.2.3.5 Re-diagnosis and exacerbation rates

23 The transition probability of re-diagnosis was determined through GDG opinion. The transition
 24 probability for correct re-diagnosis for false negatives was calculated using an assumption whereby
 25 the probability of re-diagnosis is contingent on whether the patient has an exacerbation.

1 Exacerbation rates were taken from the clinical review conducted on monitoring asthma control. For
 2 individuals with asthma who remain untreated, due to a false negative diagnosis, the exacerbation
 3 rate was taken from Harnan et al.⁶⁴⁴ As the exacerbation rate for untreated asthma was derived
 4 mostly from assumption, due to the lack of clinical data, this value was extensively tested in a
 5 sensitivity analysis. A study by Shaw et al.^{1574,1574} was chosen to reflect the exacerbation rates of a
 6 treated asthma patient as it was the most current study conducted in a UK setting. Once the
 7 exacerbation rates had been derived these were converted into transition probabilities for the
 8 respective cycle length (6 months) before inputting into the Markov model. The above conversion
 9 was done using the following formulae:

$\text{Selected rate } (r) = \frac{-\ln(1 - P)}{t}$	Where P =probability of event over time t t =time over which probability occurs (1 year)
$\text{Transition Probability } (P) = 1 - e^{-rt}$	Where r =selected rate t =cycle length (6 months)

10 For false positives there was no clinical evidence to derive the length of time an individual would
 11 retain the incorrect asthma diagnosis for. The GDG agreed this value would vary considerably, with
 12 some individuals being re-diagnosed within the year whereas others would retain the diagnosis for
 13 the rest of their life. The GDG felt the probability of re-diagnosis would be contingent on the
 14 underlying condition causing the asthma symptoms to occur. As outlined in section M.2.2.1 four
 15 conditions were used in this model:

16 *Heart failure*

17 The GDG felt that most individuals with heart failure would be re-diagnosed within a year and a few
 18 individuals may retain an asthma diagnosis beyond two years. To achieve this, an assumption was
 19 imposed that 30% of individuals would be re-diagnosed in the first 6 months and every 6 months the
 20 probability of re-diagnosis would increase by 20 percentage points. Therefore after two and a half
 21 years no individuals with heart failure would retain an asthma diagnosis in the model.

22 *COPD*

23 Individuals with mild COPD could remain misdiagnosed with asthma for a considerable length of time
 24 and the GDG therefore gave a low probability of re-diagnosis every 6 months of 10%. Every 6 months
 25 the probability of re-diagnosis would increase by 5 percentage points as the GDG felt that eventually
 26 a re-diagnosis would occur. Individuals with moderate COPD however would be re-diagnosed much
 27 sooner as their symptoms would appear far less well managed. Therefore the probability of re-
 28 diagnosis was set to 20% each 6 months and this increased by 10 percentage points for every 6
 29 months after that.

30 *Physical deconditioning*

31 Individuals with physical deconditioning were the one group the GDG agreed that re-diagnosis may
 32 never occur. Therefore the probability of re-diagnosis was set to a low 1% each 6 months and this
 33 only increased by 0.5 percentage points for every occurring 6 months.

34 *Acute symptoms*

35 Finally the GDG felt that individuals with acute symptoms would receive a re-diagnosis very quick as
 36 symptoms would completely subside over short period of time. Therefore the probability of re-
 37 diagnosis was set to 20% each 6 months and this increased by 20 percentage points for every
 38 occurring 6 months.

39 These values were extensively tested in a sensitivity analysis detailed in section M.2.5.

1 M.2.3.6 Utilities

2 *Utility in people with asthma*

3 The QoL for patients with asthma was derived from a systematic search of the literature. Only one
4 study¹¹²⁵ measured asthma utility in a UK population using EQ-5D with UK weights, as per the NICE
5 reference case. The study details asthma utility for four levels of self-reported asthma control:
6 uncontrolled, moderately controlled, well controlled and fully controlled as shown in **Table 240**.

7 **Table 240: Quality of life and level of asthma control**

Self-reported asthma control	Utility measured using EQ-5D
Very well controlled	0.9
Well controlled	0.84
Adequately controlled	0.81
Not controlled	0.8

8 *Source: McTaggart et al (2008)¹¹²⁵*

9 It was assumed that un-treated individuals with asthma will receive a QoL equal to a person with 'not
10 controlled' asthma. Individuals that are treated for asthma will achieve a higher level of control. A
11 study by Price et al details the proportion of patients being treated for asthma in the UK that are
12 experiencing either: full control, partial control or uncontrolled asthma as shown in **Table 241**.

13 **Table 241: Levels of asthma control for treated patients with asthma**

Asthma control	Proportion
Controlled	18.2%
Partially controlled	60%
Uncontrolled	21.8%

14 *Source: Price et al^{1401,1403}*

15 The study shows that while some patients achieve full control the majority achieve either partial
16 control or remain uncontrolled. It was assumed that well controlled, detailed in **Table 240**,
17 represents the QoL for partial control, and adequate control represents the QoL for uncontrolled,
18 treated asthma. Therefore the health related quality of life (HRQoL) for treated asthmatics is:

$$\begin{aligned}
 HRQoL_{Treated} = & \text{Proportion}(\text{uncontrolled}) * HRQoL(\text{adequately controlled}) \\
 & + \text{Proportion}(\text{partial control}) * HRQoL(\text{well controlled}) \\
 & + \text{Proportion}(\text{controlled}) * HRQoL(\text{very well controlled})
 \end{aligned}$$

19 Using the information detailed above the average HRQoL for treated asthma is 0.8443. Therefore the
20 HRQoL increase for treating asthma is:

$$HRQoL_{Treated} - HRQoL(\text{not controlled}) = 0.8443 - 0.8 = 0.0443$$

21

22 *Utility of exacerbation*

23 One limitation with the EQ-5D questionnaire is that the individual is asked how their health is on that
24 specific day when the questionnaire is administered. Therefore the EQ5D score does not take into
25 account the HRQoL impact from exacerbations (if the patient had no exacerbation on that day). A
26 study by Lloyd et al^{1033,1033} derives an EQ-5D measure for exacerbations. Therefore in the model a
27 patient receives a disutility if they experience an exacerbation. The size of this disutility is determined

1 by whether the exacerbation is severe and therefore requiring hospitalisation and is weighted by the
2 duration. The disutility is shown in **Table 242**.

3 **Table 242: Disutility a patient experiences with an exacerbation**

Severity of exacerbation	Quality of life decrease during exacerbation	Duration of exacerbation (years)	Disutility (QALYs)
Severe	0.56	0.08	0.0448
Non-severe	0.32	0.01	0.0032

4 Source: Lloyd et al^{1033,1033}

5 To calculate the proportion of adults that would have a hospitalised (severe) exacerbation, the
6 proportion of hospitalised exacerbations was divided by the total number of exacerbations. The total
7 number of exacerbations that occur each year was calculated by taking the annual probability of
8 having an exacerbation and multiplying this by the number of adults with asthma in the UK (4.1
9 million taken from asthma UK). The annual probability of having an exacerbation was extracted from
10 Shaw et al.¹⁵⁷⁴ The total number of annual hospitalisations in adults (40,243) was taken from the
11 National review of Asthma deaths.¹⁴⁸⁸

12 *Utility of correctly treating non-asthmatics with asthma symptoms*

13 For patients with COPD it is assumed that they will have either moderate or mild severity of COPD. In
14 the model if the spirometry shows an obstruction an assumption was made that the patient would
15 have moderate COPD whereas a spirometry showing no obstruction would indicate mild COPD. The
16 quality of life associated with COPD severity is shown in Table 243.

17 **Table 243: Quality of life for COPD patients by severity**

COPD severity	Quality of life (SE)	Quality of life if treated for asthma
Mild	0.81 (0.02)	0.765
Moderate	0.72 (0.03)	0.695
Severe	0.67 (0.05)	NA

18 Source: Spencer et al^{1657,1657}

19 In the model if the patient has COPD but is treated for asthma then they will receive a QoL in
20 between two severity levels, depending on how severe their COPD is. Therefore if a patient has mild
21 COPD and is being treated for asthma they will receive a quality of life of 0.765, which is a quality of
22 life half way between mild and moderate COPD. The GDG decided to use the value half way between
23 these points as asthma medication will slightly help treat COPD. Once the patient has been correctly
24 re-diagnosed as having COPD their QoL will increase to the mean QoL for their severity level.

25 For patients with heart failure it was assumed that the majority would be classified under the New
26 York Heart Association (NYHA) as class 2. Patients classified under NYHA class 1 are less likely to
27 present any asthma related symptoms whereas patients with NYHA class 3 and 4 are likely to present
28 non-asthma related symptoms that will indicate heart failure. The GDG made an assumption that
29 80% of patients would be class II, 10% would be class I and 10% would be class III. The quality of life
30 for each class is shown in Table 244.

31 **Table 244: Quality of life by NYHA class**

NYHA class	Quality of life (95% CI)	Quality of life if treated for asthma
I	0.855 (0.845 – 0.864)	0.771
II	0.771 (0.761 – 0.781)	0.673
III	0.673 (0.665 – 0.690)	0.532
IV	0.532 (0.480 – 0.584)	NA

1 Source: Gholer et al^{581,581}

2 As the NYHA class the patient falls into is determined by the severity of their symptoms an
3 assumption was used that patients who would fall under NYHA class II would have the quality of life
4 of a patient with class III. Therefore a patient with class II heart failure being treated for asthma will
5 have a QoL of 0.673. This QoL will increase to 0.770 once the patient has been correctly re-diagnosed
6 and is treated accordingly.

7 These quality of life increases are extensively tested in the sensitivity analyses detailed in M.2.5.

8 Individuals with either acute symptoms or physical de-conditioning will receive no quality of life
9 benefit from being correctly re-diagnosed as not having asthma. This is because any other
10 management would not be mutually exclusive with asthma medication and therefore these costs and
11 HRQoL benefits would occur in both true negatives and false positives leading to no incremental
12 benefit. Individuals with 'acute symptoms' will therefore receive a quality of life equal to the general
13 population 0.96. Individuals with physical deconditioning will receive a quality of life equal to the
14 general population minus a disutility of 0.05. Both these values were taken from Harnan et al.^{644,645}
15 This disutility takes into account their symptoms and is thus equal to the disutility of having asthma.
16 These values will not influence the cost-effectiveness of any strategy as they are not influenced by
17 whether the individual is falsely diagnosed.

18 M.2.3.7 Resource use and costs

19 Diagnostic tests – primary care

20 For diagnostic tests conducted in primary care, resource use was elicited from the GDG. This included
21 information on: the health care professional who conducts the test, the time taken to administer the
22 test, and the equipment used. Costs were then applied using data from the NHS supply chain
23 catalogue⁴²⁶ and the PSSRU^{386,386}. Costs of individual tests conducted in primary care are reported
24 below (Table 245 to Table 248).

25 **Table 245: Cost of spirometry**

Item	Quantity	Unit cost	Total Cost (quantity*unit cost)	Source
Time of GP practice nurse to conduct the test	20 minutes	£0.73 per minute	£14.66	GDG opinion, PSSRU ^{386,386}
Micro-lab spirometer ^(a)	1/1500	£1498.90 per spirometer	£1.00	GDG opinion, NHS supply catalogue ⁴²⁶
Bacterial filter, 3-litre syringe for calibration ^(a)	1/1500	£295.77 per syringe	£0.20	GDG opinion, NHS supply catalogue ⁴²⁶
Bacterial filter	1	£0.99 per filter	£0.99	NHS supply catalogue ⁴²⁶
Total			£16.86	

26 (a) To calculate the marginal cost it was assumed that the equipment lasts for 5 years and is used on average 1500 times in
27 this period.

28 **Table 246: Cost of bronchodilator reversibility**

Item	Quantity	Unit cost	Total Cost (quantity*unit cost)	Source
------	----------	-----------	---------------------------------	--------

Item	Quantity	Unit cost	Total Cost (quantity*unit cost)	Source
Time taken to administer bronchodilator and check for reversibility	20 minutes	£0.73 per minute	£14.66	GDG opinion, PSSRU ^{386,386}
Volumatic spacer	1	£3.81 per spacer	£3.81	NHS supply catalogue ⁴²⁶
MDI	1	£5.50 per MDI	£5.50	NHS supply catalogue ⁴²⁶
Spirometry equipment to check for reversibility ^(a)	1	£2.19 (see Table 245 above)	£2.19	NHS supply catalogue ⁴²⁶
Total			£26.16	

1 (a) When a bronchodilator reversibility test is being performed in the model the first spirometry reading will have already
2 been taken.

3 **Table 247: Cost of FeNO**

Item	Quantity	Unit cost	Total Cost (quantity*unit cost)	Source
Time taken to conduct test with GP practice nurse	10 minutes	£0.73 per minute	£7.30	GDG opinion, PSSRU ^{386,386}
Marginal cost of using equipment (NIOX VERO ^(a))	1	£6.36 per use	£6.36	Harnan et al ⁶⁴⁴
Total			£13.66	

4 (a) It was assumed that NIOX VERO is the most commonly used FeNO test

5 **Table 248: Cost of peak expiratory flow variability**

Item	Quantity	Unit cost	Total Cost (quantity*unit cost)	Source
Time taken to instruct patient how to use test with GP practice nurse	10 minutes	£0.73 per minute	£7.30	GDG opinion, PSSRU ^{386,386}
Time taken to interpret results by GP practice nurse	10 minutes	£0.73 per minute	£7.30	GDG opinion, PSSRU ^{386,386}
Mini wright peak flow meter	1	£6.48 per meter	£6.48	NHS supply catalogue ⁴²⁶
Total			£21.08	

6 **Diagnostic tests – secondary care**

7 The following tests are conducted in a secondary care setting. The costs of exercise and
8 histamine/methacholine challenge tests are detailed in **Table 249** and **Table 250** respectively. It is

1 assumed that a GP will refer a patient to have a challenge test and the patient will complete the test
 2 in a secondary care setting. The results of the test will be interpreted by a respiratory physician and
 3 sent back to the GP for analysis.

4 **Table 249: Cost of exercise challenge test**

Item	Quantity	Unit cost	Total cost	Source
Cost of interpreting result – 15 minutes of associate specialist time	1	£23.50	£23.50	GDG opinion, PSSRU ^{386,386}
Investigation costs	1	£167	£167	NHS reference costs ⁴²⁵ - (Complex lung function exercise testing ^(a) HRG code: DZ31Z)
Cost of GP referral	1	£37	£37	GDG opinion, PSSRU ^{386,386}
Total			£227.50	

5 (a) The HRG cost was weighted assuming that the test would only be conducted in outpatient and direct access

6 **Table 250: Cost of histamine/methacholine**

Item	Quantity	Unit cost	Total cost	Source
Cost of interpreting result – 15 minutes of associate specialist time	1	£23.50	£23.50	GDG opinion, PSSRU ^{386,386}
Investigation costs	1	£102.00	£102.00	NHS reference costs ⁴²⁵ - (Bronchial challenge studies ^(a) HRG code: DZ36Z)
Cost of GP referral	1	£37	£37	GDG opinion, PSSRU ^{386,386}
Total			£162.50	

7 (a) The HRG cost was chosen assuming that the test would only be conducted in directly accessed diagnostic services

8
 9 To parameterise the reference costs probabilistically, the distribution of best fit was found by fitting
 10 a gamma and lognormal distribution. To fit each distribution, the standard deviation of the trust cost
 11 was estimated matching the reported interquartile range to that calculated using the reported
 12 mean, and where appropriate the distribution's alpha and beta values. The distribution of best fit
 13 was that which provided the interquartile range of closest value to that reported by the NHS
 14 reference cost.

15 **Cost of asthma treatment**

16 The annual cost of asthma management was taken from a study by Price et al^{1401,1403}. A large driver of
 17 the cost of asthma management is the level of asthma control the individual achieves. Individuals
 18 achieving poor asthma control will have higher drug costs as they will be on a higher step of asthma
 19 medication receiving more expensive treatments. Likewise, individuals achieving good asthma
 20 control will have lower drug costs as they will be on a much less intensive form of treatment. The
 21 study by Price et al differentiates annual asthma costs by level of control and number of
 22 exacerbations. This annual cost incorporates: drug costs, GP consultations and hospitalisations and is

1 shown in **Table 251**. N (%) represents the number and percentage of patients that fall in a particular
 2 cohort, mean (SD) represents the mean cost and its associated standard deviation.

3 **Table 251: Annual asthma costs**

Level of GINA control		Number of exacerbations			
		0	1	2-3	4+
Controlled	N (%)	2583 (16.2%)	196 (1.2%)	38 (0.24%)	13 (0.08%)
	Mean annual cost (SD)	£180 (£225)	£284 (£287)	£471 (£408)	£573 (£481)
Partially controlled	N (%)	7079 (44.5%)	814 (5.1%)	307 (1.9%)	67 (0.42%)
	Mean annual cost (SD)	£238 (£279)	£397 (£358)	£557 (£427)	£645 (£549)
Uncontrolled	N (%)	3642 (22.8%)	745 (4.7%)	399 (2.1%)	102 (0.64%)
	Mean annual cost (SD)	£319 (£366)	£491 (£416)	£672 (£493)	£928 (£755)
Annual weighted asthma cost	£290				

4 Source: Price et al^{1401,1403}

5 Using this information the annual cost of asthma management can be calculated for the average
 6 asthma patient by taking a weighted average. This is done by weighting the cost of asthma
 7 management by the proportion of patients experiencing a certain number of exacerbations at a
 8 certain level of control. This average cost is equal to £290.

9 *Annual cost of asthma treatment for non-asthmatics*

10 Individuals who do not have asthma but are prescribed asthma medication (false positive) are likely
 11 to have a different annual cost compared to individuals with asthma. This has been incorporated into
 12 the model by extrapolating from the data presented in **Table 251**.

13 For individuals with acute symptoms they are likely to appear to be achieving full asthma control as
 14 their symptoms will pass with time. As they don't have asthma they will not experience any
 15 exacerbations. Therefore the cost given to these individuals in the model is the cost associated with
 16 controlled asthma and zero exacerbations which in **Table 251** is £180.

17 For individuals with either heart failure or physical de-conditioning their symptoms will be worse and
 18 it will appear that their asthma may be uncontrolled, however they won't experience any
 19 exacerbations. Therefore for these individuals a weighted cost of asthma management was
 20 calculated based on the number of individuals experiencing zero exacerbations but achieving
 21 differing levels of asthma control. As there is no data on the perceived level of asthma control
 22 achieved by non-asthmatics an assumption was made that the proportions achieving a certain level
 23 for control will be the same as asthmatics. This information is displayed in **Table 252** and has been
 24 extrapolated from the data presented in Table 251. The GDG also noted that once the individual has
 25 been diagnosed with heart failure some individuals will retain their incorrect asthma diagnosis and
 26 remain on asthma treatment for the rest of their life. Therefore in the model 25% of the cost of
 27 asthma management will be retained after the individual has been diagnosed as having heart failure.
 28 This value was removed in a sensitivity analysis detailed in section M.2.5.

29 **Table 252: Annual asthma costs for people with an incorrect diagnosis of asthma who have either**
 30 **heart failure or physical deconditioning**

Level of GINA control	Number of exacerbations
	0

		Number of exacerbations
Controlled	(%)	(19.4%)
	Mean (SD)	£180 (£225)
Partially controlled	(%)	(53.2%)
	Mean (SD)	£238 (279)
Uncontrolled	(%)	(27.4%)
	Mean (SD)	£319 (£366)
Annual average asthma cost	£248.91	

1

2 Finally for COPD patients it was assumed that if they were treated for asthma then they would incur
3 the same costs as an asthma patient. This is likely to be an underestimate as COPD patients
4 exacerbate more than asthma patients especially if they are being treated for asthma as opposed to
5 COPD. This will make the results more conservative for strategies with higher specificities.

6 These costs are tested in the sensitivity analysis in section M.2.5.

7 *Adding uncertainty around asthma costs*

8 As shown by the large standard deviations in **Table 251**, there is a great deal of uncertainty around
9 the annual cost of asthma. This uncertainty was captured by attaching gamma distributions to each
10 combination of control and exacerbation. The distribution parameters attached are shown in **Table**
11 **253**. Alpha and lambda parameters were calculated using the mean and standard deviation detailed
12 in **Table 251**.

13 **Table 253: Gamma distribution parameters for annual asthma costs^(a)**

Level of control/no. of exacerbations	Point estimate	Alpha	Lambda
Controlled / 0	£180	0.64	0.004
Partially controlled / 0	£238	0.72	0.003
Uncontrolled / 0	£319	0.76	0.002
Controlled / 1	£284	0.98	0.003
Partially controlled / 1	£397	1.23	0.003
Uncontrolled / 1	£491	1.39	0.003
Controlled / 2-3	£472	1.34	0.003
Partially controlled / 2-3	£557	1.7	0.003
Uncontrolled / 2-3	£672	1.86	0.003
Controlled / 4+	£573	1.4	0.002
Partially controlled / 4+	£645	1.38	0.002
Uncontrolled / 4+	£928	1.51	0.002

14 (a) Numbers are rounded to 2 decimal places or nearest integer

15

16 *Annual cost of non-asthmatic treatment*

17 For patients with COPD and heart failure once they are correctly re-diagnosed the NHS will incur the
18 costs of their respective treatment rather than asthma medication.

19 The costs for COPD management were taken from the NICE COPD guideline.¹²¹³ In the guideline the
20 annual incremental costs of a patient with mild COPD, relative to the general population, were
21 £149.68. For patients with moderate COPD this incremental cost increases to £307.74. Therefore in

1 the model once a patient with COPD is correctly re-diagnosed and treated for COPD, the NHS will
2 incur these costs rather than asthma management costs.

3 For heart failure patients the NHS will incur the cost of heart failure medication once the patient is
4 correctly re-diagnosed. This cost was estimated to be £135 per year in the recent acute heart failure
5 guideline¹²¹⁴.

6 *Cost of exacerbations*

7 In the model exacerbation costs are calculated for patients who have an exacerbation whilst they are
8 not being treated for asthma. This cost is dependent on whether the exacerbation is severe. If the
9 exacerbation is not severe then the cost includes one GP appointment (£37 from PSSRU^{386,386}) and a
10 course of oral steroids with Prednisolone (cost=£1.33 from NHS drug tariff¹²³⁰). If the exacerbation is
11 severe then the patient will be hospitalised and the cost of asthma hospitalisation will be added (cost
12 = £873.74 from NHS reference cost⁴²⁵).

13 Therefore the average cost of an exacerbation is:

$$\begin{aligned} \text{Average cost of exacerbation} \\ &= \text{Prob}(\text{hospitalisation}) * \text{cost}(\text{hospitalisation}) \\ &\quad - (1 - \text{Prob}(\text{Hospitalisation})) * \text{cost}(\text{non - severe exacerbation}) \end{aligned}$$

14 Once the patient is being treated for asthma the exacerbation costs have already been taken into
15 account as reported in Table 251 and therefore these costs as calculated above are excluded in these
16 patients to avoid double counting.

17 **M.2.4 Computations**

18 The model was constructed in TreeAge Pro 2009^{1785,1785} and was evaluated by cohort simulation.
19 Time dependency was built in by cross referencing the cohorts age as a respective risk factor for
20 mortality.

21 QALYs for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time
22 spent in the alive state of the model was weighted by a utility value that is dependent on the time
23 spent in the model and the health state. QALYs were then discounted to reflect time preference
24 (discount rate = 3.5%) using the following formula:

25

$\text{Discounted total} = \frac{\text{Total}}{(1 + r)^n}$	Where: <i>r</i> =discount rate per annum <i>n</i> =time (years)
--	---

26 QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the
27 discounted QALYs per cycle. The total discounted QALYs were the sum of the discounted QALYs per
28 cycle.

29 Costs per cycle, C(t), were calculated in the same way as QALYs. Costs were discounted to reflect
30 time preference (discount rate = 3.5%) in the same way as QALYs using the formula above.

31 *Estimating cost-effectiveness*

32 The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is
33 calculated by dividing the difference in costs associated with two alternatives by the difference in
34 QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold

1 the result is considered to be cost-effective. If both costs are lower and QALYs are higher the option
 2 is said to dominate and an ICER is not calculated.

$ICER = \frac{Costs (B) - Costs (A)}{QALYs (B) - QALYs (A)}$	Cost-effective if: • ICER < Threshold
Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	

3 When there are more than two comparators, as in this analysis, options must be ranked in order of
 4 increasing cost then options ruled out by dominance or extended dominance before calculating ICERs
 5 excluding these options. An option is said to be dominated, and ruled out, if another intervention is
 6 less costly and more effective. An option is said to be extendedly dominated if a combination of two
 7 other options would prove to be less costly and more effective.

8 It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness
 9 results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a
 10 comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the
 11 total costs (formula below). The decision rule then applied is that the comparator with the highest
 12 NMB is the most cost-effective option at the specified threshold. That is the option that provides the
 13 highest number of QALYs at an acceptable cost.

$Net\ Monetary\ Benefit\ (X) = (QALYs\ (X) \times \lambda) - Costs\ (X)$	Cost-effective if: • Highest net benefit
Where: λ = threshold (£20,000 per QALY gained)	

14 Both methods of determining cost-effectiveness will identify exactly the same optimal strategy. For
 15 ease of computation NMB is used in this analysis to identify the optimal strategy.

16 Results are also presented graphically where total costs and total QALYs for each diagnostic strategy
 17 are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on
 18 the graph where the slope represents the incremental cost-effectiveness ratio.

19 **M.2.5 Sensitivity analyses**

20 The sensitivity analyses conducted below were undertaken to test some of the key assumptions
 21 employed in the model.

22 **Table 254: Sensitivity analyses conducted**

Analysis	Parameter	Description	Values	Comment
S1	Probability of COPD, physical deconditioning, heart failure or acute symptoms being cause of asthmatic symptoms	As the exact distribution of these underlying conditions is unknown this sensitivity analysis addresses different distributions between the four conditions. The model was run eight times with each condition being given a higher proportion (35%) once and a lower proportion (15%) once. The distribution between the remaining three	a) Probability of COPD being cause of symptoms: 15%, 35% b) Probability of obesity being cause of symptoms: 15%, 35% c) Probability of heart failure being cause	As there is no indication of what this distribution might be extreme values were run to cover a large range.

Analysis	Parameter	Description	Values	Comment
		conditions was set to be equal.	of symptoms: 15%, 35% d) Probability of symptoms being acute: 15%, 35%	
S2	Sensitivity and specificity of bronchodilator reversibility	In the clinical review two papers were identified for bronchodilator reversibility that used the correct cut-off and had the right population. In the base case an average was taken of the two studies. This sensitivity analysis re-runs the model using both sources separately.	a) Sensitivity: 61% Specificity: 80% b) Sensitivity: 17% Specificity: 61%	Diagnostic accuracy taken from Chhabra et al ^{313,313} and Kim et al ^{870,873}
S3	Sensitivity and specificity of FeNO	In the clinical review one other paper was identified for FeNO that used the 40ppb cut-off and had the right population. The model was re-run using these values.	Sensitivity: 79% Specificity: 89%	Diagnostic accuracy taken from Fukuhara 2012 ^{535,535}
S4	Sensitivity and specificity of MCT	In the clinical review one other study was identified for MCT that used the correct cut-off and had the right population. The model was re-run using these values.	Sensitivity: 97% Specificity: 83%	Diagnostic accuracy taken from Niemen 1992 ^{1241,1241}
S5	Sensitivity and specificity of spirometry	In the clinical review one other study was identified for spirometry that used the correct cut-off and had the right population. The model was re-run using these values.	Sensitivity: 29% Specificity: 59%	Diagnostic accuracy taken from Schneider 2009 ^{1535,1537}
S6	Probability of re-diagnosis for false positives.	This parameter was derived from clinical judgement as no data exists on what the real value is likely to be. Two scenarios were considered, one where re-diagnosis occurs much faster (probability	Probability of re-diagnosis is twice as likely, all relevant probabilities doubled. Probability of re-	As there is no indication of what this value might be extreme values were run to cover a wide range.

Analysis	Parameter	Description	Values	Comment
		of re-diagnosis is higher) and one where re-diagnosis occurs much slower (probability of re-diagnosis is lower).	diagnosis is more unlikely, all relevant probabilities halved.	
S7	Probability of re-diagnosis for false negatives	This parameter was derived from clinical judgement as no data exists on what the real value is likely to be. An assumption was made that a patient with asthma would always be diagnosed within a year. This assumption was tested by running the model twice, once where this value is halved and once where this value is doubled.	Maximum length of time for an asthmatic to remain undiagnosed: 6 months, 2 years	As there is no indication of what this value might be extreme values were run to cover a wide range.
S8	Cost of asthma medication for false positives	This parameter was derived by extrapolating from robust data on annual asthma costs. Two scenarios were considered: one where asthma treatment costs were 25% higher and one where asthma treatment costs were 25% lower.	Asthma treatment costs for patients with COPD: £218, £363 Asthma treatment costs for patients with acute symptoms: £135, £225 Asthma treatment costs for patients with obesity: £186, £311 Asthma treatment costs for patients with heart failure: £186, £311	As there is no indication of what this value might be extreme values were run to cover a wide range.
S9	Strength of dependence between PEFv and BDR	This parameter was derived from clinical judgement as no data could be found on its exact value. This value was increased to reflect the possibility of PEFv results being more conditionally dependent on the result from BDR.	Strength of dependence between BDR and PEFv: 0.5	As there is no indication of what this value might be extreme values were run to cover a wide range.
S10	Strength of dependence between challenge tests	This parameter was derived from clinical	Strength of dependence	As there is no indication of what

Analysis	Parameter	Description	Values	Comment
	and BDR	judgement as no data could be found on its exact value. This value was increased to reflect the possibility of challenge test results being more conditionally dependent on the result from a BDR test.	between histamine challenge test and BDR: 0.75	this value might be extreme values were run to cover a wide range.
S11	Strength of dependence between challenge tests and PEFv	This parameter was derived from clinical judgement as no data could be found on its exact value. This value was increased to reflect the possibility of challenge test results being more conditionally dependent on the result from PEFv.	Strength of dependence between histamine challenge test and PEFv: 0.75	As there is no indication of what this value might be extreme values were run to cover a wide range.
S12	Quality of life improvement for COPD patients being correctly treated for COPD as opposed to asthma.	This parameter was extrapolated from the literature using GDG opinion. Two sensitivities were run, one where QoL improvements for COPD patients are 50% higher and one where they are 50% lower.	QoL increase for a mild severity COPD patient being correctly treated: 0.01 – 0.06 QoL increase for a moderate COPD patient being correctly treated: 0.02 – 0.09	As there is no indication of what this value might be extreme values were run to cover a wide range.
S13	Quality of life improvement for heart failure patients being correctly treated for heart failure as opposed to asthma.	This parameter was extrapolated from the literature using GDG opinion. Two sensitivities were run, one where QoL improvements for heart failure patients are 50% higher and one where they are 50% lower.	QoL increase for a heart failure patient being correctly treated: 0.04 – 0.15	As there is no indication of what this value might be extreme values were run to cover a wide range.
S14	Re-diagnosis costs	This parameter was extrapolated using GDG opinion. Sensitivity was run where re-diagnosis costs only included one GP appointment. This can be seen as the minimum cost it could be.	Cost of re-diagnosis: £37	As there is no indication of what this value might be the lowest plausible estimate was used as an extreme value.
S15	Asthma prevalence	This parameter was derived from a meta-analysis. The model was re-run using the lower	Asthma prevalence: 0.37, 0.43	

Analysis	Parameter	Description	Values	Comment
		and upper limits of the 95% confidence interval.		
S16	Cost of methacholine challenge tests	A threshold analysis was run around the cost of methacholine challenge tests to see when treatment decisions would change.	Threshold analysis: Value run from £50 - £600	
S17	Conducting all primary care tests in one appointment	In the base case it was assumed that all primary care tests would be performed in one sitting. This sensitivity analysis adds the cost of one GP appointment to each primary care test	Cost of BDR, FeNO and PEFv increased by one GP appointment (£37)	
S18	Exacerbation rate for a untreated asthmatic	In the base case this value was based on weak data. For ethical reasons the exacerbation rate of an untreated asthmatic is unlikely to be known. The exacerbation rate for an untreated asthmatic will have an ambiguous effect on the model results as a high exacerbation rate is associated with disutility and a slightly higher mortality rate; however a high exacerbation rate means patients are re-diagnosed quicker which means a higher quality of life.	Threshold analysis: Exacerbation rate of untreated asthmatic run from 0.5 – 1.5.	As there is no indication of what this value might be extreme values were run to cover a wide range.
S19	Discount rate	Discount rate was changed from 3% for costs and QALYs to 1.5%. This is to reflect uncertainty around the true discount rate.	Discount rate: 1.5%	
S20	Probability that a heart failure patient retains an incorrect asthma diagnosis permanently	The GDG noted that even after the true cause of symptoms has been identified, some heart failure patients will retain a diagnosis of asthma as the two diseases are not	Probability of heart failure patient retaining asthma diagnosis: 0%	

Analysis	Parameter	Description	Values	Comment
		necessarily mutually exclusive. In the base case this value was set as 25%. This assumption was removed in this sensitivity analysis.		
S21	Sensitivity and specificity of MCT	A two way sensitivity analysis was conducted on these two values running the diagnostic sensitivity from 90 – 98% and the specificity from 80 – 99%. This range covers the uncertainty surrounding what the diagnostic accuracy is of these tests in light of the clinical evidence and conditional dependence.	Sensitivity of MCT: 90-98% Specificity of MCT: 80-99%	

1

2 M.2.6 Interpreting Results

3 NICE's report 'Social value judgements: principles for the development of NICE guidance'¹²¹⁵ sets out
4 the principles that GDGs should consider when judging whether an intervention offers good value for
5 money. In general, an intervention was considered to be cost-effective if either of the following
6 criteria applied (given that the estimate was considered plausible):

- 7 • The intervention dominated other relevant strategies (that is, it was both less costly in terms of
8 resource use and more clinically effective compared with all the other relevant alternative
9 strategies), or
- 10 • The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared
11 with the next best strategy.

12

13 As we have several interventions, we use the NMB to rank the strategies on the basis of their relative
14 cost-effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000
15 per QALY gained.

16 M.2.7 Model validation

17 The model was developed in consultation with the GDG; model structure, inputs and results were
18 presented to and discussed with the GDG for clinical validation and interpretation.

19 The model was systematically checked by the health economist undertaking the analysis; this
20 included inputting null and extreme values and checking that results were plausible given inputs. The
21 model was peer reviewed by a second experienced health economist from the NCGC; this included
22 systematic checking all of the model calculations.

1 M.3 Results

2 M.3.1 Base case

3 The results below in **Table 255** show that diagnostic strategy 3 has the highest net monetary benefit
 4 and is therefore the most cost-effective way of diagnosing asthma. Strategy 6 produces the highest
 5 number of QALYs however is not deemed cost-effective at a £20,000 per QALY threshold. Strategy 1
 6 produces the least QALYs and the highest cost.

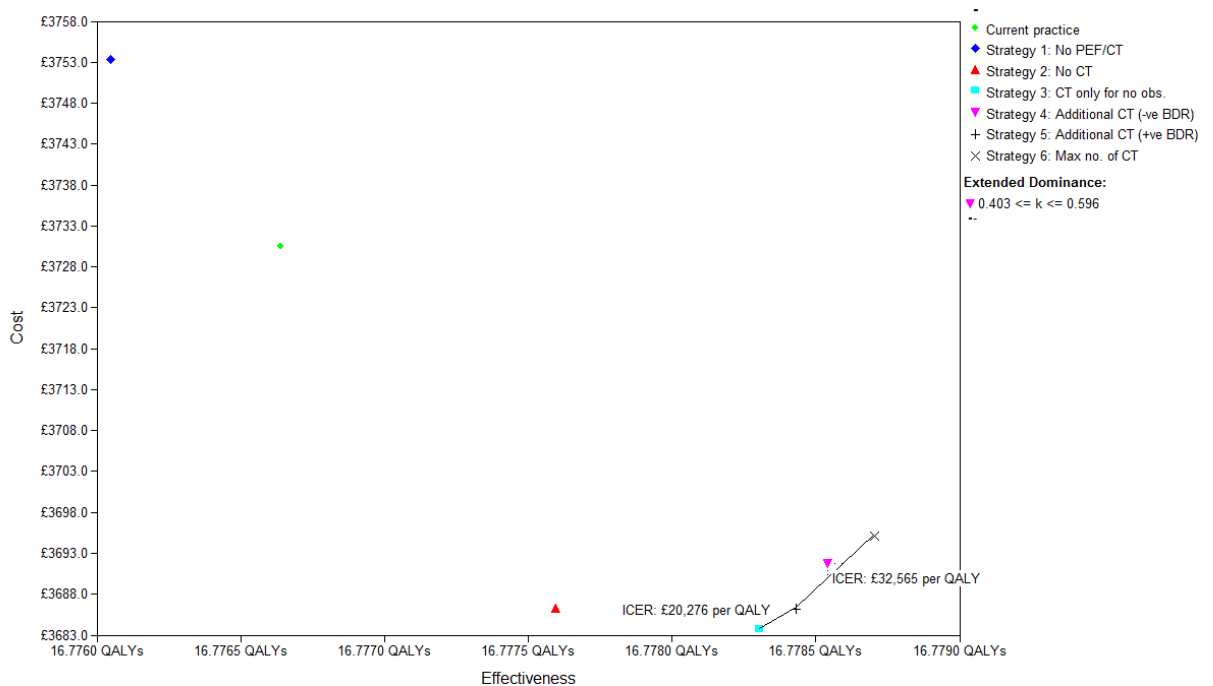
7 **Table 255: Base case results (probabilistic)**

Strategy	Mean per patient		NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
	QALYs	Cost			
Current practice	16.7766	£3,730	£331,802	6	6%
Strategy 1	16.7760	£3,753	£331,768	7	0%
Strategy 2	16.7776	£3,686	£331,866	5	19%
Strategy 3	16.7783	£3,683	£331,882	1	44%
Strategy 4	16.7785	£3,691	£331,878	4	0%
Strategy 5	16.7784	£3,686	£331,881	2	23%
Strategy 6	16.7787	£3,695	£331,879	3	8%

8 (a) Full details on each strategy is covered in section M.2.1.1

9 **Figure 315** below shows the results from **Table 255** above on a cost-effectiveness plane. As you can
 10 see current practice and strategy 1 are dominated options, producing lower health gains at a higher
 11 cost relative to other strategies. Strategies 4 and 5 are extendedly dominated.

12 **Figure 315: Cost-effectiveness plane showing incremental costs and QALYs of each individual**
 13 **strategy**



14

1 **Table 256** below shows the overall sensitivity and specificity of each diagnostic pathway, that is the
 2 percentage of patients with asthma that receive a true positive diagnosis and the percentage of
 3 patients without asthma that receive a true negative diagnosis.

4 **Table 256: Diagnostic accuracies of each strategy**

	Current practice	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5	Strategy 6
Sensitivity	100%	90.3%	89.3%	86.3%	88.7%	87.7%	90.3%
Specificity	65.8%	69.1%	82.4%	89.5%	89.4%	89.4%	89.4%

5 *Note: Accuracies rounded to one decimal place*

6 **Table 256** shows that no strategy has a single highest value for sensitivity and specificity though
 7 strategy 6 has the highest diagnostic odds ratio. Finally Table 257 details the cost of diagnostic tests
 8 associated with each strategy.

9 **Table 257: Cost of testing in each strategy**

	Current practice	Strategy 1	Strategy 2	Strategy 3	Strategy 4	Strategy 5	Strategy 6
Cost associated with diagnostic tests	£0	£42	£52	£92	£100	£95	£103

10 Table 257 shows that although the strategies that include challenge tests cost more the increase in
 11 cost is far less than the cost of a single challenge tests as the majority of individuals will not go on to
 12 receive one.

13 M.3.2 Sensitivity analyses

14 The following sensitivity analyses were run deterministically. Of the 21 sensitivity analyses
 15 conducted, as detailed in section M.2.5, the following resulted in a change in conclusions of the
 16 model :

17 *S2a: Changing the sensitivity and specificity of BDR to 61% and 80% respectively.*

18 Table 258 below shows the results of just the non-dominated strategies. As you can see strategy 5 is
 19 now the most cost-effective strategy at a £20,000 per QALY threshold. This is because a higher
 20 sensitivity of BDR means that more patients with asthma will receive a positive BDR result. As the
 21 pathway continues after a positive BDR it becomes more cost-effective to continue testing after
 22 negative test results to ensure false negatives are kept to a minimum. Likewise now the specificity is
 23 higher, more non-asthmatics receive a negative BDR result; therefore it becomes less cost-effective
 24 to continue testing after negative BDR results as the number of false negatives is already quite low.

25 **Table 258: Results of sensitivity analysis S2a**

Strategy	Mean per patient		ICER (per QALY gained)
	QALYs	Cost	
Strategy 3 (CT only after no obs)	16.8355	£3,550	-
Strategy 5 (additional CT after -ve BDR)	16.8357	£3,552	£10,667
Strategy 6 (largest amount of CT)	16.8358	£3,561	£56,755

26

1 *S2b: Changing the sensitivity and specificity of BDR to 17% and 61% respectively.*

2 Table 259 below shows the results of just the non-dominated strategies. Now strategy 5 is
3 extendedly dominated . As the sensitivity of BDR is much lower very few asthmatics receive a
4 positive BDR result. Likewise the low specificity means that lots of non-asthmatics will receive a
5 positive BDR result. After a positive BDR test the individual will receive a FeNO test. If the FeNO
6 comes out negative then, with these BDR diagnostic accuracies, it is highly likely that the individual
7 does not have asthma thus making challenge testing beyond this point less cost-effective. Likewise as
8 the majority of asthmatics will receive a negative BDR result it will be more cost-effective to keep
9 testing beyond this point to ensure these false negatives are rectified.

10 **Table 259: Results of sensitivity analysis S2b**

Strategy	Mean per patient		ICER (per QALY gained)
	QALYs	Cost	
Strategy 3 (CT only after no obs)	16.7838	£3,692	-
Strategy 4 (additional CT after -ve BDR)	16.7841	£3,699	£24,281
Strategy 6 (largest amount of CT)	16.7842	£3,703	£60,422

11

12 *S3: Changing the sensitivity and specificity of FeNO to 79% and 89% respectively.*

13 The results in Table 260 show that the only non-dominated strategies are strategy 2, 5 and 6. As the
14 FeNO specificity is much higher it becomes less cost-effective to continue testing after a positive
15 result. Therefore if the individual has a non-obstructive spirometry and a positive FeNO then it
16 becomes less cost-effective to continue testing after that point. Likewise a lower sensitivity means it
17 is more cost-effective to keep testing after a negative FeNO result to ensure false negative results are
18 reversed. Taking these two points into account strategy 3 becomes less cost-effective and strategies
19 5 and 6 become more cost-effective causing strategy 3 to become extendedly dominated.

20 **Table 260: Results of sensitivity analysis S3**

Strategy	Mean per patient		ICER (per QALY gained)
	QALYs	Cost	
Strategy 2 (No CT)	16.7832	£3,659	-
Strategy 5 (additional CT after +ve BDR)	16.7838	£3,670	£19,307
Strategy 6 (largest amount of CT)	16.7843	£3,684	£28,691

21 *S4: Changing the sensitivity and specificity of MCT to 97% and 83% respectively*

22 The results in Table 261 show that the results from the base case are sensitive to changes in the
23 diagnostic accuracy of a methacholine challenge test. In this sensitivity analysis the specificity is
24 drastically decreased to 83%, from 99%. The sensitivity is increased however from 93% to 97%. As
25 challenge tests are leading to fewer true negatives strategy 3 no longer dominates. It is worth noting
26 that additional challenge tests after a bronchodilator reversibility test are no longer cost-effective.
27 This is because although these additional challenge tests increase the sensitivity of the diagnostic
28 pathway they now significantly reduce the specificity.

29 **Table 261: Results of sensitivity analysis S4**

Strategy	Mean per patient		ICER (per QALY gained)
	QALYs	Cost	

Strategy	Mean per patient		ICER (per QALY gained)
	QALYs	Cost	
Strategy 2 (No CT)	16.7832	£3,692	-
Strategy 3 (CT only after no obs)	16.7838	£3,698	£8,530
Strategy 5 (additional CT after +ve BDR)	16.7840	£3,708	£62,477
Strategy 6 (largest amount of CT)	16.7840	£3,717	£170,957

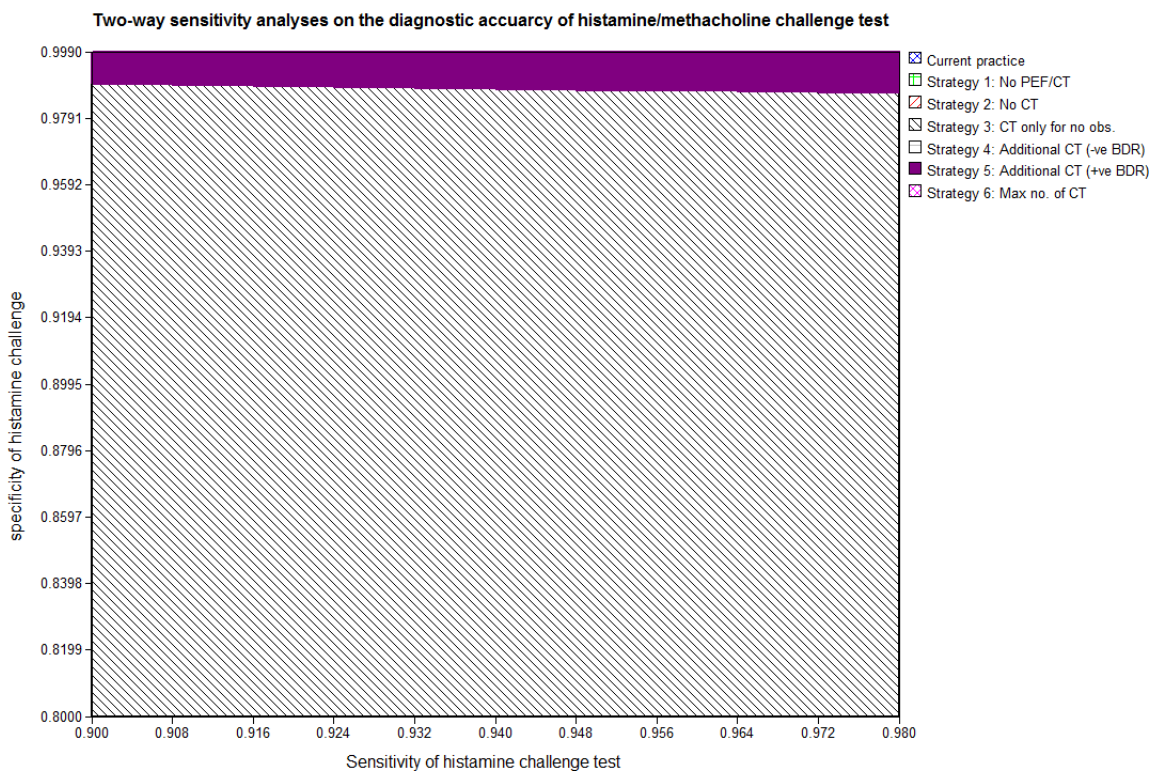
1 *S15: Threshold analysis on the cost of methacholine challenge test.*

2 The sensitivity analysis showed that if the cost of a methacholine challenge test was £88 lower at £75
 3 then strategy 6 (maximum number of challenge tests) becomes the new most cost-effective strategy.
 4 Likewise if the cost of the test was £87 higher at £240 then strategy 2 (no challenge tests) becomes
 5 the most cost-effective option. In reality as the methacholine challenge test is an infrequently used
 6 test; if this test was to be used more frequently then the costs could fall due to economies of scale.
 7 Therefore the likelihood of the test cost exceeding £240 is unlikely.

8 *S20: Two way sensitivity analysis on the sensitivity and specificity of MCT*

9 Figure 316 below shows the most cost-effective strategy for a range of different values used for the
 10 sensitivity and specificity of a MCT. The shaded colour indicates which strategy is most cost-effective
 11 at particular co-ordinates on the graph, with sensitivity being on the x-axis and specificity being on
 12 the y-axis. The graph shows that challenge tests stil cost-effective if the sensitivity and specificity are
 13 far lower than the values used in the base case (93% sensitivity and 99% specificity). There is no
 14 clinical evidence to suggest the values are this low and conditional depondence would not cause the
 15 overall sensitivity AND specificity to decrease.

16 **Figure 316: Two way sensitivity analysis on sensitivity and specificity of a MCT**



17

1 M.4 Discussion

2 M.4.1 Summary of results

3 This analysis showed that providing challenge tests as part of a diagnostic pathway for individuals
4 who present with asthma symptoms, have a non-obstructive spirometry and conflicting PEFv and
5 FeNO results (strategy 3) is the most cost-effective strategy at a £20,000 per QALY threshold. Further
6 challenge testing on patients with an obstructive spirometry provided higher health outcomes
7 however was not cost-effective at a £20,000 per QALY threshold. All other strategies were either
8 dominated or extendedly dominated.

9 The sensitivity analyses show that there is an element of uncertainty regarding the use of challenge
10 tests for individuals who have an obstructive spirometry. The value of these additional challenge
11 tests (those detailed in strategies 4, 5 and 6) is contingent on the diagnostic accuracy of
12 bronchodilator reversibility tests, FeNO and methacholine challenge tests. This level of uncertainty
13 has been captured in the recommendations whereby these tests are considered but not routinely
14 offered.

15 In all sensitivity analysis a diagnostic pathway that incorporated challenge testing was always a cost-
16 effective strategy. This is despite the fact there are many aspects of the model that reduce the
17 cost-effectiveness of challenge testing. For example it is assumed there is no mortality impact from
18 falsely diagnosing individuals who have COPD and heart failure with asthma. Secondly the model
19 does not cover all illnesses that could receive a false diagnosis of asthma. Conditions such as lung
20 cancer and tuberculosis could have profound health consequences if misdiagnosed as asthma.

21 With regards to the routine use of challenge tests in asthma diagnosis for individuals with
22 unobstructive spirometry (strategy 3) the model results are highly robust to changes in all key
23 assumptions made within the model. Therefore although there is uncertainty regarding conditional
24 dependence and the health and cost consequences of false diagnoses, solving this uncertainty will
25 not change the conclusions of the model.

26 M.4.2 Limitations and interpretation

27 The main limitation with the model is the lack of clinical data available to inform some of the key
28 parameters; mainly those surrounding misdiagnosis for non-asthmatics. To compensate for this, all
29 the assumptions made have been conservative towards strategies that produce higher specificities.
30 Firstly the model assumes that 50% of patients without asthma forego no quality of life from being
31 diagnosed with asthma. In reality this number is likely to be an overestimate and there are likely to
32 be some adverse effects of asthma medication as well that have not been captured. Secondly severe
33 illnesses such as lung cancer have not been captured in this model which would have drastic quality
34 of life impact if misdiagnosed as asthma. Finally no mortality effects have been captured for heart
35 failure patients from foregoing correct treatment. All of this means that challenge testing for patients
36 with non-obstructive spirometry is likely to be more cost-effective than is depicted in the model. It is
37 worth noting that these limitations were extensively tested in the sensitivity analyses and challenge
38 testing remained cost-effective at a £20,000 per QALY threshold in all of them.

39 Another limitation is that the evidence collected for the diagnostic accuracy of each test was not
40 conducted in the appropriate subgroup of patients. For example in the diagnostic pathway ideally we
41 would want to know the diagnostic accuracy of PEFv in a subgroup of patients who present
42 symptoms of asthma and have no obstruction and a negative FeNO. Instead the diagnostic accuracy
43 was taken from a review on all patients who present asthma symptoms. This issue was tackled for
44 the majority of tests, as detailed in section M.2.2.3, however conditional dependence was not fully
45 incorporated for challenge tests in the model. A sensitivity analysis showed that both the sensitivity

1 and specificity of a methacholine challenge test would have to decrease significantly to make them
2 no longer cost-effective at a £20,000 per QALY threshold therefore indicating that conditional
3 dependence is unlikely to have an impact of the model results.

4

5 **M.4.3 Generalisability to other populations or settings**

6 The results produced in this analysis are specific to a UK setting. To generalise the results to other
7 countries the costs used and asthma prevalence parameter would need to be re-evaluated as these
8 are likely to be country specific. Consideration also needs to be made as to how challenge tests are
9 conducted. In this analysis it is assumed the GP refers the patient for the challenge test where it is
10 performed and analysed in a secondary care setting. The results are then referred back to the GP
11 where they discuss treatment options with the patient. Other methods of conducting the challenge
12 test will have different cost implications and therefore make the results less generalizable to other
13 settings.

14 It is worth noting that these results are not generalisable for children aged 16 or younger. The main
15 reason for this is that the asthma prevalence in this population is very different. In a child population
16 asthma is likely to be a much more common cause of a chronic cough. As asthma prevalence is higher
17 this will increase the cost-effectiveness of more sensitive diagnostic strategies. Secondly children will
18 not have other common conditions such COPD or heart failure for example. This will affect the final
19 cost and health outcomes of each diagnostic strategy.

20 **M.4.4 Comparisons with published studies**

21 This is the first economic evaluation that addresses the cost-effectiveness of diagnostic pathways for
22 diagnosing asthma. However other studies have attempted to assess the cost-effectiveness of
23 asthma diagnostic tests on their own rather than as part of a pathway. To do this these studies have
24 to make similar assumptions outlined in the methods above. Only one study attempts to do this and
25 that is a study by Harnan et al.⁶⁴⁴ The approach taken by Harnan et al was to assume that non-
26 asthmatics had a disutility that remained until the correct diagnosis was made. This disutility was
27 equal to the difference in quality of life between an asthmatic and a non-asthmatic. This approach
28 attaches a much higher quality of life loss to incorrect diagnosis than the methods used in our model
29 as it assumes all non-asthmatics will forego treatment that will cure them of their asthmatic
30 symptoms. The approach by Harnan also overestimates the cost-savings to the NHS. If an individual is
31 being treated for asthma then they forego correct medication, therefore the unnecessary asthma
32 medication is a cost but there are savings being made by not prescribing the correct medication. The
33 overall cost to the NHS from incorrectly prescribing asthma medication is therefore lower as money
34 is not spent on the correct medication. Therefore relative to other methods the results produced in
35 this analysis are much more conservative for strategies with higher specificities. As the results from
36 Harnan et al are for singular diagnostic tests, their results are not comparable to the analysis
37 presented above.

38 **M.4.5 Conclusions**

39 The main conclusion to be drawn from this model is that there is a place for routine challenge testing
40 in a diagnostic pathway, despite its initial high cost. This is because its initial high costs are then
41 offset by reduced unnecessary asthma management and a gain in QALYs. This conclusion was robust
42 to a wide range of sensitivity analyses. A second important conclusion is that there is scope for
43 further challenge tests, conducted on patients further down the pathway after an obstructive
44 spirometry, to be cost-effective at a £20,000 per QALY threshold. In the base case the ICER for
45 providing these extra challenge tests was £32,565 per QALY. However the sensitivity analyses
46 showed there were some scenarios where it was cost-effective to do extra challenge tests,

1 particularly for individuals who receive a positive bronchodilator result. The GDG believed further
2 challenge tests would be cost-effective in some situations. For example if another diagnosis, such as
3 COPD, is considered likely then further challenge testing should not be considered. Therefore these
4 additional challenge tests should not be routinely carried out, unlike those placed in strategy 3.

5 **M.4.6 Implications for future research**

6 Areas in the model that were most uncertain are difficult to resolve with further research due to
7 ethical implications. For example the difference in quality of life between treated and untreated
8 patients with asthma, or the quality of life lost by treating a heart failure patient with asthma
9 medication. Although there was considerable uncertainty surrounding some diagnostic accuracies
10 and conditional dependence the model results were robust to large changes in these parameters.
11 Therefore additional research in these areas will not lead to any changes in management. One key
12 area of uncertainty revolved around the diagnostic accuracy of mannitol. There was limited evidence
13 on the diagnostic accuracy of mannitol and it is a cheaper test to perform relative to other challenge
14 tests. There is also scope for mannitol to be conducted in primary care. If mannitol was proven to
15 have a higher sensitivity and specificity then it could be a more cost-effective replacement for
16 methacholine in the diagnostic pathway.
17

1 Appendix N: Research recommendations

2 N.1 High-priority research recommendations

3 **N.1.1.1 Research question 1:** What is the acceptability and diagnostic accuracy of objective tests that could
4 be used to comprise a diagnostic pathway for asthma in children aged 5-16 years old (for example,
5 exercise challenge, direct bronchial challenge with histamine or methacholine, indirect bronchial
6 challenge with mannitol and peripheral blood eosinophil count)?

7 **Why this is important:** Asthma is a common condition, diagnosed in nearly 1 in 10 children. There
8 are no validated and reliable objective criteria for diagnosing asthma, so the vast majority of asthma
9 diagnoses are currently based on symptoms and signs. However, symptoms and signs consistent with
10 a diagnosis of asthma are not specific to the condition and can be present in other illnesses. This
11 diagnostic uncertainty results in many children being incorrectly diagnosed with asthma, and many
12 children with asthma in whom the diagnosis is delayed or missed. A single objective measure, or set
13 of objective measures, that can be performed easily in non-specialist clinical settings (although it is
14 noted that challenge tests need to be performed in specialist settings) will help improve diagnostic
15 certainty and reduce the proportion of children treated inappropriately for asthma. This would
16 ensure that children with the condition are identified and treated early.

17 **Criteria for selecting high-priority research recommendations:**

PICO question	<p>Population: Children aged 5-16 years with respiratory symptoms.</p> <p>Index test: Exercise challenge, direct bronchial challenge with histamine or methacholine, indirect bronchial challenge with mannitol and peripheral blood eosinophil count.</p> <p>Reference standard: Physician diagnosis of asthma with an objective test (e.g. spirometry +/- BDR and FeNO test).</p> <p>Outcome: Diagnostic accuracy (sensitivity and specificity); serious adverse events; adverse events.</p>
Importance to patients or the population	Correct and timely diagnosis of asthma in children will lead to appropriate treatment and improve patient outcomes.
Relevance to NICE guidance	Data from this research question will improve the sensitivity and specificity of the diagnostic algorithm in a future update of the NICE guideline.
Relevance to the NHS	Appropriate identification of children with asthma will reduce over-diagnosis and result in a reduction of inappropriate treatment. This will result in cost savings to the NHS.
National priorities	This is appropriate for the priority areas of improved management of long term conditions and reduction in respiratory morbidity and mortality.
Current evidence base	There is very little high quality data available on objective tests for the diagnosis of asthma in children aged 5-16 years. The current data available are inconsistent and are of limited utility in setting clear objective measurements in this age group.
Equality	n/a
Study design	This requires primary research in children who have clinical respiratory illnesses. Cross-sectional studies would be used for the assessment of the diagnostic accuracy of one (or a combination) of objective tests in the diagnosis of asthma or non-asthma, as determined by the reference standard. Randomised controlled trials could also be used to compare the downstream effects of test accuracy on patient outcomes.
Feasibility	Most secondary and tertiary clinical facilities will be able to participate in a multicentre study which would allow the rapid recruitment of the required number of children to give clear answers to the research question.

Other comments	Asthma is one of the most common clinical diagnoses made in children and leads to the prescription and consumption of preventive drugs that have known side-effects. Reduction in incorrect diagnosis of asthma could be viewed as a public health measure and the studies suggested would reduce the drug-load and cost-burden of unnecessary drugs.
Importance	<ul style="list-style-type: none"> • High: the research is essential to inform future updates of key recommendations in the guideline.

1N.1.1.2 Research question 2: What is the clinical and cost effectiveness of using an indirect bronchial challenge test with mannitol to diagnose asthma in adults and young people older than 16?

Why this is important: Chronic airway inflammation is associated with bronchial hyper-responsiveness, which is integral to defining asthma. Bronchial challenge testing can help diagnose asthma and assess response to inhaled corticosteroid therapy. It can also be used to monitor asthma control, alongside assessing symptoms and lung function. It is increasingly used in asthma management, although currently most tests are performed only in specialised centres or research settings.

Indirect challenge tests with inhaled mannitol act via active inflammatory cells and mediators, whereas direct challenge tests with inhaled histamine or methacholine act directly on bronchial smooth muscle. Indirect challenge testing is more specific but less sensitive than direct challenges.

Direct challenge testing may not identify a person who will respond to inhaled steroids. A positive result to an indirect challenge may reflect active airway inflammation that is likely to respond to inhaled corticosteroid therapy. Because a response to mannitol indicates active airway inflammation, identifying non-responsiveness in treated patients may help demonstrate good asthma control with inhaled corticosteroid therapy and identify people less likely to deteriorate after a dose reduction.

Mannitol bronchial challenge testing is quicker and simpler than current direct tests (which are generally confined to specialist respiratory centres), and uses a standardised inhaler device, so is potentially more useful in primary care.

Criteria for selecting high-priority research recommendations:

PICO question	<p>Population: Adults and young people aged over 16 years with respiratory symptoms.</p> <p>Index test: Indirect BCT with mannitol.</p> <p>Comparison: Direct BCT with histamine or methacholine.</p> <p>Reference standard: Physician diagnosis of asthma with an objective test.</p> <p>Outcome: Diagnostic accuracy (sensitivity and specificity); adverse events.</p>
Importance to patients or the population	<p>Asthma is a treatable, but as yet incurable, chronic inflammatory condition of the lungs. A number of recent studies and reports highlight significant variations in the standard of care across the country with evidence that poor quality care is associated with worse outcomes, poorer quality of life and increased healthcare utilisation.</p> <p>Asthma is one of the most prevalent long-term conditions in the UK. It affects 5.4 million people, is a leading cause of avoidable hospital admissions, and is responsible for more than £1 billion of NHS spending every year. Premature mortality rates from asthma are over 1.5 times higher in the UK than in the rest of Europe, but there is no reason why the standard of care in the UK should be any lower than that of other European countries.^{427,1934}</p>
Relevance to NICE guidance	Clarification of the role of mannitol BCT both in terms of diagnostic accuracy compared to direct BCTs and as a potential tool in the monitoring of asthma would allow the NICE guideline on the diagnosis and monitoring of asthma to make firm recommendations regarding its use in clinical practice.

Relevance to the NHS	Asthma continues to result in a significant number of avoidable deaths, admissions and quality of life impairment, all with associated costs. Better diagnosis and monitoring of asthma will reduce healthcare utilisation, reduce the economic burden to the NHS and improve quality of life to people with asthma.
National priorities	The NHS Atlas of Variation in Healthcare demonstrates that there is significant variation in health outcomes for asthma across the NHS in England. The National Review of Asthma Deaths (NRAD) ¹⁴⁸⁸ identified a number of quality and safety concerns related to the provision of asthma care in the UK. It raised particular concern around standards in primary care concluding that there was an urgent need to tackle 'complacency' about asthma.
Current evidence base	Indirect BCTs (such as mannitol) are more specific, though less sensitive, than direct BCT (such as methacholine, histamine) for identifying patients with active asthma. The potential for monitoring asthma with airway hyper-responsiveness is of particular interest to clinicians. Sont el al. demonstrated that management of asthma therapy based on reducing BHR in conjunction with symptoms and lung function leads to more effective control of asthma than management based on symptom control alone. The current evidence base suggests bronchial challenge testing is useful in the diagnosis of asthma. Mannitol BCT has high specificity for the diagnosis of asthma, although the sensitivity is only moderate when compared to direct BCTs (e.g. methacholine, histamine). The clinical efficacy and cost-effectiveness of mannitol BCT within a diagnostic algorithm for suspected asthma requires more research particularly in patients not receiving inhaled corticosteroids (ICS). The potential use of the mannitol challenge to assist monitoring of asthma in clinical practice is also of particular interest with respect to facilitating down titration of ICS and worthy of further research. The mannitol BCT provides a standardised, reproducible, rapid and simple test that does not require specialised equipment and may have some practical advantages, particularly for use in primary care.
Equality	Asthma affects all ages and ethnic groups, and the design of the research needs to encompass this.
Study design	Appropriately designed and powered real world randomised controlled trials: a) comparing mannitol BCT to direct BCT in the diagnosis of asthma in adults. b) comparing mannitol BCT to current recommended guideline based approach in the monitoring of asthma in adults. Particularly important outcome measures will include healthcare utilisation, exacerbation frequency, cumulative steroid burden (oral and inhaled) and cost-effectiveness.
Feasibility	Asthma is very common and uncontrolled in over half of all patients. Mannitol BCT was developed to solve some of the practical issues associated with other BCTs and to make BCTs more widely available to clinicians. It is feasible and practical to recommend future research in this area.
Other comments	None.
Importance	<ul style="list-style-type: none"> High: the research is essential to inform future updates of key recommendations in the guideline.

1N.1.1.3 Research question 3: What is the clinical and cost effectiveness of using electronic alert systems designed to monitor and improve adherence with regular inhaled maintenance therapy in people with asthma?

Why this is important: Adherence with regular maintenance inhaled corticosteroids, on their own or in combination with long-acting beta agonists, is of paramount importance to achieve control of asthma and prevent asthma attacks. Published evidence in patients with severe asthma suggests that

1 at least 30% of patients are partially or non-adherent with their prescribed medications¹¹⁹³, and the
2 Royal College of Physicians' National Review of Asthma Deaths(NRAD)¹⁴⁸⁸ demonstrated that poor
3 adherence was associated with 38% of asthma deaths.

4 **Criteria for selecting high-priority research recommendations:**

PICO question	<p>Population: Adults, children and young people with mild to moderate asthma.</p> <p>Intervention: Monitoring adherence using different technologies/devices (eg prescription and refill monitoring systems; electronic monitoring inhalers).</p> <p>Comparison: Usual care; different frequencies of monitoring adherence using different technologies/devices.</p> <p>Outcomes: Mortality; QoL; exacerbations; unscheduled healthcare utilisation; adherence; asthma control.</p>
Importance to patients or the population	<p>Adherence with regular inhaled asthma therapies is suboptimal in a significant proportion of patients with asthma. Targetted intervention studies, that have improved adherence, have demonstrated a significant improvement in asthma control and reduced healthcare utilisation.</p> <p>Asthma outcomes have not improved in the last 15 years and the personal and economic costs of poor control are high. The efficient use of systems to monitor adherence and improve patient adherence and outcomes via feedback mechanisms, and the integration of these new technologies into healthcare are important for patients and for healthcare systems in terms of convenience, costs and outcomes.</p>
Relevance to NICE guidance	<p>Identification of clinically and cost-effective methods of monitoring adherence will allow the NICE guideline on Asthma: Diagnosis and Monitoring to make recommendations on the appropriate use of adherence monitoring strategies in NHS care.</p>
Relevance to the NHS	<p>Asthma continues to lead to avoidable deaths and considerable unscheduled health care utilization. Improved adherence with prescribed therapies will have a significant impact on health care utilization and improve asthma related quality of life.</p>
National priorities	<p>Reducing mortality considered amenable to healthcare is the overarching indicator of Domain 1 of the NHS Outcomes Framework, and poor adherence has been identified in the national review of Asthma deaths as a potentially avoidable factor in asthma deaths. Improving outcomes in asthma are highlighted in the National Strategy in COPD and Asthma as a national priority.</p>
Current evidence base	<p>There is a very limited current evidence base on the best monitoring method to monitor and feedback on a person's adherence to asthma maintenance therapy, in order to improve patient outcomes of QOL, morbidity and mortality. The majority of published studies have been conducted in patients with severe asthma, which comprise less than 5% of the asthma population.</p> <p>Further research is required to determine the optimal method of monitoring adherence for improving adherence and patient outcomes, particularly in people with mild to moderate asthma.</p>
Equality	<p>Asthma affects all ages and ethnic groups, and the design of the research needs to encompass this. In particular, the study of adherence monitoring interventions needs to ensure that the programmes are accessible to those with learning and physical disabilities, non-English speakers, different age groups and those with health literacy problems.</p>
Study design	<p>Cluster randomised controlled trials comparing monitoring adherence using different technologies/devices. Implicit in the investigation of the best monitoring method or device, is that poor adherers will be detected and feedback will improve adherence to controller medication and therefore improve patient outcomes and asthma control. A range of studies may be needed, including 'efficacy' trials and more pragmatic 'real-world' effectiveness and implementation trials. Studies will need to compare the different</p>

	devices/strategies that are currently available to monitor adherence and feedback this information to patients with the aim of improving adherence and patient outcomes. Studies need to include health economic evaluation and be of sufficient duration to confirm persistence of benefit (minimum of 12 months). Studies should be adequately powered to detect sub-groups who are likely to respond or not respond to this strategy.
Feasibility	Asthma is common and uncontrolled in over half of all patients. Multiple different technologies to monitor adherence are already available.
Other comments	There are commercial implications to technologies designed to monitor adherence and commercial partnership is possible. Intellectual property rights issues will need to be considered.
Importance	<ul style="list-style-type: none"> High: the research is essential to inform future updates of key recommendations in the guideline.

1N.1.1.4 Research question 4: What is the current frequency and the current method being used to check the inhaler technique of people with asthma? What is the optimal frequency and the best method of checking inhaler technique to improve clinical outcomes for people with asthma?

Why this is important: The knowledge and understanding of how to use an inhaler properly is the cornerstone of asthma management and symptom control. There has been an increase in the types of inhaler devices and the types of delivery system available. The various types of drugs for asthma control are also available in different inhaler devices on their own and in combination of two drugs. It is therefore vital for patients to learn the proper inhaler technique for their device to ensure optimum drug delivery to the lungs for asthma control.

Criteria for selecting high-priority research recommendations:

PICO question	<p>Population: Adults, children and young people aged 5-16 years with a confirmed diagnosis of asthma; children 0-5 years with recurrent wheeze.</p> <p>Intervention: Electronic devices to monitor inhaler technique; visual assessment by doctor, nurse or pharmacist.</p> <p>Comparison: Different frequencies of monitoring inhaler technique; monitoring using electronic devices vs. monitoring by visual assessment.</p> <p>Outcomes: Mortality; QoL; exacerbations; unscheduled healthcare utilisation; adherence; asthma control.</p>
Importance to patients or the population	Proper inhaler technique for optimum drug delivery to the lungs of people with asthma is vital for asthma control. Asthma exacerbations can occur frequently if not properly controlled. This has a significant impact on the quality of life and constitutes a considerable healthcare burden with pressures on secondary care emergency departments. There is a lack of objective evidence that regular review of inhaler technique improves asthma control and reduces exacerbations. This is important because checking inhaler technique is a simple intervention that if effective could result in lower doses of inhaled steroids to control the asthma and in a reduction of acute exacerbations.
Relevance to NICE guidance	The answer to this question will allow NICE to make a definitive statement on the optimal frequency and the best method of checking inhaler technique to improve clinical outcome for people with asthma.
Relevance to the NHS	Acute asthma attacks are one of the commonest reasons for visits to hospital emergency departments. The most expensive expenditure for the NHS is on prescribing the inhaled drugs used for respiratory conditions. It is estimated that the top three most expensive drugs in the NHS are inhalers. It is important to teach patients with asthma the correct technique for using their inhalers. It is equally important to review their inhaler technique regularly. Current guidance is to check the patient's inhaler technique annually. The inhalers should only be prescribed after patient has received training in the use of the device and have

	<p>demonstrated satisfactory technique.</p> <p>Satisfactory understanding of individual inhaler techniques and regular checking by the clinicians and pharmacists is vital to improving clinical outcomes for control of asthma.</p>
National priorities	<p>The intervention is simple and could result in better asthma control without increasing medication use. The 'prescribing and medicine uses' recommendation from NRAD (National Review of Asthma Deaths)¹⁴⁸⁸ is to assess inhaler technique routinely and formally document at every annual review. It should also be checked by the pharmacist when a new device is dispensed.</p>
Current evidence base	<p>There is a lack of good quality data available. Different studies used non-standardised scores making comparisons difficult. Teaching inhaler technique has been shown to improve correct usage but it is less clear if that leads to improved asthma control.</p> <p>For 'monitoring inhaler technique vs no monitoring' evidence was only available in adults from one small RCT and evidence was of low and very low quality for all outcomes.</p> <p>For 'Monitoring using an electronic training device and physician feedback compared to physician feedback only', evidence in adults was available from 2 studies, and in children from 1 study. Evidence for all outcomes was of low and very low quality.</p> <p>Based on the NRAD report, people with asthma who are unable to use their inhaler correctly are at risk of poor asthma control, potentially resulting in an asthma attack. It is recorded in the report that only 96 out of 135 (71%) patients had an assessment of inhaler technique.</p>
Equality	<p>Asthma affects all ages and ethnic groups, and the design of the research needs to encompass this. In particular, the study needs to ensure that the programmes are accessible to those with learning and physical disabilities, non-English speakers, different age groups and those with health literacy problems.</p>
Study design	<p>A systematic review is needed first to elucidate the current frequency and the current method being used to check inhaler technique. This will inform randomised control trials to investigate the optimal frequency and best method of checking inhaler technique.</p>
Feasibility	<p>Due to the multiple different types of inhaler currently available it will be difficult to develop a single study to answer this critical research question. However, it will be possible to look at dry powder and metered dose inhalers separately to address the issues of how best to teach inhaler technique and the optimal frequency for monitoring it.</p> <p>All primary and secondary care facilities will be able to participate in a multicentre study which would allow the rapid recruitment of the required number of participants to give a clear answer to the research question.</p>
Other comments	<p>It is important to study simple techniques that improve control without increases in steroid medication.</p> <p>Trials to check inhaler technique for monitoring asthma control will attract commercial sponsors. However given the size of the problem, the potential impact to the patients and the NHS and the favourable policy context, a high quality study addressing this question would be an appropriate target for NIHR funding.</p>
Importance	<ul style="list-style-type: none"> • High: the research is essential to inform future updates of key recommendations in the guideline.

1N.1.1.5 **Research question 5:** What is the long-term (more than 12 months) clinical and cost effectiveness of
 2 using tele-healthcare as a means to monitor asthma control in children, young people and adults?
 3 Modalities of tele-healthcare can include telephone interview (healthcare professional involvement)
 4 and internet or smartphone-based monitoring support (no healthcare professional involvement).

5 **Why this is important:** Asthma outcomes have not improved in the past 15 years, and the personal
 6 and economic costs of poor control are high. Computers and smartphones play an ever-greater role
 7 in modern life, with a growing proportion of the population using them regularly for work, leisure,
 8 communication and information. The efficient use of distance monitoring systems and the
 9 integration of new technologies into healthcare are important for patients and for healthcare
 10 systems in terms of convenience, costs and outcomes.

11 **Criteria for selecting high-priority research recommendations:**

PICO question	<p>Population: Adults, children and young people with a confirmed diagnosis of asthma.</p> <p>Intervention: Monitoring asthma control using telephone interview with a healthcare professional and internet/smartphone-based monitoring support.</p> <p>Comparison: Usual care; monitoring asthma control with healthcare professional involvement e.g. telephone interview vs. monitoring asthma control with no healthcare professional involvement e.g. internet/smartphone-based monitoring support.</p> <p>Outcome: Mortality; QoL; exacerbations; unscheduled healthcare utilisation; adherence; asthma control.</p>
Importance to patients or the population	Asthma is a long-term and incurable condition, and outcomes remain sub-optimal. Regular monitoring and self-management are recommended in guidelines to improve outcomes, but can be difficult to achieve in practice. New technologies can be used to improve communication between patient and clinician and to provide individualised education and self-management support.
Relevance to NICE guidance	Clarification of the role of tele-healthcare in asthma will allow the NICE guidelines relating to the diagnosis and monitoring of asthma to make recommendations on the appropriate use of tele-healthcare strategies in NHS care.
Relevance to the NHS	Asthma continues to result in avoidable deaths, admissions and quality of life impairment, all with associated costs. More efficient monitoring can allow proactive care to prevent adverse outcomes and so potentially reduces health resource use and costs by more efficient care.
National priorities	Reducing mortality considered amenable to healthcare is the overarching indicator of Domain 1 of the NHS Outcomes Framework, and inadequate monitoring has been identified in the national review of Asthma deaths as a potentially avoidable factor in asthma deaths. Improving outcomes in asthma are highlighted in the National Strategy in COPD and Asthma as a national priority.
Current evidence base	The current evidence base of tele-healthcare in asthma is inadequate and contradictory; some studies have indicated potential benefits, but some have not. Further research is required to identify the modality of tele-healthcare that is most effective (e.g. telephone support, internet/smartphone based monitoring and self-management support), qualifying the acceptability, benefits, risks and costs associated with different programmes in different patient groups.
Equality	Asthma affects all ages and ethnic groups, and the design of the research needs to encompass this. In particular, the study of digital technology interventions needs to ensure that the programmes are accessible to those with learning and physical disabilities, non-English speakers, different age groups and those with health literacy problems.
Study design	Appropriately designed and powered randomised controlled trials comparing tele-healthcare interventions with usual care and with other monitoring

	strategies. A range of studies may be needed, including 'efficacy' trials and more pragmatic 'real-world' effectiveness and implementation trials. Cluster randomisation is likely to be needed to prevent 'contamination' of control groups. Studies need to include health economic evaluation and be of sufficient length to confirm persistence of benefit (minimum of 12 months). Studies should be adequately powered to detect sub-groups who are likely to respond or not respond to this strategy.
Feasibility	Asthma is very common and uncontrolled in over half of all patients. With technological advances, access to tele-healthcare and digital technologies is common and relatively inexpensive.
Other comments	There are potential commercial implications to tele-healthcare monitoring systems, and commercial partnership is possible. IPR issues will need to be carefully considered.
Importance	<ul style="list-style-type: none"> • High: the research is essential to inform future updates of key recommendations in the guideline.

1 N.2 Other research recommendations

- 2 6. What is the clinical and cost effectiveness of using validated quality of life questionnaires and the
- 3 RCP 3 Questions as tools to monitor asthma control in adults and young people aged over 16
- 4 years?
- 5 7. What is the clinical and cost effectiveness of using validated paediatric questionnaires to monitor
- 6 asthma control in children aged 5-16 years old with asthma?
- 7 8. What is the clinical and cost effectiveness of using blood eosinophils as a tool to monitor asthma
- 8 control?
- 9 9. Which patient groups are likely to benefit from FeNO monitoring to guide asthma management,
- 10 for example, individuals with atopy, frequent asthma attacks, poor adherence?
- 11 10. What is the clinical and cost effectiveness of FeNO-guided monitoring of asthma in real-world
- 12 settings?
- 13

1 **Appendix O: Contributors to the guideline**

2 **NICE project team**

- 3 • Sarah Willett – Guideline Lead
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- 9 • Gareth Haman – Editor

10 **Stakeholders**

- 11 • TBC

12

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