

NEW ZEALAND HEALTH TECHNOLOGY ASSESSMENT (NZHTA)
THE CLEARING HOUSE FOR HEALTH OUTCOMES AND
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Department of Public Health and General Practice
Christchurch School of Medicine and Health Sciences, Christchurch, New Zealand

Validity of clinical history and laboratory tests in the diagnosis of asthma

A critical appraisal of the literature

Rob Weir
Peter Day

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CONTACT DETAILS

New Zealand Health Technology Assessment
The Clearing House for Health Outcomes and Health Technology Assessment
Department of Public Health and General Practice
Christchurch School of Medicine and Health Sciences
P O Box 4345
Christchurch
New Zealand
Tel: +64 3 364 1152 Fax: +64 3 364 1152

E-mail: nzhta@chmeds.ac.nz

Web Site: <http://nzhta.chmeds.ac.nz>

LIST OF ABBREVIATIONS

Δ	=	change in
%PV	=	% of predicted value
95%CI	=	95% confidence interval
abs.	=	absolute
AIA	=	aspirin intolerant asthma
ASA	=	acetylsalicylic acid
ATA	=	aspirin tolerant asthma
ATS	=	American Thoracic Society
BaS	=	barium swallow
BHR	=	bronchial hyper-responsiveness
Bronch.	=	bronchoscopy
cf.	=	compared with
CHF	=	congestive heart failure
CIC	=	carbachol inhalational challenge
CNPC	=	chronic non-productive cough
COPD	=	chronic obstructive pulmonary disease
CXR	=	chest Xray
diff.	=	differential
dx	=	diagnosis
ECP	=	eosinophil cationic protein
ENT	=	ear, nose and throat examination
esoph	=	esophageal
FEV ₁	=	forced expiratory volume in one second
FOT	=	forced oscillation technique
FVC	=	forced vital capacity
GINA	=	Global Information Network on Asthma
Hx	=	history
IgE	=	Immunoglobulin type E

init.	=	initial
ITT	=	intention to treat
max.	=	maximum
Meth.	=	methacholine
mg	=	milligrams
ml	=	millilitres
MI	=	myocardial infarction
N/A	=	not available
NPV	=	negative predictive value
<i>n.s.</i>	=	not statistically significant
NSAID	=	non-steroidal anti-inflammatory drug
NSW	=	New South Wales
OPD	=	outpatient department
OR	=	odds ratio
PC ₁₅	=	provocation concentration (usually methacholine or histamine) to cause a 15% fall in FEV ₁
PC ₂₀	=	provocation concentration (usually methacholine or histamine) to cause a 20% fall in FEV ₁
PEFR	=	peak expiratory flow rate
PPV	=	positive predictive value
pred.	=	predicted
PV	=	predicted value
R _{aw}	=	airway resistance
resp.	=	respiratory
SIGN	=	Scottish Intercollegiate Guidelines Network
SOB	=	shortness of breath
SPT	=	skin prick testing
SXR	=	sinus Xray
T _{rs}	=	time constant of respiratory system
µg	=	micrograms
µmol	=	micromoles

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Scope of systematic review of asthma diagnosis

The development of this systematic review protocol involved extensive consultation between NZHTA and the Diagnosis Sub-committee of the Asthma Working Group of the New Zealand Guidelines Group.

SEARCH METHODOLOGY

Search strategy

Searches were restricted to information published from 1st January 1997 onwards, in English. Original searches were carried out in January 2001. Infants and children were excluded. Chronic obstructive respiratory disease was also excluded.

An additional very broad combined search of the Pre-Medline, Medline, Embase, Current Contents, and Cinahl databases for papers on any aspect of asthma in New Zealand was also completed in March 2001.

Principal sources of information

The following databases were searched using the search strategies outlined in Appendix 1:

Bibliographic databases

- Medline
- Embase
- Cinahl
- Current Contents
- Science Citation Index

Review databases

- Cochrane Library
- Best Evidence
- Centre for Reviews & Dissemination databases

Library catalogues

- New Zealand Ministry of Health library
- New Zealand Bibliographic database - Te Puna
- US National Library of Medicine
- World Health Organisation

Websites

- Health Canada
 - US Centers for Disease Control
-

- British Thoracic Society
- EGuidelines (UK)
- University of Dundee Asthma Research Unit
- UK General Practice Airways Group
- UK Department of Health publications
- Meta-register of Controlled Trials
- TRIP - Turning Research into Practice
- Health Evidence Bulletins Wales
- OMNI - Organised Medical Networked Information
- European Federation of Asthma and Allergy Associations
- GINA - Global Information Network on Asthma
- Canadian Office for Health Technology Assessment
- Canadian Network for Asthma Care
- Canadian Lung Association
- Canadian Thoracic Society
- Asthma Society of Canada
- ClinicalTrials.gov
- American Academy of Allergy Asthma and Immunology
- JAMA Asthma Information Center - Physicians Section
- US National Heart, Lung, and Blood Institute
- US Asthma Clinical Research Network
- US National Institute of Allergy and Infections Diseases
- Thoracic Society of New Zealand and Australia
- Australian Department of Health & Aged Care
- Ministerial Asthma Working Party

Note: hand searching of journals, contacting of manufacturers, or contacting of authors for unpublished research was not undertaken during the search process.

Major search terms used

- Index terms from Medline (MeSH headings): asthma, diagnosis, asthma-diagnosis-differential, sensitivity and specificity, forced expiratory volume, peak expiratory flow rate, hay fever, rhinitis, cough, dyspnea,eczema
- Index terms from Embase: asthma, diagnosis, asthma-diagnosis, differential diagnosis, forced expiratory volume, peak expiratory flow rate, cough, dyspnea, eczema, hay fever, rhinitis
- Additional keywords used: (not standard index terms): short* near breath*, dyspnoea, wheeze, tight* near chest, allerg*, atop*
- Keywords used for exclusions: child*, infan*, paediatric* or pediatric* [as *title* words or words in *journal titles*], chronic obstructive, coad, copd [as *title* words], asthma-chemically induced

The complete search strategies are given in Appendix 1.

STUDY INCLUSION CRITERIA

Studies published in English language from 1997 onwards are included. The population of interest is defined as adults with acute or chronic asthma, including aspirin, exercise and occupational induced asthma. A strict definition of adult based on age inclusion criteria has been avoided. Where both children and adults make up the study population these studies have been included.

Studies appraised were restricted to systematic reviews or original research appearing in the published literature.

Studies were included if they compared the validity of various symptoms, signs and investigations (henceforth referred to in aggregate as “screening tests”) between people with and with out asthma. The screening tests of interest were:

- cough
- wheeze
- dyspnoea
- past history of asthma
- family history of asthma
- allergen induced symptoms
- peak expiratory flow rate (PEFR)
- spirometry
- challenge testing
- sputum eosinophils
- sputum eosinophil cationic protein (ECP)
- serum ECP
- blood eosinophils
- serum IgE.

Models that included the above screening tests were also included in this review.

STUDY EXCLUSION CRITERIA

Studies were excluded if they only included children (classified as 12 years or younger or an article using the term ‘child’ or ‘children’ or ‘paediatric’ or ‘pediatric’). Letters, non-systematic reviews, editorials and comments were also excluded.

PATIENT OUTCOMES

When possible, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were presented in the results. Other measures of effect were used as necessary.

STUDY SELECTION

Studies were selected for appraisal using a two-stage process. Initially the titles and abstracts (where available) identified from the search strategy were scanned and excluded as appropriate. The full text articles were retrieved for the remaining studies and these were appraised if they fulfilled the study selection criteria outlined above.

There were 1402 studies identified by the search strategy (see appendix 1). Ninety-six full text articles were obtained after excluding studies from the search titles and abstracts. A further 62 of these full text articles did not fulfil the inclusion criteria. Therefore, 34 articles were fully appraised and are included in this report.

EVIDENCE TABLES

Key information summaries including study reference, study design, study grading, country in which the study was performed, screening and reference tests, patient inclusion and exclusion criteria, sample size, results (including relevant statistical data) and comments on internal validity issues arising from the study appraisal were presented in the form of evidence tables. Methodology for calculating sensitivity, specificity, PPV and NPV is presented in Appendix 2.

All studies were appraised using modified SIGN (Scottish Intercollegiate Guidelines Network) methodology checklists (see example in Appendix 3). The evaluation criteria are defined by a series of questions covering study internal validity. These questions addressed the quality of the study research question(s), validity of the reference standard, blinding between measurement of the screening and reference standard, timing of measuring the reference standard, use of a valid design, presentation of sensitivity and specificity data, appropriate statistical analysis and participation rate. Other criteria were dependent on the study design used.

The final grading (1++, 1+, 1-, 2++, 2+ or 2-) was allocated based upon the study design and study quality. A grading of 1 required the use of a randomised controlled trial design.

For a randomised controlled trial to receive a 1++ grading the following criteria needed to be fulfilled:

- clearly defined study question
- a clear description of an adequate randomisation process
- absence of baseline differences in demographic variables, markers of asthma severity and other potential confounding variables between intervention groups post-randomisation
- an adequate concealment method and use of double blinding
- outcomes measured in a standard, valid and reliable way
- all study arms treated equally
- at least 80% of the sample randomised were included in the presented analyses
- an intention to treat (ITT) analysis was presented
- pharmaceutical company involvement was restricted to either funding alone or no involvement.

Factors that automatically consigned randomised controlled trials to a 1- grading included:

- open study
- study groups were not treated equally
- ITT analysis not presented
- significant omissions or errors in patient demographic information and outcome results.

Combinations of two or more of the following also resulted in a 1- grading:

- baseline study differences, single blind, less than 80% of the participant's randomised were analysed, and pharmaceutical company staff were included at authorship level.

All other randomised controlled trials were graded as 1+.

All non-randomised controlled trials received a grading of 2. These studies were further divided into 2++, 2+ or 2- dependent on the internal validity of the studies.

For a study to receive a 2++ grading the following criteria were required:

- a valid reference standard (including a combination of an appropriate clinical history and reversible airflow limitation)
- blinding between screening test and reference test measurements
- patients selected were independent of the reference standard results
- a valid design was used
- participants in asthma and non-asthma groups were comparable (apart from the diagnosis of asthma)
- the participation rate was greater than 80% and there were no significant differences between the participants and non-participants across a range of factors
- measurement of the screening and reference test was made in a standard, valid and reliable manner

Furthermore, the sensitivity and specificity should be presented or calculable from the data presented.

A study received a grading of 2- if one or more of the following criteria were present:

- the reference standard was unsatisfactory (e.g. reliance on clinical history alone)
- the reference standard included the same test as that used for screening
- the participation rate was under 60%
- measurements were not performed using a standard, valid or reliable method
- baseline differences between asthma and non-asthma groups existed
- at least three of the following limitations existed:
 - blinding between test and reference standard was not described
 - data was not presented on whether patients were selected independent of reference results
 - it was unclear if the reference standard was measured before the screening test
 - participation rate was not documented
 - differences between asthma and non-asthma populations were not documented
 - there was doubt about differentiation between participants with and without asthma.

Furthermore, a study was graded as 2- if the sensitivity and specificity was not presented and could not be calculated.

All other non-randomised controlled trials were categorised as 2+.

When possible, the PPV and NPV were calculated based on an asthma prevalence of 25%. This was performed by adjusting the number of people who did not have asthma (based on reference standard) so that total people with asthma (based on reference standard) were 25% of the total sample size. The proportion of people with positive and negative screening tests was unchanged before and after this adjustment. The prevalence of 25% was selected based on the article by D'Souza et al. (1999).

Study limitations

Systematic reviews are limited by the quality of the studies included in the review and the methodology of the systematic review.

There was one randomised controlled trial (cross over design) appraised in this review. However, this study had significant limitations and was assigned a 1- grading. Ordinarily studies graded as 1- should be excluded so considerable caution should be applied in considering the implications of this study. The reader is warned not to assume it is of high quality since it was in grading category 1. Eleven of 34 studies (32%) received a grading of 2+ and 22 of 34 (65%) 2-. As with the study graded as 1-, ordinarily studies graded as 2- would be excluded. Therefore, the reader should use these studies with caution.

Common limitations to the study designs included:

- lack of blinding between the screening and reference test measurements
- poor documentation about key variables of validity (participation rate, patient selection methods, blinding between the measurement of screening and reference tests, lack of comparison between participants and non-participants)
- sensitivity and specificity data not presented.

There is no single, universally accepted gold standard test for asthma. Potential implications include:

- difficulty assessing the validity of screening tests when diagnostic misclassification is a potential issue
- a range of “gold standards” were used so comparison between studies is difficult.

Individual study limitations are described in the comments section of the evidence tables.

Limitations to the review methodology that need to be considered in developing an asthma diagnostic guideline include restriction to:

- articles published from 1997 onwards
- the published literature
- English language articles
- reviewing each study by one researcher only.

In developing a guideline for asthma diagnosis consideration will need to be given to studies published pre-1997. The vast majority of articles of interest were published in the pre-1997 time period so methods should be developed by the guidelines group to assess whether the new evidence presented in this review is sufficient to alter any recommendations included in previous evidence-based guidelines.

Restriction to the published literature is likely to lead to bias since the unpublished literature tends to consist of studies not identifying a significant result.

Restriction by language may result in study bias but the direction of this bias cannot be determined.

Although two researchers appraised the articles included in this review they did not cross validate the data extraction and appraisal process.

None of the articles appraised were set in New Zealand. Therefore, the generalisability of these studies to the New Zealand setting needs to be considered.

The studies were initially selected by examining the abstracts of these articles. Therefore, it is possible that some studies were inappropriately excluded prior to examination of the full text article.

There has been no attempt to summarise the results by screening test. The results have been presented by screening test. This has necessitated the inclusion of the same study in more than one table at times (since more than one screening test was used).

This review was conducted over a limited time frame (January 2001 – May 2001).

Evidence tables

Wheeze

Table 1: Validity of wheeze as a diagnostic indicator of asthma

Study Source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes			Comments
(Lai et al. 1997) Cross-sectional Grade 2+ Country: China	<u>Tests:</u> Video and written questionnaire examining: Wheeze Night wheeze Exercise wheeze Night cough Severe wheeze Asthma ever <u>Reference:</u> PC ₂₀ (methacholine)	<u>Inclusion criteria:</u> 12-18 year old school children	189		Wheeze (video)	Wheeze (written)	<ul style="list-style-type: none"> Mean age 14 and female 41% 16 of 189 had bronchial hyperresponsiveness (BHR), 32 had a history of ever having asthma, 14 of the 16 with BHR had a history of ever being diagnosed with asthma. Reference for asthma was BHR – may have low sensitivity for asthma which could artificially reduce the specificity of the screening symptoms Unclear whether investigators were blinded to reference and screening results but reference standard produces a firm outcome. Reference standard was measured after the screening tests. ¹Based on asthma prevalence of 25% ²Based on asthma prevalence of 10% Study also presented under cough and asthma ever
(Lai et al. 1997) Cross-sectional Grade 2+ Country: China	<u>Tests:</u> Video and written questionnaire examining: Wheeze Night wheeze Exercise wheeze Night cough Severe wheeze Asthma ever <u>Reference:</u> PC ₂₀ (methacholine)	<u>Inclusion criteria:</u> 12-18 year old school children	189		Exercise wheeze (video)	Exercise wheeze (written)	<ul style="list-style-type: none"> Mean age 14 and female 41% 16 of 189 had bronchial hyperresponsiveness (BHR), 32 had a history of ever having asthma, 14 of the 16 with BHR had a history of ever being diagnosed with asthma. Reference for asthma was BHR – may have low sensitivity for asthma which could artificially reduce the specificity of the screening symptoms Unclear whether investigators were blinded to reference and screening results but reference standard produces a firm outcome. Reference standard was measured after the screening tests. ¹Based on asthma prevalence of 25% ²Based on asthma prevalence of 10% Same study as above Study also presented under cough and asthma ever

Table 1: Validity of wheeze as a diagnostic indicator of asthma (*continued*)

Study Source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes		Comments
(Lai et al. 1997) Cross-sectional Grade 2+ Country: China	<u>Tests:</u> Video and written questionnaire examining: Wheeze Night wheeze Exercise wheeze Night cough Severe wheeze Asthma ever <u>Reference:</u> PC ₂₀ (methacholine)	<u>Inclusion criteria:</u> 12-18 year old school children	189	Night wheeze (video)	Night wheeze (written)	<ul style="list-style-type: none"> ▪ Mean age 14 and female 41% ▪ 16 of 189 had bronchial hyperresponsiveness (BHR), 32 had a history of ever having asthma, 14 of the 16 with BHR had a history of ever being diagnosed with asthma. ▪ Reference for asthma was BHR – may have low sensitivity for asthma which could artificially reduce the specificity of the screening symptoms ▪ Unclear whether investigators were blinded to reference and screening results but reference standard produces a firm outcome. Reference standard was measured after the screening tests. ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10% ▪ Same study as above ▪ Study also presented under cough and asthma ever
(Lai et al. 1997) Cross-sectional Grade 2+ Country: China	<u>Tests:</u> Video and written questionnaire examining: Wheeze Night wheeze Exercise wheeze Night cough Severe wheeze Asthma ever <u>Reference:</u> PC ₂₀ (methacholine)	<u>Inclusion criteria:</u> 12-18 year old school children	189	Severe wheeze (video)	Severe wheeze (written)	<ul style="list-style-type: none"> ▪ Mean age 14 and female 41% ▪ 16 of 189 had bronchial hyperresponsiveness (BHR), 32 had a history of ever having asthma, 14 of the 16 with BHR had a history of ever being diagnosed with asthma. ▪ Reference for asthma was BHR – may have low sensitivity for asthma which could artificially reduce the specificity of the screening symptoms. ▪ Unclear whether investigators were blinded to reference and screening results but reference standard produces a firm outcome. Reference standard was measured after the screening tests. ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10% ▪ Same study as above ▪ Study also presented under cough and asthma ever

Table 1: Validity of wheeze as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(de Marco et al. 1998) Cross-sectional Grade 2- Country: Italy	<u>Tests:</u> Wheeze Dyspnoea Asthma attack Ever asthma <u>Reference:</u> Clinician consensus based on standard questionnaire, lung function including methacholine challenge and skin testing.	<u>Inclusion criteria:</u> Age 20-44 Resident in selected parts of Italy	811	Wheeze Sensitivity (%) 69 Specificity (%) 91 PPV ¹ (%) 71 NPV ¹ (%) 90 PPV ² (%) 46 NPV ² (%) 96	<ul style="list-style-type: none"> ▪ Demographic details not supplied ▪ 105 participants labelled as having asthma ▪ Response rate 44% ▪ Possibility of recall bias ▪ Reference and screening tests were not independent ▪ Clinical judgement used in determining the presence of asthma - criteria not stipulated ▪ ¹Based on prevalence of asthma of 25% ▪ ²Based on asthma prevalence of 10% ▪ Study also presented under asthma ever, dyspnoea and dyspnoea with wheeze

Table 1: Validity of wheeze as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes			Comments
(Thiadens et al. 1998a) Cross-sectional Grade 2- Country: Netherlands	<p><u>Tests:</u> Current: Wheeze Dyspnoea with wheeze Night cough Prolonged expiration Past: Night cough Dyspnoea Wheeze Allergen induced symptoms Family history of asthma</p> <p><u>Reference:</u> One or more episodes of wheeze, cough or dyspnoea lasting > 3 weeks and PC₂₀ ≤ 15.6 µmol methacholine or FEV₁ improved ≥ 9% of predicted post 400 µg salbutamol</p>	<p><u>Inclusion criteria:</u> Age 18-75 Cough ≥ 2 weeks</p> <p><u>Exclusion criteria:</u> Previous diagnosis of asthma or COPD Pregnancy Cardiovascular or concomitant pulmonary diseases.</p>	192	Adjusted odds ratio ¹ (95%CI)	Current wheeze 3.5 (2.0, 6.6)	Wheeze in past year 2.9 (1.5, 4.9)	<ul style="list-style-type: none"> ▪ Mean age 44 and female 62% ▪ Mean FEV₁ 91%PV (all participants), 86%PV (asthma group) ▪ 74 participants classified with asthma, 14 classified with OPD ▪ Asthma and COPD groups combined for analysis – decreasing the specificity of the reference standard ▪ Asthma definition may have missed some cases due to the requirement for symptoms of acute asthma lasting 3 weeks at some time during the past year. Some cases may also have been over-inclusive due to the high PC₂₀ cut off. ▪ Unclear if the screening symptoms and the reference standard were measured independently (blindly). ▪ 192 of 221 eligible (87%) patients participated in the study. There were no age or gender differences between participants and non-participants. ▪ Sensitivity and specificity data was not provided in the study. This data could be calculated for an overall model. ▪ ¹Asthma and COPD combined ▪ Study also presented under cough, dyspnoea, dyspnoea with wheeze, prolonged expiration, allergen induced symptoms, family history and models predicting the diagnosis of asthma

Table 1: Validity of wheeze as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Thiadens et al. 2000) Cross-sectional Grade 2- Country: Netherlands	<u>Tests:</u> Wheeze Allergen induced symptoms Dyspnoea attacks <u>Reference:</u> Combination of ≥1 episode wheeze, SOB or cough for more than 3 weeks in past year, and FEV ₁ improved ≥ 9%PV post 400 µg salbutamol or PC ₂₀ ≤ 15.6 µmol methacholine	<u>Inclusion criteria:</u> Age 18-75 Cough ≥ 2 weeks <u>Exclusion criteria:</u> Prior diagnosis of asthma or COPD Pregnancy Cardiovascular disease Other respiratory disease	192	Current wheeze (within 2 weeks) OR 4.0 (95%CI) (1.3,12.4)	<ul style="list-style-type: none"> ▪ Mean age 44 and female 63% ▪ Mean FEV₁ 91%PV ▪ Primary care setting ▪ Results presented restricted to 80 patients with symptoms consistent with acute bronchitis (29 were diagnosed with asthma using the criteria listed) ▪ No documentation concerning blinding between screening results and reference results ▪ Participation rate 87% ▪ Study also presented under dyspnoea and allergen induced symptoms

Cough

Table 2: Validity of cough as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments																								
(Lai et al. 1997) Cross-sectional Grade 2+ Country: China	<u>Tests:</u> Video and written questionnaire examining: Wheeze Night wheeze Exercise wheeze Night cough Severe wheeze Asthma ever <u>Reference:</u> PC ₂₀ (methacholine)	<u>Inclusion criteria:</u> 12-18 year old school children	189	<table border="1"> <thead> <tr> <th></th> <th>Night cough (video)</th> <th>Night cough (written)</th> </tr> </thead> <tbody> <tr> <td>Number</td> <td>189</td> <td>189</td> </tr> <tr> <td>Sensitivity (%)</td> <td>31</td> <td>38</td> </tr> <tr> <td>Specificity (%)</td> <td>68</td> <td>65</td> </tr> <tr> <td>PPV¹ (%)</td> <td>24</td> <td>27</td> </tr> <tr> <td>NPV¹ (%)</td> <td>75</td> <td>76</td> </tr> <tr> <td>PPV² (%)</td> <td>10</td> <td>11</td> </tr> <tr> <td>NPV² (%)</td> <td>90</td> <td>90</td> </tr> </tbody> </table>		Night cough (video)	Night cough (written)	Number	189	189	Sensitivity (%)	31	38	Specificity (%)	68	65	PPV ¹ (%)	24	27	NPV ¹ (%)	75	76	PPV ² (%)	10	11	NPV ² (%)	90	90	<ul style="list-style-type: none"> ▪ Mean age 14 and female 41% ▪ 16 of 189 had bronchial hyperresponsiveness (BHR), 32 had a history of ever having asthma, 14 of the 16 with BHR had a history of ever being diagnosed with asthma ▪ Reference for asthma was BHR – may have low sensitivity for asthma which could artificially reduce the specificity of the screening symptoms ▪ Unclear whether investigators were blinded to reference and screening results but reference standard produces a hard outcome. Reference standard was measured after the screening tests. ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10% ▪ Study also presented under wheeze and asthma ever
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Sensitivity (%)	31	38																											
Specificity (%)	68	65																											
PPV ¹ (%)	24	27																											
NPV ¹ (%)	75	76																											
PPV ² (%)	10	11																											
NPV ² (%)	90	90																											
(Rietveld et al. 1999) Grade 2+ Case control Country: Netherlands	<u>Tests:</u> Cough <u>Reference:</u> Based on recent challenge testing	<u>Inclusion criteria:</u> Age 7-17 (asthma) Referred from general and respiratory physicians Healthy controls recruited through newspaper advertisements	60	<table border="1"> <thead> <tr> <th></th> <th>Cough</th> </tr> </thead> <tbody> <tr> <td>Sensitivity (%)</td> <td>69</td> </tr> <tr> <td>Specificity (%)</td> <td>43</td> </tr> <tr> <td>PPV¹ (%)</td> <td>29</td> </tr> <tr> <td>NPV¹ (%)</td> <td>81</td> </tr> <tr> <td>PPV² (%)</td> <td>12</td> </tr> <tr> <td>NPV² (%)</td> <td>93</td> </tr> </tbody> </table>		Cough	Sensitivity (%)	69	Specificity (%)	43	PPV ¹ (%)	29	NPV ¹ (%)	81	PPV ² (%)	12	NPV ² (%)	93	<ul style="list-style-type: none"> • Mean age 12 (asthma group) and female 38% • Mean age and age range not stated for healthy volunteers • Thirty patients classified with asthma • Reference: Standard lacks details regarding type of challenge test and cut off values set • Blinding between screening and reference measurements not documented • No baseline comparison between asthma and control group • Drop out rate 1% • ¹Based on asthma prevalence of 25% • ²Based on asthma prevalence of 10% 										
	Cough																												
Sensitivity (%)	69																												
Specificity (%)	43																												
PPV ¹ (%)	29																												
NPV ¹ (%)	81																												
PPV ² (%)	12																												
NPV ² (%)	93																												

Table 2: Validity of cough as a diagnostic indicator of asthma (*continued*)

Study Source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes			Comments
(Thiadens et al. 1998a) Cross-sectional Grade 2- Country: Netherlands	<p><u>Tests:</u> Current: Wheeze Dyspnoea with wheeze Night cough Prolonged expiration Past: Night cough Dyspnoea Wheeze Allergen induced symptoms Family history of asthma</p> <p><u>Reference:</u> One or more episodes of wheeze, cough or dyspnoea lasting > 3 weeks and PC₂₀ ≤ 15.6 µmol methacholine or FEV₁ improved ≥ 9% of predicted post 400 µg salbutamol</p>	<p><u>Inclusion criteria:</u> Age 18-75 Cough ≥ 2 weeks</p> <p><u>Exclusion criteria:</u> Previous diagnosis of asthma or COPD Pregnancy Cardiovascular or concomitant pulmonary diseases</p>	192	Adjusted odds ratio ¹ (95%CI)	1.4 (0.7, 2.5)	Night cough Night cough in past year 0.8 (0.4, 1.6)	<ul style="list-style-type: none"> Mean age 44 and female 62% Mean FEV₁ 91%PV (all participants), 86%PV (asthma group) 74 participants classified with asthma, 14 classified with COPD Asthma and COPD groups combined for analysis – decreasing the specificity of the reference standard Asthma definition may have missed some cases due to the requirement for symptoms of acute asthma lasting 3 weeks at some time during the past year. Some cases may also have been over-inclusive due to the high PC₂₀ cut off Unclear if the screening symptoms and the reference standard were measured independently (blindly) 192 of 221 eligible (87%) patients participated in the study. There were no age or gender differences between participants and non-participants. Sensitivity and specificity data was not provided in the study. This data could be calculated for an overall model. ¹Asthma and COPD combined Study also presented under wheeze, dyspnoea, dyspnoea with wheeze, prolonged expiration, allergen induced symptoms, family history and models predicting the diagnosis of asthma

Asthma ever

Table 3: Validity of a past history of asthma as a diagnostic indicator of asthma

Study Source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Lai et al. 1997) Cross-sectional Grade 2+ Country: China	<u>Tests:</u> Video and written questionnaire examining: Wheeze Night wheeze Exercise wheeze Night cough Severe wheeze Asthma ever <u>Reference:</u> PC ₂₀ (methacholine)	<u>Inclusion criteria:</u> 12-18 year old school children	189	Asthma ever (written) Number 189 Sensitivity (%) 88 Specificity (%) 90 PPV ¹ (%) 75 NPV ¹ (%) 96 PPV ² (%) 49 NPV ² (%) 99	<ul style="list-style-type: none"> ▪ Mean age 14 and female 41% ▪ 16 of 189 had bronchial hyperresponsiveness (BHR), 32 had a history of ever having asthma, 14 of the 16 with BHR had a history of ever being diagnosed with asthma. ▪ Reference for asthma was BHR – may have low sensitivity for asthma which could artificially reduce the specificity of the screening symptoms ▪ Unclear whether investigators were blinded to reference and screening results but reference standard produces a firm outcome. Reference standard was measured after the screening tests. ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10% ▪ Study also presented under wheeze and cough
(de Marco et al. 1998) Cross-sectional Grade 2- Country: Italy	<u>Tests:</u> Wheeze Dyspnoea Asthma attack Ever asthma <u>Reference:</u> Clinician consensus based on standard questionnaire, lung function including methacholine challenge and skin testing.	<u>Inclusion criteria:</u> Age 20-44 Resident in selected parts of Italy	811	Asthma ever Sensitivity (%) 68 Specificity (%) 98 PPV ¹ (%) 92 NPV ¹ (%) 90 PPV ² (%) 79 NPV ² (%) 96	<ul style="list-style-type: none"> ▪ Demographic details not supplied ▪ 105 participants labelled as having asthma ▪ Response rate 44% ▪ Possibility of recall bias ▪ Reference and screening tests were not independent ▪ Clinical judgement used in determining the presence of asthma – criteria not stipulated ▪ ¹Based on prevalence of asthma of 25% ▪ ²Based on asthma prevalence of 10% ▪ Study also presented under wheeze, dyspnoea and dyspnoea with wheeze

Dyspnoea

Table 4: Validity of dyspnoea as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(de Marco et al. 1998) Cross-sectional Grade 2- Country: Italy	<u>Tests:</u> Wheeze Dyspnoea Asthma attack Ever asthma <u>Reference:</u> Clinician consensus based on standard questionnaire, lung function including methacholine challenge and skin testing.	<u>Inclusion criteria:</u> Age 20-44 Resident in selected parts of Italy	811	Dyspnoea Sensitivity (%) 32 Specificity (%) 94 PPV ¹ (%) 64 NPV ¹ (%) 81 PPV ² (%) 37 NPV ² (%) 93	<ul style="list-style-type: none"> ▪ Demographic details not supplied ▪ 105 participants labelled as having asthma ▪ Response rate 44% ▪ Possibility of recall bias ▪ Reference and screening tests were not independent ▪ Clinical judgement used in determining the presence of asthma – criteria not stipulated ▪ ¹Based on prevalence of asthma of 25% ▪ ²Based on asthma prevalence of 10% ▪ Study also presented under wheeze, asthma ever, and dyspnoea with wheeze

Table 4: Validity of dyspnoea as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Thiadens et al. 1998a) Cross-sectional Grade 2- Country: Netherlands	<u>Tests:</u> Current: Wheeze Dyspnoea with wheeze Night cough Prolonged expiration Past: Night cough Dyspnoea Wheeze Allergen induced symptoms Family history of asthma <u>Reference:</u> One or more episodes of wheeze, cough or dyspnoea lasting > 3 weeks and PC ₂₀ ≤ 15.6 µmol methacholine or FEV ₁ improved ≥ 9% of predicted post 400 µg salbutamol	<u>Inclusion criteria:</u> Age 18-75 Cough ≥ 2 weeks <u>Exclusion criteria:</u> Previous diagnosis of asthma or COPD Pregnancy Cardiovascular or concomitant pulmonary diseases.	192	Current SOB SOB in past year Adjusted odds ratio ¹ (95%CI) 4.2 (2.1, 7.7) 3.4 (1.7, 6.7)	<ul style="list-style-type: none"> ▪ Mean age 44 and female 62% ▪ Mean FEV₁ 91%PV (all participants), 86%PV (asthma group) ▪ 74 participants classified with asthma, 14 classified with COPD ▪ Asthma and COPD groups combined for analysis – decreasing the specificity of the reference standard ▪ Asthma definition may have missed some cases due to the requirement for symptoms of acute asthma lasting 3 weeks at some time during the past year. Some cases may also have been over-inclusive due to the high PC₂₀ cut off. ▪ Unclear if the screening symptoms and the reference standard were measured independently (blindly) ▪ 192 of 221 eligible (87%) patients participated in the study. There were no age or gender differences between participants and non-participants. ▪ Sensitivity and specificity data was not provided in the study. This data could be calculated for an overall model. ▪ ¹Asthma and COPD combined. ▪ Study also presented under wheeze, cough, dyspnoea with wheeze, prolonged expiration, allergen induced symptoms, family history and models predicting the diagnosis of asthma

Table 4: Validity of dyspnoea as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Thiadens et al. 2000) Cross-sectional Grade 2- Country: Netherlands	<u>Tests:</u> Wheeze Allergen induced symptoms Dyspnoea attacks <u>Reference:</u> Combination of ≥1 episode wheeze, SOB or cough for more than 3 weeks in past year, and FEV ₁ improved ≥ 9%PV post 400 µg salbutamol or PC ₂₀ ≤ 15.6 µmol methacholine	<u>Inclusion criteria:</u> Age 18-75 Cough ≥ 2 weeks <u>Exclusion criteria:</u> Prior diagnosis of asthma or COPD Pregnancy Cardiovascular disease Other respiratory disease	192	Dyspnoea in past year OR 3.2 (95%CI) (1.1,10.3)	<ul style="list-style-type: none"> ▪ Mean age 44 and female 63% ▪ Mean FEV₁ 91%PV ▪ Primary care setting ▪ Results presented restricted to 80 patients with symptoms consistent with acute bronchitis (29 were diagnosed with asthma using the criteria listed) ▪ No documentation concerning blinding between screening results and reference results ▪ Participation rate 87% ▪ Study also presented under wheeze and allergen induced symptoms

Attacks of dyspnoea with wheeze

Table 5: Validity of dyspnoea with wheeze as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(de Marco et al. 1998) Cross-sectional Grade 2- Country: Italy	<u>Tests:</u> Wheeze Dyspnoea Asthma attack Ever asthma <u>Reference:</u> Clinician consensus based on standard questionnaire, lung function including methacholine challenge and skin testing.	<u>Inclusion criteria:</u> Age 20-44 Resident in selected parts of Italy	811	Asthma attack Sensitivity (%) 34 Specificity (%) 100 PPV ¹ (%) 100 NPV ¹ (%) 82 PPV ² (%) 100 NPV ² (%) 93	<ul style="list-style-type: none"> ▪ Demographic details not supplied ▪ 105 participants labelled as having asthma ▪ Response rate 44% ▪ Possibility of recall bias ▪ Reference and screening tests were not independent ▪ Clinical judgement used in determining the presence of asthma – criteria not stipulated ▪ ¹Based on prevalence of asthma of 25% ▪ ²Based on asthma prevalence of 10% ▪ Study also presented under wheeze, asthma ever and dyspnoea

Table 5: Validity of dyspnoea with wheeze as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Thiadens et al. 1998a) Cross-sectional Grade 2- Country: Netherlands	<p><u>Tests:</u> Current: Wheeze Dyspnoea with wheeze Night cough Prolonged expiration Past: Night cough Dyspnoea Wheeze Allergen induced symptoms Family history of asthma</p> <p><u>Reference:</u> One or more episodes of wheeze, cough or dyspnoea lasting > 3 weeks and PC₂₀ ≤ 15.6 µmol methacholine or FEV₁ improved ≥ 9% of predicted post 400 µg salbutamol</p>	<p><u>Inclusion criteria:</u> Age 18-75 Cough ≥ 2 weeks</p> <p><u>Exclusion criteria:</u> Previous diagnosis of asthma or COPD Pregnancy Cardiovascular or concomitant pulmonary diseases</p>	192	<p>Current SOB and wheeze</p> <p>Adjusted odds ratio¹ (95%CI)</p> <p>7.3 (2.5, 22.1)</p>	<ul style="list-style-type: none"> ▪ Mean age 44 and female 62% ▪ Mean FEV₁ 91%PV (all participants), 86%PV (asthma group) ▪ 74 participants classified with asthma, 14 classified with COPD ▪ Asthma and COPD groups combined for analysis – decreasing the specificity of the reference standard ▪ Asthma definition may have missed some cases due to the requirement for symptoms of acute asthma lasting 3 weeks at some time during the past year. Some cases may also have been over-inclusive due to the high PC₂₀ cut off. ▪ Unclear if the screening symptoms and the reference standard were measured independently (blindly) ▪ 192 of 221 eligible (87%) patients participated in the study. There were no age or gender differences between participants and non-participants. ▪ Sensitivity and specificity data was not provided in the study. This data could be calculated for an overall model. ▪ ¹Asthma and COPD combined ▪ Study also presented under wheeze, cough, dyspnoea, prolonged expiration, allergen induced symptoms, family history and models predicting the diagnosis of asthma

Prolonged expiration

Table 6: Validity of prolonged expiration as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Thiadens et al. 1998a) Cross-sectional Grade 2- Country: Netherlands	<p><u>Tests:</u> Current: Wheeze Dyspnoea with wheeze Night cough Prolonged expiration Past: Night cough Dyspnoea Wheeze Allergen induced symptoms Family history of asthma</p> <p><u>Reference:</u> One or more episodes of wheeze, cough or dyspnoea lasting > 3 weeks and $PC_{20} \leq 15.6 \mu\text{mol}$ methacholine or FEV_1 improved $\geq 9\%$ of predicted post 400 μg salbutamol</p>	<p><u>Inclusion criteria:</u> Age 18-75 Cough ≥ 2 weeks</p> <p><u>Exclusion criteria:</u> Previous diagnosis of asthma or COPD Pregnancy Cardiovascular or concomitant pulmonary diseases</p>	192	<p>Prolonged Expiration</p> <p>Adjusted odds ratio¹ (95%CI) (1.7, 9.4)</p>	<ul style="list-style-type: none"> ▪ Mean age 44 and female 62% ▪ Mean FEV_1 91%PV (all participants), 86%PV (asthma group) ▪ 74 participants classified with asthma, 14 classified with COPD ▪ Asthma and COPD groups combined for analysis – decreasing the specificity of the reference standard ▪ Asthma definition may have missed some cases due to the requirement for symptoms of acute asthma lasting 3 weeks at some time during the past year. Some cases may also have been over-inclusive due to the high PC_{20} cut off. ▪ Unclear if the screening symptoms and the reference standard were measured independently (blindly) ▪ 192 of 221 eligible (87%) patients participated in the study. There were no age or gender differences between participants and non-participants. ▪ Sensitivity and specificity data was not provided in the study. This data could be calculated for an overall model. ▪ ¹Asthma and COPD combined ▪ Study also presented under wheeze, cough, dyspnoea, dyspnoea with wheeze, allergen induced symptoms, family history and models predicting the diagnosis of asthma

Allergen induced symptoms

Table 7: Validity of allergen induced symptoms as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Thiadens et al. 1998a) Cross-sectional Grade 2- Country: Netherlands	<p><u>Tests:</u> Current: Wheeze Dyspnoea with wheeze Night cough Prolonged expiration Past: Night cough Dyspnoea Wheeze Allergen induced symptoms Family history of asthma</p> <p><u>Reference:</u> One or more episodes of wheeze, cough or dyspnoea lasting > 3 weeks and $PC_{20} \leq 15.6$ μmol methacholine or FEV₁ improved $\geq 9\%$ of predicted post 400 μg salbutamol</p>	<p><u>Inclusion criteria:</u> Age 18-75 Cough ≥ 2 weeks</p> <p><u>Exclusion criteria:</u> Previous diagnosis of asthma or COPD Pregnancy Cardiovascular or concomitant pulmonary diseases</p>	192	<p>Allergen induced symptoms</p> <p>Adjusted odds ratio¹ (95%CI) (1.9, 13.7)</p>	<ul style="list-style-type: none"> ▪ Mean age 44 and female 62% ▪ Mean FEV₁ 91%PV (all participants), 86%PV (asthma group) ▪ 74 participants classified with asthma, 14 classified with COPD ▪ Asthma and COPD groups combined for analysis – decreasing the specificity of the reference standard ▪ Asthma definition may have missed some cases due to the requirement for symptoms of acute asthma lasting 3 weeks at some time during the past year. Some cases may also have been over-inclusive due to the high PC₂₀ cut off. ▪ Unclear if the screening symptoms and the reference standard were measured independently (blindly) ▪ 192 of 221 eligible (87%) patients participated in the study. There were no age or gender differences between participants and non-participants. ▪ Sensitivity and specificity data was not provided in the study. This data could be calculated for an overall model. ▪ ¹Asthma and COPD combined ▪ Study also presented under wheeze, cough, dyspnoea, dyspnoea with wheeze, allergen induced symptoms, family history and models predicting the diagnosis of asthma

Table 7: Validity of allergen induced symptoms as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Thiadens et al. 2000) Cross-sectional Grade 2- Country: Netherlands	<u>Tests:</u> Wheeze Allergen induced symptoms Dyspnoea attacks <u>Reference:</u> Combination of ≥ 1 episode wheeze, SOB or cough for more than 3 weeks in past year, and FEV ¹ improved $\geq 9\%$ PV post 400 μg salbutamol or PC ²⁰ ≤ 15.6 μmol methacholine	<u>Inclusion criteria:</u> Age 18-75 Cough ≥ 2 weeks <u>Exclusion criteria:</u> Prior diagnosis of asthma or COPD Pregnancy Cardiovascular disease Other respiratory disease	192	Allergen induced symptoms OR 5.2 (95%CI) (1.1,26.3)	<ul style="list-style-type: none"> ▪ Mean age 44 and female 63% ▪ Mean FEV¹ 91%PV ▪ Primary care setting ▪ Results presented restricted to 80 patients with symptoms consistent with acute bronchitis (29 were diagnosed with asthma using the criteria listed) ▪ No documentation concerning blinding between screening results and reference results ▪ Participation rate 87% ▪ Study also presented under wheeze and dyspnoea

Family history

Table 8: Validity of a family history of asthma as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Thiadens et al. 1998a) Cross-sectional Grade 2- Country: Netherlands	<p><u>Tests:</u> Current: Wheeze Dyspnoea with wheeze Night cough Prolonged expiration Past: Night cough Dyspnoea Wheeze Allergen induced symptoms Family history of asthma</p> <p><u>Reference:</u> One or more episodes of wheeze, cough or dyspnoea lasting > 3 weeks and $PC_{20} \leq 15.6$ μmol methacholine or FEV₁ improved $\geq 9\%$ of predicted post 400 μg salbutamol</p>	<p><u>Inclusion criteria:</u> Age 18-75 Cough ≥ 2 weeks</p> <p><u>Exclusion criteria:</u> Previous diagnosis of asthma or COPD Pregnancy Cardiovascular or concomitant pulmonary diseases</p>	192	<p>Family history</p> <p>Adjusted odds ratio¹ 1.0 (95%CI) (0.8, 2.8)</p>	<ul style="list-style-type: none"> ▪ Mean age 44 and female 62% ▪ Mean FEV₁ 91%PV (all participants), 86%PV (asthma group) ▪ 74 participants classified with asthma, 14 classified with COPD ▪ Asthma and COPD groups combined for analysis – decreasing the specificity of the reference standard ▪ Asthma definition may have missed some cases due to the requirement for symptoms of acute asthma lasting 3 weeks at some time during the past year. Some cases may also have been over-inclusive due to the high PC₂₀ cut off. ▪ Unclear if the screening symptoms and the reference standard were measured independently (blindly) ▪ 192 of 221 eligible (87%) patients participated in the study. There were no age or gender differences between participants and non-participants. ▪ Sensitivity and specificity data was not provided in the study. This data could be calculated for an overall model. ▪ ¹Asthma and COPD combined ▪ Study also presented under wheeze, cough, dyspnoea, dyspnoea with wheeze, prolonged expiration, allergen induced symptoms and models predicting the diagnosis of asthma

Models predicting the diagnosis of asthma

Table 10: Validity of clinically based models as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Thiadens et al. 1998a) Cross-sectional Grade 2- Country: Netherlands	<p><u>Tests:</u> Current: Wheeze Dyspnoea with wheeze Night cough Prolonged expiration Past: Night cough Dyspnoea Wheeze Allergen induced symptoms Family history of asthma</p> <p><u>Reference:</u> One or more episodes of wheeze, cough or dyspnoea lasting > 3 weeks and $PC_{20} \leq 15.6$ μmol methacholine or FEV₁ improved $\geq 9\%$ of predicted post 400 μg salbutamol</p>	<p><u>Inclusion criteria:</u> Age 18-75 Cough ≥ 2 weeks</p> <p><u>Exclusion criteria:</u> Previous diagnosis of asthma or COPD Pregnancy Cardiovascular or concomitant pulmonary diseases</p>	192	<p>Model¹</p> <p>Sensitivity (%) 59 Specificity (%) 90 PPV² (%) 66 NPV² (%) 87 PPV³ (%) 40 NPV³ (%) 95</p>	<ul style="list-style-type: none"> ▪ Mean age 44 and female 62% ▪ Mean FEV₁ 91%PV (all participants), 86%PV (asthma group) ▪ 74 participants classified with asthma, 14 classified with COPD ▪ Asthma and COPD groups combined for analysis – decreasing the specificity of the reference standard ▪ Asthma definition may have missed some cases due to the requirement for symptoms of acute asthma lasting 3 weeks at some time during the past year. Some cases may also have been over-inclusive due to the high PC₂₀ cut off. ▪ Unclear if the screening symptoms and the reference standard were measured independently (blindly) ▪ 192 of 221 eligible (87%) patients participated in the study. There were no age or gender differences between participants and non-participants. ▪ Sensitivity and specificity data was not provided in the study. This data could be calculated for an overall model. ▪ ¹Model : (1.5*Allergen induced symptoms) + (1*prolonged expiration) + (1*current wheezing) + (1*dyspnoea) + (1*female) + (pack-years smoking/25). Cut off of 3 was used ▪ ²Based on asthma prevalence of 25% ▪ ³Based on asthma prevalence of 10% ▪ Study also presented under wheeze, cough, dyspnoea, dyspnoea with wheeze, prolonged expiration, allergen induced symptoms and family history

Table 10: Validity of clinically based models as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes		Comments
(Thiadens et al. 1998b) Cross-sectional Grade 2- Country: Netherlands	<u>Tests:</u> PEFR variability <u>Reference:</u> One or more episodes of wheeze, cough or dyspnoea lasting > 3 weeks and PC ₂₀ ≤ 15.6 µmol methacholine or FEV ₁ improved ≥ 9% of predicted post 400 µg salbutamol	<u>Inclusion criteria:</u> Age 18-75 Cough ≥ 2 weeks <u>Exclusion criteria:</u> Previous diagnosis of asthma or COPD Pregnancy Cardiovascular or concomitant pulmonary diseases	182	Model ¹ Cut off score 3	Model ¹ Cut off score 4	<ul style="list-style-type: none"> ▪ Mean age 44 and female 64% ▪ Mean FEV₁ 92%PV ▪ 69 participants had asthma, 12 COPD ▪ Model presented excluded participants with COPD ▪ Asthma definition may have missed some cases due to the requirement for symptoms of acute asthma lasting 3 weeks at some time during the past year. Some cases may also have been over-inclusive due to the high PC₂₀ cut off. ▪ Unclear if the screening symptoms and the reference standard were measured independently (blindly) ▪ 192 of 221 eligible (87%) patients participated in the study. There were no age or gender differences between participants and non-participants. ▪ ¹Model: Score = diurnal PEFR variability >15% + 4 (if female sex) ▪ ²Based on asthma prevalence of 25% ▪ ³Based on asthma prevalence of 10%
				Sensitivity (%) Specificity (%) PPV ² (%) NPV ² (%) PPV ³ (%) NPV ³ (%)	16 48 56 20 11 17 67 54 4 6 86 78	

PEFR

Table 11: Validity of PEFR as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes			Comments
(den Otter et al. 1997) Cross-sectional Grade 2+ Country: Netherlands	<u>Tests:</u> PEFR variability (var.) <u>Reference:</u> PC ₂₀ histamine	<u>Inclusion criteria:</u> Age 25-70 years Recruited from 10 general practices ≥ 1 symptom or sign of asthma (criteria stipulated) <u>Exclusion criteria:</u> Unable to use a PEFR meter Unable to complete a diary	323	PEFR var. ≥ 5%	PEFR var. ≥ 10%	PEFR var. ≥ 15%	<ul style="list-style-type: none"> ▪ Mean age 43 and female 58% ▪ Mean FEV₁ 95%PV ▪ 131 patients were classified with asthma ▪ Unclear if investigators were blinded to the reference and screening results ▪ Sensitivity and specificity data based on PC₂₀. Other criteria used to establish asthma in the study (presence of appropriate signs and symptoms and reversible component) changed the number of asthmatics from 131 (based on PC₂₀) to 143. ▪ Participation rate 61% (non-participants had a lower reversibility component) ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10%
				Sensitivity (%)	56	14	5
				Specificity (%)	69	96	97
				PPV ¹ (%)	38	54	36
				NPV ¹ (%)	82	77	75
				PPV ² (%)	17	28	16
				NPV ² (%)	93	91	90

Table 11: Validity of PEFr as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Thiadens et al. 1999) Prospective cross-sectional study Grade 2+ Country: Netherlands	Chronic cough: <u>Tests:</u> FEV ₁ PEFR <u>Reference:</u> Positive broncho-dilator response 9 %PV after inh 400 µg salbutamol	<u>Inclusion criteria:</u> Age 18-75 Cough 2 weeks <u>Exclusion criteria:</u> Previous dx of asthma or COPD Pregnancy Patients with cardiovascular disease, concomitant pulmonary disease	240	TEST / RESULT Positive BHR with PEFr measurements and reference of (FEV ₁ ≥ 9%PV after treatment) ≥ 10% baseline Sensitivity (%) 56 Specificity (%) 85 PPV (%) 36 NPV (%) 93 ≥ 15% baseline Sensitivity (%) 44 Specificity (%) 94 PPV (%) 52 NPV (%) 92 ≥ 20% baseline Sensitivity (%) 25 Specificity (%) 98 PPV (%) 67 NPV (%) 90 ≥ 40 l/min Sensitivity (%) 53 Specificity (%) 87 PPV (%) 39 NPV (%) 92 ≥ 60 l/min Sensitivity (%) 28 Specificity (%) 95 PPV (%) 45 NPV (%) 90 ≥ 80 l/min Sensitivity (%) 13 Specificity (%) 99 PPV (%) 57 NPV (%) 88	PEFR <ul style="list-style-type: none"> ▪ Mean age 45, female 60%, median smoking pack years 2.1, FEV₁ 91 %PV, PEFr85 %PV ▪ Of 256 patients meeting inclusion criteria, 240 participated ▪ General practice primary care setting, patients seen by independent investigator at time of GP visit ▪ Successive tests were not measured independently (blind) ▪ Bronchodilator response proportional changes in PEFr of 10, 15 and 20% and absolute changes of 40, 60 and 80 L/min compared with "reference" ΔFEV₁ ≥ 9%PV. These showed high NPV's and specificities but low sensitivities and PPV's showing PEFr as having poor diagnostic properties. ▪ Cut off values may result in loss of statistical power and arbitrariness given data are continuous rather than dichotomous ▪ PPV and NPV based on asthma prevalence of 25% could not be determined

Table 11: Validity of PEFR as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments	
(Kunzli et al. 1999) Cross-sectional Grade 2- Country: Switzerland	<u>Tests:</u> PEFR variability <u>Reference:</u> 4 definitions of asthma used: Physician diagnosed asthma Current asthma Wheezing without colds Hyper-responsiveness ($\geq 20\%$ decrease in FEV ₁ post ≤ 2 mg methacholine)	<u>Inclusion criteria:</u> Based on a random population study – random sample of healthy, nonsmoking adults and all participants with respiratory symptoms or bronchial responsiveness	3074	PEFR variability $\geq 30\%$ Number with positive diagnosis Sensitivity (%) Specificity (%) PPV ¹ (%) NPV ¹ (%) PPV ² (%) NPV ² (%)	Physician diagnosed asthma 316 11 98 65 77 38 91 Current asthma 167 14 98 70 77 44 91 Wheezing without cold 359 8 98 57 76 31 91 Reactive airways 646 4 99 57 76 31 90	<ul style="list-style-type: none"> Mean age 43 and female 51% Validity also assessed for PEFR variability $\geq 20\%$ and $\geq 50\%$ but results best for $\geq 30\%$ Choice of patients was not independent of reference standard Reference and screening tests were probably not measured blind Participation rate 55% (drop out rate of 41% in initial population based sampling) ¹Based on asthma prevalence of 25% ²Based on asthma prevalence of 10%
(Enright et al. 1997) Cross-sectional Grade 2- Country: United States	<u>Tests:</u> PEFR lability <u>Reference:</u> ATS criteria for asthma (based on a single question from an ATS designed questionnaire)	<u>Inclusion criteria:</u> Surviving members of the Adventist Health Smog Study (consisting of non-smokers and started 16 years prior to this study) Age <80 years at start of the year in which this study was conducted	1223	PEFR lability in women with current asthma PEFR lability in women without current asthma <i>P</i> value PEFR lability in men with current asthma PEFR lability in men without current asthma <i>P</i> value	<ul style="list-style-type: none"> Mean age 66 and female 62% Mean FEV₁ 97%PV 45 with current asthma Test and reference standard measurements were not independent Results not presented that would allow calculation of sensitivity and specificity Participation rate 64% No comparison between participants and non-participants Uncertainty about the validity of the reference standard 	

Table 11: Validity of PEFr as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments																																		
(Giannini et al. 1997) Cross-sectional Grade 2- Country: Italy	<u>Tests:</u> PEFR <u>Reference:</u> FEV ₁ > 15% decrease in response to challenge (allergen, toluene, exercise, ultrasonically nebulised distilled water, methacholine)	<u>Inclusion criteria:</u> Suspected bronchial asthma	184	<table border="0"> <tr> <td></td> <td>Allergen</td> <td>Toluene</td> <td>Exercise</td> <td>H₂O</td> <td>Methacholine</td> </tr> <tr> <td>Observations</td> <td>353</td> <td>220</td> <td>148</td> <td>60</td> <td>218</td> </tr> <tr> <td>Sensitivity¹ (%)</td> <td>70</td> <td>57</td> <td>30</td> <td>100</td> <td>57</td> </tr> <tr> <td>Specificity¹ (%)</td> <td>84</td> <td>77</td> <td>86</td> <td>66</td> <td>82</td> </tr> </table>		Allergen	Toluene	Exercise	H ₂ O	Methacholine	Observations	353	220	148	60	218	Sensitivity ¹ (%)	70	57	30	100	57	Specificity ¹ (%)	84	77	86	66	82	<ul style="list-style-type: none"> Female 28% No details about inclusion or exclusion criteria or the study population Reference and screening tests were not independent Participation rate not documented ¹Sensitivity and specificity based on Δ PEFr > 15% 										
	Allergen	Toluene	Exercise	H ₂ O	Methacholine																																		
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(Leroyer et al. 1998) Prospective cross-sectional study Grade 2- Country: Canada	Serial monitoring of PEFr and FEV ₁ in dx of occupational asthma <u>Tests:</u> PEFR FEV ₁ <u>Reference:</u> PC ₂₀ Of <16 mg/ml methacholine	<u>Inclusion criteria:</u> Age 22-59 History suggestive of occupational asthma Worsening asthma symptoms at workplace	20	<table border="0"> <tr> <td>TEST / RESULT</td> <td>PEFR</td> </tr> <tr> <td><u>Occupational asthma</u> Dx performance PEFr results - all best values (graphs)</td> <td></td> </tr> <tr> <td>N</td> <td>20</td> </tr> <tr> <td>Sensitivity (%)</td> <td>73</td> </tr> <tr> <td>Specificity (%)</td> <td>100</td> </tr> <tr> <td>PPV¹ (%)</td> <td>100</td> </tr> <tr> <td>NPV¹ (%)</td> <td>92</td> </tr> <tr> <td>PPV² (%)</td> <td>100</td> </tr> <tr> <td>NPV² (%)</td> <td>97</td> </tr> <tr> <td>Dx performance PEFr results – best of two reproducible values (graphs)</td> <td></td> </tr> <tr> <td>N</td> <td>20</td> </tr> <tr> <td>Sensitivity (%)</td> <td>55</td> </tr> <tr> <td>Specificity (%)</td> <td>100</td> </tr> <tr> <td>PPV¹ (%)</td> <td>100</td> </tr> <tr> <td>NPV¹ (%)</td> <td>87</td> </tr> <tr> <td>PPV² (%)</td> <td>100</td> </tr> <tr> <td>NPV² (%)</td> <td>95</td> </tr> </table>	TEST / RESULT	PEFR	<u>Occupational asthma</u> Dx performance PEFr results - all best values (graphs)		N	20	Sensitivity (%)	73	Specificity (%)	100	PPV ¹ (%)	100	NPV ¹ (%)	92	PPV ² (%)	100	NPV ² (%)	97	Dx performance PEFr results – best of two reproducible values (graphs)		N	20	Sensitivity (%)	55	Specificity (%)	100	PPV ¹ (%)	100	NPV ¹ (%)	87	PPV ² (%)	100	NPV ² (%)	95	<ul style="list-style-type: none"> Mean age 40, female 25%, mean duration of exposure 13 years, of symptoms 5 years, 40% of patients used β_2-adrenergic agents alone or as-needed, 50% inhaled steroids regularly and β_2-adrenergic agents as-needed Hospital department setting, patient referrals for investigation of possible occupational asthma Patients were not screened for smoking status or complicating respiratory conditions On-site investigators not blinded to previous history and treatments of patients and monitoring PEFR and FEV₁ monitoring not supervised, 27% of PEFr readings and 33% of FEV₁ readings did meet reproducibility criteria. These were included in the analysis. Diagnosis of occupational asthma based upon diary results being analysed in a blind randomised fashion by three investigators. Visual analysis required agreement by two of the three and a specific positive PC₂₀ test as the gold standard. PC₂₀ test data made available to investigators. Usage of asthmatic therapy permitted during study, not clear how this was accounted for in monitoring and in administration of PC₂₀ tests and in analysis PC₂₀ asthma gold standard attained in 17 patients. Occupational asthma diagnosed in 11 (55%) patients, non-occupational asthma in 6 (30%) Study also presented under spirometry ¹Based on asthma prevalence of 25% ²Based on asthma prevalence of 10%
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Spirometry

Table 12: Validity of spirometry as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments																																			
(Quadrelli et al. 1999) Case control Grade 2+ Country: Argentina	<p><u>Tests:</u> FEV₁ response to bronchodilator: Absolute change (Δabs.) % initial FEV₁ (%init.) % FEV₁ PV (Δ%pred.) % maximal possible result (Δ%max.)</p> <p><u>Reference:</u> Asthma: ATS criteria, non smoker COPD: heavy current or ex-smokers, no asthma history, report chronic cough and sputum</p>	<p><u>Inclusion criteria:</u> Routine visit to chest clinic – asthma or COPD</p> <p><u>Exclusion criteria:</u> Other respiratory disease Previous thoracic surgery History suggestive of asthma and smoker History suggestive of COPD and non-smoker Current systemic steroid therapy</p>	200	<table border="1"> <thead> <tr> <th></th> <th>Δabs.</th> <th>Δ%init.</th> <th>Δ%pred.</th> <th>Δ%max.</th> </tr> </thead> <tbody> <tr> <td>Sensitivity (%)</td> <td>70</td> <td>85</td> <td>67</td> <td>7</td> </tr> <tr> <td>Specificity (%)</td> <td>71</td> <td>50</td> <td>71</td> <td>98</td> </tr> <tr> <td>PPV¹ (%)</td> <td>45</td> <td>36</td> <td>44</td> <td>54</td> </tr> <tr> <td>NPV¹ (%)</td> <td>88</td> <td>91</td> <td>87</td> <td>76</td> </tr> <tr> <td>PPV² (%)</td> <td>21</td> <td>16</td> <td>20</td> <td>28</td> </tr> <tr> <td>NPV² (%)</td> <td>96</td> <td>97</td> <td>95</td> <td>90</td> </tr> </tbody> </table>		Δ abs.	Δ %init.	Δ %pred.	Δ %max.	Sensitivity (%)	70	85	67	7	Specificity (%)	71	50	71	98	PPV ¹ (%)	45	36	44	54	NPV ¹ (%)	88	91	87	76	PPV ² (%)	21	16	20	28	NPV ² (%)	96	97	95	90	<ul style="list-style-type: none"> Mean age 55 and female 48% in asthma group; mean age 67 and female 21% in COPD group Mean FEV₁ 60%PV in asthma group; mean FEV₁ 40% in COPD group Analysis presented restricted to asthma patients with FEV₁ < 55%PV (n=61). COPD patients (n=58) Blinding between reference and screening tests not described Participation rate not described ¹Based on asthma prevalence of 25% ²Based on asthma prevalence of 10%
	Δ abs.	Δ %init.	Δ %pred.	Δ %max.																																				
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Table 12: Validity of spirometry as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Palombini et al. 1999) Cross-sectional Grade 2+ Country: Brazil	Chronic cough: <u>Tests:</u> Sinus CT Rhinoscopy Spirometry Carbachol inhalational challenge (CIC) Chest CT Esoph. pH Bronch. <u>Reference:</u> 12 month treatment for symptoms	<u>Inclusion criteria:</u> Age >12 Cough 3 weeks Normal/near normal CXR <u>Exclusion criteria:</u> Smoker	78	TEST / RESULT Spirometry Number 78 Sensitivity (%) 26 Specificity (%) 81 PPV ¹ (%) 31 NPV ¹ (%) 77 PPV ² (%) 13 NPV ² (%) 91 <i>P</i> value (association between final dx and test) <i>P</i> > 0.44	<ul style="list-style-type: none"> ▪ Mean age 57 and female 64% ▪ University OPD setting ▪ Potentially selected population due to referral patterns ▪ Not specified if successive tests and specific test and reference standard measured blind ▪ Reference standard was response to therapy- measurable in 94% ▪ 151 causes of cough in 78 patients diagnosed ▪ Final diagnosis based on pre-treatment criteria being met and cough stopped after specific treatment ▪ Asthma detected in 59% of patients ▪ Lack of data on spirometry and CIC testing methods ▪ Study also presented under PC₂₀ ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10% ▪ CIC results not presented because outcome criteria were not stipulated

Table 12 Validity of spirometry as a diagnostic indicator of asthma (*continued*)

Study Source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Schmekel and Smith 1997) Case control Grade 2+ Country: Sweden	<u>Tests:</u> Forced oscillation technique (FOT) FEV ₁ <u>Reference:</u> Hx of recurring attacks of SOB with wheezing, meeting the ATS clinical criteria, including prior demonstration of reversible airway obstruction ≥ 15% or an abnormal broncho-provocation test	<u>Inclusion criteria:</u> Random selection of asthma patients and healthy controls. <u>Exclusion criteria:</u> Airway infection or acute exacerbation 3 weeks prior to test or cardiorespiratory disease other than asthma	29	FOT FEV ₁ Sensitivity (%) 89 Specificity (%) 100 PPV ¹ (%) 100 NPV ¹ (%) 96 PPV ² (%) 100 NPV ² (%) 99	<ul style="list-style-type: none"> ▪ Mean age 34 and female 69% ▪ Mean FEV₁ 93%PV (asthma – 91%PV) ▪ Twenty patients classified with asthma ▪ FOT measured at 6 time intervals, FEV₁ only one time but results were only presented for one time measurement of FOT (7 mins post isocapnic cold air challenge). FEV₁ measured 8 mins post isocapnic cold air challenge ▪ Unclear if the investigators were blinded to the reference results ▪ Method of selecting healthy volunteers not clear ▪ Appears to be set in a hospital setting ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10%
(Morris et al. 1998) Cross-sectional Grade 2- Country: England	<u>Tests:</u> T _{rs} –time constant of respiratory system, measured during normal tidal respiration. <u>Reference:</u> R _{aw} – airway resistance	<u>Inclusion criteria:</u> Patients referred to lung function laboratory with a putative diagnosis of airflow obstruction <u>Exclusion criteria:</u> Restrictive lung disease FEV ₁ /FVC > 80% Reduced total lung capacity	118	T _{rs} Sensitivity (%) 75 Specificity (%) 85	<ul style="list-style-type: none"> ▪ Mean age 50 and female 47% ▪ Mean FEV₁ 61%PV ▪ Patients with asthma, COPD and bronchiectasis ▪ PPV and NPV could not be calculated due to lack of sample size data on patients with and without asthma ▪ Laboratory supported by a pharmaceutical company ▪ The specificity of R_{aw} for asthma is not clear hence the reference standard used should be treated with caution ▪ Independence of test and reference tests not clear from the study design ▪ Participation rate not documented

Table 12 Validity of spirometry as a diagnostic indicator of asthma (*continued*)

Study Source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Smyrniotis et al. 1998) Prospective cross-sectional study Grade 2- Country: USA	Chronic cough: <u>Tests:</u> CXR SXR PC ₂₀ BaS Esoph. pH Bronch. Spirometry <u>Reference for asthma:</u> Specific therapy eliminating cough	<u>Inclusion criteria:</u> Age 64 Cough 3 weeks Normal/near normal CXR <u>Exclusion criteria:</u> Smoker	30	TEST / RESULT Spirometry Number of patients 5 Sensitivity (%) 100 Specificity (%) 75 PPV (%) 25 NPV (%) 100	<ul style="list-style-type: none"> Mean age 70 and female 40% University medical centre pulmonary clinic setting Not specified if successive tests and specific test and reference standard measured independently (blind) 40 causes of cough in 30 patients diagnosed Final diagnosis based on pre-treatment criteria being met and cough stopped after specific treatment When more than one disease fulfilled pre-treatment criteria, therapy instituted in order that these were fulfilled Asthma detected in 17% of 40 causes, 85% of cases were attributable to GERD, PNDS and asthma. In 5 patients (71%) with asthma, chronic cough was the sole presenting manifestation Study objective to evaluate the spectrum and frequency of causes of chronic cough in older patients not the validity of tests PC₂₀ and spirometry in forming the diagnosis of asthma Insufficient information to calculate PPV and NPV based on an asthma prevalence of 25% Study also presented under PC₂₀
(Leroyer et al. 1998) Prospective cross-sectional study Grade 2- Country: Canada	Serial monitoring of PEFr and FEV ₁ in dx of occupational asthma <u>Tests:</u> PEFR Spirometry <u>Reference:</u> PC ₂₀ of <16 mg/ml methacholine	<u>Inclusion criteria:</u> Age 22-59 History suggestive of occupational asthma Worsening asthma symptoms at workplace	20	TEST / RESULT Spirometry Dx performance FEV ₁ results - all best values (graphs) N 20 Sensitivity (%) 73 Specificity (%) 100 PPV (%) N/A NPV (%) N/A Dx performance FEV ₁ results – best of two reproducible values (graphs) N 20 Sensitivity (%) 55 Specificity (%) 100 PPV (%) N/A NPV (%) N/A	<ul style="list-style-type: none"> Mean age 40, female 25%, mean duration of exposure 13 years, of symptoms 5 years, 40% of patients used β_2-adrenergic agents alone or as-needed, 50% inhaled steroids regularly and β_2-adrenergic agents as-needed Hospital department setting, patient referrals for investigation of possible occupational asthma Patients were not screened for smoking status or complicating respiratory conditions On-site investigators not blinded to previous history and treatments of patients and monitoring PEFR and FEV₁ monitoring not supervised, 27% of PEFr readings and 33% of FEV₁ readings did meet reproducibility criteria. These were included in the analysis. Diagnosis of occupational asthma based upon diary results being analysed in a blind randomised fashion by three investigators. Visual analysis required agreement by two of the three and a specific positive PC₂₀ test as the gold standard. PC₂₀ test data made available to investigators Usage of asthmatic therapy permitted during study, not clear how this was accounted for in monitoring and in administration of PC₂₀ tests and in analysis PC₂₀ asthma gold standard attained in 17 patients. Occupational asthma diagnosed in 11 (55%) patients, non-occupational asthma in 6 (30%) Study also presented under PEFr

PC₂₀

Table 13: Validity of challenge testing with methacholine or histamine as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Hedman et al. 1998) Cross-sectional Grade 2+ Country: Finland	<u>Tests:</u> Rapid methacholine challenge <u>Reference:</u> Based on clinical evaluation. Requirements included: FEV ₁ or PEFr variation of ≥ 15% post medication or ≥ 20% variation in daily PEFr monitoring or ≥ 15% decrease in FEV ₁ after specific allergen or exercise test.	<u>Inclusion criteria:</u> Clinic referral for dyspnoea, wheeze or cough of unknown cause FEV ₁ ≥95%PV <u>Exclusion criteria:</u> Previous diagnosis of asthma Used inhaled steroids in 4 weeks preceding study Respiratory infection in 4 weeks prior to study Pharmaceutical limitations	230	PC ₂₀ PC ₁₅ Sensitivity (%) 77 84 Specificity (%) 82 69 PPV ¹ (%) 59 47 NPV ¹ (%) 91 93 PPV ² (%) 32 23 NPV ² (%) 97 97	<ul style="list-style-type: none"> ▪ Mean age 44 and female 61% ▪ Mean FEV₁ 92%PV ▪ 61 patients classified with asthma ▪ Blinding between the measurement of screening and reference tests ▪ Reference was appropriate for the screening test being considered ▪ The tests were compared in a valid design and measurement methodology was well described and valid ▪ Asthmatic and non-asthmatic groups were treated identically ▪ Participation rate not documented ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10%

Table 13: Validity of challenge testing with methacholine or histamine as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Marchesani et al. 1998) Prospective cross-sectional study Grade 2+ Country: Italy	Chronic cough <u>Tests:</u> History/ physical exam SXR CXR Spirometry PC ₂₀ Skin prick test (SPT) Bronch. Oesophago-gastroscopy Esoph. pH <u>Reference:</u> Dx specific therapy resulting in satisfactory improvement or complete resolution of cough	<u>Inclusion criteria:</u> Age 18-75 Cough 4 weeks Resistance to conventional therapy, lack of obvious cause	92	TEST / RESULT PC ₂₀ <400 µg methacholine and successful response to therapy Number of patients 88 Sensitivity (%) 100 Specificity (%) 73 PPV ¹ (%) 55 NPV ¹ (%) 100 PPV ² (%) 29 NPV ² (%) 100	PC ₂₀ <ul style="list-style-type: none"> ▪ Mean age 51, female 78%, mean duration of cough 33 months, smokers 14%, ex-smokers 13%. In asthma group n=12, female 75%, smoker and ex-smoker 25%. ▪ OPD setting, patient referrals due to unexplained cough ▪ Anatomical diagnostic protocol with well defined criteria (reversible airways obstruction or a PC₂₀ <400 µg methacholine) ▪ Successive tests were not measured independently (blind) of each other ▪ Diagnoses accepted as valid on basis of test pre-treatment criteria and subjective patient report of cough relief from diagnosis specific therapy ▪ Cause of cough identified in 81 patients (93%), 6 patients had 2 causes. Specific therapy was successful in 79/87 (91%) of patients. Results refer to 87/92 patients, 5 were lost to follow-up. ▪ Of 12 patients identified with asthma, 3 had allergic bronchial asthma according to SPTs ▪ A negative PC₂₀ excluded asthma as a possible cause of cough, but false positives were high (23%) ▪ Unclear from methodology what stepwise method was used for spirometry and PC₂₀ tests ▪ Study also presented under spirometry ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10%

Table 13: Validity of challenge testing with methacholine or histamine as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(McGarvey et al. 1998) Prospective cross-sectional study Grade 2- Country: UK	Chronic non-productive cough (CNPC) <u>Tests:</u> History/ physical exam PEFR (home) PC ₂₀ (histamine) ENT Sinus CT Esoph. pH <u>Reference:</u> Dx specific therapy resulting in satisfactory improvement or complete resolution of cough	<u>Inclusion criteria:</u> Age 18-75 Cough 3 weeks Life-time non-smokers Normal CXR and spirometric measurements <u>Exclusion criteria:</u> Previous history of chest disease, upper respiratory tract infection or taking angiotensin converting enzyme inhibitors	43	<u>TEST / RESULT</u> Dx of cough variant asthma based on PC ₂₀ 8 mg/ml histamine challenge and successful response to therapy Sensitivity (%) Specificity (%) Number positive tests Number responding to treatment PPV (%)	PC ₂₀ N/A N/A 17 15 88 <ul style="list-style-type: none"> ▪ Mean age 48, female 67%, mean duration of cough 67 months. In cough variant asthma group n=10, mean age 47, female 90%, dual dx group n=8, mean age=43, female 63%. ▪ Positive history is any of cough at night, or precipitated by cold air, exercise, aerosols ▪ Hospital care setting, patients referrals to chest clinic ▪ Cause of cough identified in 35 patients (82%), 8 patients had 2 causes ▪ Not specified if successive tests measured independently (blind), sensitivity and specificity not presented ▪ Diagnoses accepted as valid on basis of history/investigation and subjective patient report of cough relief based on diagnosis specific therapy ▪ PEFR monitoring data was not processed due to poor compliance ▪ Of 15 patients identified with asthma, 6 later developed symptoms despite treatment ▪ Study also presented under history ▪ Unable to calculate sensitivity and specificity date

Table 13: Validity of challenge testing with methacholine or histamine as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments																				
(Smyrniotis et al. 1998) Prospective cross-sectional study Grade 2- Country: USA	Chronic cough: <u>Tests:</u> CXR SXR PC ₂₀ BaS Esoph. pH Bronch. Spirometry <u>Reference for asthma:</u> Specific therapy eliminating cough	<u>Inclusion criteria:</u> Age 64 Cough 3 weeks Normal/near normal CXR <u>Exclusion criteria:</u> Smoker	30	TEST / RESULT PC ₂₀ FEV ₁ PC ₂₀ Number of patients 24 Sensitivity (%) 100 Specificity (%) 95 PPV (%) 87 NPV (%) 100	<ul style="list-style-type: none"> Mean age 70 and female 40% University medical centre pulmonary clinic setting Not specified if successive tests and specific test and reference standard measured independently (blind) 40 causes of cough in 30 patients diagnosed Final diagnosis based on pre-treatment criteria being met and cough stopped after specific treatment When more than one disease fulfilled pre-treatment criteria, therapy instituted in order that these were fulfilled Asthma detected in 17% of 40 causes, 85% of cases were attributable to GERD, PNDS and asthma. In 5 patients (71%) with asthma, chronic cough was the sole presenting manifestation Study objective to evaluate the spectrum and frequency of causes of chronic cough in older patients not the validity of tests PC₂₀ and spirometry in forming the diagnosis of asthma Insufficient information to calculate PPV and NPV based on an asthma prevalence of 25% Study also presented under spirometry 																				
(Irwin et al. 1997) Randomised controlled trial Grade 1- Country: United States	<u>Tests:</u> Methacholine challenge following metaproterenol <u>Reference:</u> Response to inhaled steroid and bronchodilator	<u>Inclusion criteria:</u> Adult, non smoking patients referred for investigation of chronic cough (≥ 3 weeks duration) Positive PC ₂₀ (methacholine ≤ 10 μmol) <u>Exclusion criteria:</u> Other medical conditions requiring therapy Abnormal baseline spirometry	15	<table border="1"> <thead> <tr> <th></th> <th>Meth.</th> <th>Placebo</th> <th>P value (Meth. V placebo)</th> </tr> </thead> <tbody> <tr> <td><u>Asthma</u> Decrease in PC₂₀</td> <td>1.2</td> <td>1.1</td> <td><i>n.s.</i></td> </tr> <tr> <td><i>P</i> value (cf. baseline)</td> <td><i>P</i>=.03</td> <td><i>P</i>=.01</td> <td></td> </tr> <tr> <td><u>Non-asthma</u> Decrease in PC₂₀ (asthma group)</td> <td>1.7</td> <td>0.7</td> <td><i>n.s.</i></td> </tr> <tr> <td><i>P</i> value (cf. baseline)</td> <td><i>n.s.</i></td> <td><i>n.s.</i></td> <td></td> </tr> </tbody> </table>		Meth.	Placebo	P value (Meth. V placebo)	<u>Asthma</u> Decrease in PC ₂₀	1.2	1.1	<i>n.s.</i>	<i>P</i> value (cf. baseline)	<i>P</i> =.03	<i>P</i> =.01		<u>Non-asthma</u> Decrease in PC ₂₀ (asthma group)	1.7	0.7	<i>n.s.</i>	<i>P</i> value (cf. baseline)	<i>n.s.</i>	<i>n.s.</i>		<ul style="list-style-type: none"> Mean age 55 and female 16%, n=9 in asthma group Mean FEV₁ 96%PV Low study power Randomisation method not described Study double blind for cross over phase but determination of reference diagnosis was not blind Four drop outs after screening tests – no data on these drop outs
	Meth.	Placebo	P value (Meth. V placebo)																						
<u>Asthma</u> Decrease in PC ₂₀	1.2	1.1	<i>n.s.</i>																						
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Table 13: Validity of challenge testing with methacholine or histamine as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Bai et al. 1998) Cross-sectional Grade 2- Country: Australia	<u>Tests:</u> Positive BHR based on: PC ₂₀ histamine 3.9 µmol Or increase in FEV ₁ of ≥ 15% post bronchodilator <u>Reference:</u> One of: Wheeze in last 12 months Asthma attack Chest tightness Recent nebuliser use Wheeze following exercise Chest tightness on waking SOB at rest	<u>Inclusion criteria:</u> Parents of randomly selected school children aged 8 to 11 years in 2 regions of NSW	1527	BHR Sensitivity (%) 18 Specificity (%) 97 PPV ¹ (%) 67 NPV ¹ (%) 78 PPV ² (%) 40 NPV ² (%) 91	<ul style="list-style-type: none"> ▪ 91% of participants between 30 and 50 years ▪ 58% female ▪ 461 patients classified with asthma ▪ Reference standard of doubtful validity – specificity is likely to be a major problem ▪ Unclear whether the reference standard and screening test were measured independently (blindly) ▪ The participation rate could not be evaluated ▪ No attempt has been made to control confounding (eg history of smoking, diagnosis of COPD) ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10%
(Couto et al. 1997) Cross-sectional Grade 2- Country: Portugal	<u>Tests:</u> PC ₂₀ methacholine <u>Reference:</u> Asthma diagnosis – basis unclear	<u>Inclusion criteria:</u> Asthma	314	PC ₂₀ (25 mg in 1.5 mls) sensitivity (%) 61	<ul style="list-style-type: none"> ▪ Mean age 38 and female 47% ▪ Criteria for asthma diagnosis not stated ▪ No comparison group so investigators were not blind to the reference diagnosis and specificity, PPV, NPV could not be calculated ▪ Participation rate not stated

Table 13: Validity of challenge testing with methacholine or histamine as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes				Comments
(Prieto et al. 1998) Case control Grade 2- Country: Spain	<u>Tests:</u> PC ₂₀ (methacholine) Maximal response and position of methacholine concentration response curve <u>Reference:</u> Asthma – history of asthma (variable wheeze, dyspnoea, chest tightness or cough) and one of: increase in FEV ₁ ≥ 15% post bronchodilator or PC ₂₀ ≤ 8 mg/ml	<u>Inclusion criteria:</u> Asthma and allergic rhinitis patients, healthy volunteers Age 18-60 Life long non-smoker <u>Exclusion criteria:</u> Chronic bronchitis, emphysema or resp. tract infection in the 4 weeks before study Pregnancy Significant renal, hepatic or cardiovascular disease. Pharmaceutical limitations	228	Asthma PC ₂₀ (mg/ml) (range)	Allergic rhinitis 0.8 (0.1, 17.4)	Healthy volunteers 14.1 (0.4, 200.0)	P value 93.3 (1.2, 200.0) P < 0.01 (Asthma v rhinitis and asthma v healthy)	<ul style="list-style-type: none"> ▪ Mean age 31 and female 59% ▪ Mean FEV₁ 98%PV in asthma group ▪ Population selected from outpatients, laboratory staff and students ▪ Diagnosis of asthma and screening test were not independent (this was a major limitation) ▪ Difference between asthma and non-asthma groups greater than reported since a proportion of participants in the latter groups did not reduce their FEV₁ ≥ 20% at maximal methacholine concentration (200 mg/ml) ▪ Sensitivity and specificity data not provided and could not be calculated

Table 13: Validity of challenge testing with methacholine or histamine as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Hsu et al. 1997) Cross-sectional Grade 2- Country: Taiwan	<u>Tests:</u> Sputum diff. count Blood diff. Serum IgE <u>Reference:</u> Episodic wheezing + SOB + positive bronchodilator and/or positive PC ₂₀	<u>Inclusion criteria:</u> Episodic dyspnoea, wheezing or cough for > 3 weeks <u>Exclusion criteria:</u> Recent MI Pregnancy Recent systemic infection	114	PC ₂₀ (< 8 mg/ml) Number tested 114 Sensitivity (%) 87 Specificity (%) 73 PPV ¹ (%) 52 NPV ¹ (%) 94 PPV ² (%) 26 NPV ² (%) 98	<ul style="list-style-type: none"> ▪ Mean age 53 ▪ Mean FEV₁ 66%PV including 63%PV in asthma group ▪ 52 patients classified with asthma, 25 COPD, 25 cough and 12 CHF ▪ Potential for overlap between asthma and COPD groups ▪ Unclear whether investigators were blind to the reference diagnosis ▪ PC₂₀ was not independent of the reference standard so this result should be treated with considerable caution ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10% ▪ Study also presented under sputum eosinophils, blood eosinophils and serum IgE

Sputum eosinophils

Table 14: Validity of sputum eosinophilia as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Hsu et al. 1997) Cross-sectional Grade 2- Country: Taiwan	<u>Tests:</u> Sputum diff. Count Blood diff. Serum IgE <u>Reference:</u> Episodic wheezing + SOB + positive bronchodilator and/or positive PC ₂₀	<u>Inclusion criteria:</u> Episodic dyspnoea, wheezing or cough for > 3 weeks <u>Exclusion criteria:</u> Recent MI Pregnancy Recent systemic infection	114	Sputum eosinophils (≥5%) Number tested 114 Sensitivity (%) 92 Specificity (%) 74 PPV ¹ (%) 54 NPV ¹ (%) 97 PPV ² (%) 28 NPV ² (%) 99	<ul style="list-style-type: none"> Mean age 53 Mean FEV₁ 66%PV including 63%PV in asthma group 52 patients classified with asthma, 25 COPD, 25 cough and 12 CHF Potential for overlap between asthma and COPD groups suggesting the specificity should be higher than indicated in the presented results Unclear whether investigators were blind to the reference diagnosis ¹Based on asthma prevalence of 25% ²Based on asthma prevalence of 10% Study also presented under PC₂₀, blood eosinophils and serum IgE
(Spanevello et al. 1997) Case control Grade 2- Country: Italy	<u>Tests:</u> Sputum eosinophil count Sputum ECP <u>Reference:</u> Asthma: History of intermittent wheeze, cough, chest tightness or dyspnoea and an improvement in FEV ₁ ≥ 20% after salbutamol when FEV ₁ ≤ 70%PV or PC ₂₀ methacholine ≤ 8 mg/ml when FEV ₁ ≥ 70%PV	<u>Inclusion criteria:</u> Diagnosis of asthma, seasonal rhinitis or healthy subjects < 15% variability in daily PEFr measurements for the 2 weeks of the study Healthy subjects were non-smokers, FEV ₁ > 80%PV and PC ₂₀ methacholine > 16 mg/ml	88	Sputum eosinophil (%) Asthma 12.2% Rhinitis 0.4% Healthy 0.4%	<ul style="list-style-type: none"> Mean age 39 and female 50% Mean FEV₁ 91%PV in asthma group 53 patients classified with asthma Valid reference standard used and reference measurements were blind to screening results No sensitivity and specificity data No analysis of statistical significance presented for differences between the three groups for sputum eosinophil level Study aimed to assess reproducibility rather than validity Study also presented under sputum ECP

Table 14: Validity of sputum eosinophilia as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Park et al. 1998) Case control Grade 2- Country: Korea	<u>Tests:</u> Sputum eosinophils Sputum ECP <u>Reference:</u> Asthma: Fluctuating respiratory symptoms (dyspnoea, wheeze, cough). Improvement in PEFr of >20% post 200 µg salbutamol or chronic use of anti-inflammatory treatment. PC ₂₀ methacholine <25 mg/ml.	<u>Inclusion criteria:</u> Visited allergy clinic for evaluation of respiratory symptoms <u>Exclusion criteria:</u> No anti-inflammatory use for 2 weeks before induced sputum	68	Sputum eosinophil (≥5%) Sensitivity (%) 85 Specificity (%) 93 PPV ¹ (%) 80 NPV ¹ (%) 95 PPV ² (%) 57 NPV ² (%) 98	<ul style="list-style-type: none"> ▪ Mean age 40 and female 49% ▪ Mean FEV₁ 83%PV in asthma group ▪ 41 patients classified with asthma ▪ Reference standard: response to bronchodilator likely to have low sensitivity, use of anti-inflammatory likely to lack specificity (eg. possibility of COPD), PC₂₀ criteria likely to have high specificity and therefore low sensitivity ▪ Selection methods not described in detail – some concern about independence ▪ Blinding between screening and reference measurements not documented ▪ Participation rate not documented ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10% ▪ Study also presented under sputum ECP

Table 14: Validity of sputum eosinophilia as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments																
(Alvarez et al. 2000) Grade 2- Case control Country: Spain	<u>Tests:</u> Serum and sputum eosinophil and ECP <u>Reference:</u> Asthma: Recurrent attacks of wheezing, cough, breathlessness and chest tightness	<u>Inclusion criteria:</u> Asthma, rhinitis and healthy controls. Conducted in a hospital setting. History of respiratory symptoms lasting 12-24 months required in the asthma and rhinitis groups <u>Exclusion criteria:</u> Smoking Respiratory infection during the past 2 months Treated with corticosteroids within 2 months	56	<table border="0"> <tr> <td></td> <td>Sputum Eosinophils (%)</td> <td>P value (versus asthma)</td> <td></td> </tr> <tr> <td>Asthma</td> <td>10</td> <td></td> <td></td> </tr> <tr> <td>Rhinitis</td> <td>3</td> <td>$P < 0.03$</td> <td></td> </tr> <tr> <td>Healthy controls</td> <td>0</td> <td>$P < 0.0001$</td> <td></td> </tr> </table>		Sputum Eosinophils (%)	P value (versus asthma)		Asthma	10			Rhinitis	3	$P < 0.03$		Healthy controls	0	$P < 0.0001$		<ul style="list-style-type: none"> ▪ Mean age 22 and female 43% ▪ Mean FEV₁ 100%PV in asthma group ▪ 31 patients classified with asthma ▪ Reference: based on clinical history only so may lack specificity ▪ Screening and reference standards were measured blind ▪ Sensitivity and specificity not calculated ▪ Study also presented under sputum ECP, serum ECP and blood eosinophils
	Sputum Eosinophils (%)	P value (versus asthma)																			
Asthma	10																				
Rhinitis	3	$P < 0.03$																			
Healthy controls	0	$P < 0.0001$																			

Table 14: Validity of sputum eosinophilia as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Fujimoto et al. 1997) Case control Grade 2- Country: Japan	<u>Tests:</u> Sputum eosinophil count Sputum ECP <u>Reference:</u> Asthma: History of intermittent wheeze, cough, chest tightness or dyspnoea, documented reversible airflow limitation and hyper-responsiveness to methacholine	<u>Inclusion criteria:</u> Age 17-74 years Asthma patients recruited from outpatient clinic No respiratory infection for 1 month prior to sputum collection Healthy volunteers	45	Sputum eosinophil (%) Asthma 18.2 Healthy 0.04 P value $P < 0.05$	<ul style="list-style-type: none"> ▪ Mean age 45 and female 53% in asthma (n=36); mean age 33 and female 22% in healthy volunteers (n=9) ▪ Screening tests were not measured blind to the reference standard ▪ Sensitivity and specificity data not presented and could not be assessed ▪ No statistical comparison presented for baseline differences between asthma and healthy volunteer groups (gender differences between the two groups were not statistically significant using Fishers exact test) ▪ Participation rate not stated ▪ Study also presented under sputum ECP

Sputum ECP

Table 15: Validity of sputum eosinophil cationic protein as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Spanevello et al. 1997) Case control Grade 2- Country: Italy	<p><u>Tests:</u> Sputum eosinophil count Sputum ECP</p> <p><u>Reference:</u> Asthma: History of intermittent wheeze, cough, chest tightness or dyspnoea and an improvement in FEV₁ ≥ 20% after salbutamol when FEV₁ ≤ 70%PV or PC₂₀ methacholine ≤ 8 mg/ml when FEV₁ ≥ 70%PV</p>	<p><u>Inclusion criteria:</u> Diagnosis of asthma, seasonal rhinitis or healthy subjects</p> <p>< 15% variability in daily PEFr measurements for the 2 weeks of the study</p> <p>Healthy subjects were non-smokers, FEV₁ > 80%PV and PC₂₀ methacholine > 16 mg/ml</p>	88	<p>Sputum ECP (µg/L)</p> <p>Asthma 827 Rhinitis 127 Healthy 157</p>	<ul style="list-style-type: none"> ▪ Mean age 39 and female 50% ▪ Mean FEV₁ 91%PV in asthma group ▪ 53 patients classified with asthma ▪ Valid reference standard used and reference measurements were blind to screening results ▪ No sensitivity and specificity data ▪ No analysis of statistical significance presented for differences between the three groups for sputum ECP level ▪ Study aimed to assess reproducibility rather than validity ▪ Study also presented under sputum eosinophils

Table 15: Validity of sputum eosinophil cationic protein as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Park et al. 1998) Case control Grade 2- Country: Korea	<u>Tests:</u> Sputum eosinophils Sputum ECP <u>Reference:</u> Asthma: Fluctuating respiratory symptoms (dyspnoea, wheeze, cough). Improvement in PEFr of >20% post 200 µg salbutamol or chronic use of anti-inflammatory treatment. PC ₂₀ methacholine <25 mg/ml.	<u>Inclusion criteria:</u> Visited allergy clinic for evaluation of respiratory symptoms <u>Exclusion criteria:</u> No anti-inflammatory use for 2 weeks before induced sputum	68	Sputum ECP (≥ 100 µg/L) Sensitivity (%) 68 Specificity (%) 56 PPV ¹ (%) 34 NPV ¹ (%) 84 PPV ² (%) 15 NPV ² (%) 94	<ul style="list-style-type: none"> ▪ Mean age 40 and female 49% ▪ Mean FEV₁ 83%PV in asthma group ▪ 41 patients classified with asthma ▪ Reference standard: response to bronchodilator likely to have low sensitivity, use of anti-inflammatory likely to lack specificity (eg. possibility of COPD), PC₂₀ criteria likely to have high specificity and therefore low sensitivity ▪ Selection methods not described in detail – some concern about independence ▪ Blinding between screening and reference measurements not documented ▪ Participation rate not documented ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10% ▪ Study also presented under sputum eosinophils

Table 15: Validity of sputum eosinophil cationic protein as a diagnostic indicator of asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Alvarez et al. 2000) Grade 2- Case control Country: Spain	<u>Tests:</u> Serum and sputum eosinophil and ECP <u>Reference:</u> Asthma: Recurrent attacks of wheezing, cough, breathlessness and chest tightness	<u>Inclusion criteria:</u> Asthma, rhinitis and healthy controls Conducted in a hospital setting History of respiratory symptoms lasting 12-24 months required in the asthma and rhinitis groups <u>Exclusion criteria:</u> Smoking Respiratory infection during the past 2 months Treated with corticosteroids within 2 months	56	Sputum ECP (µg/L) Asthma 19.0 Rhinitis 11.8 Healthy controls 3.4 P value (versus asthma) P <0.032 P <0.001	<ul style="list-style-type: none"> ▪ Mean age 22 and female 43% ▪ Mean FEV₁ 100%PV in asthma group ▪ 31 patients classified with asthma ▪ Reference: based on clinical history only so may lack specificity ▪ Screening and reference standards were measured blind ▪ Sensitivity and specificity not calculated ▪ Study also presented under sputum eosinophils, serum ECP and blood eosinophils
(Fujimoto et al. 1997) Case control Grade 2- Country: Japan	<u>Tests:</u> Sputum eosinophil count Sputum ECP <u>Reference:</u> Asthma: History of intermittent wheeze, cough, chest tightness or dyspnoea, documented reversible airflow limitation and hyper-responsiveness to methacholine	<u>Inclusion criteria:</u> Age 17-74 years Asthma patients recruited from outpatient clinic No respiratory infection for 1 month prior to sputum collection Healthy volunteers	45	Sputum ECP (µg/L) Asthma 526 Healthy 18 P value P < 0.05	<ul style="list-style-type: none"> • Mean age 45 and female 53% in asthma (n=36); mean age 33 and female 22% in healthy volunteers (n=9) • Screening tests were not measured blind to the reference • Sensitivity and specificity data not presented and could not be assessed • No statistical comparison presented for baseline differences between asthma and healthy volunteer groups (gender differences between the two groups were not statistically significant using Fishers exact test) • Participation rate not stated • Study also presented under sputum ECP

Serum ECP

Table 16: Validity of serum eosinophil cationic protein as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes			Comments
(Perfetti et al. 1999) Case control Grade 2- Country: Italy	<u>Tests:</u> Serum ECP PC ₂₀ methacholine <u>Reference:</u> History of cough, wheeze, dyspnoea or chest tightness or reversible and variable airflow limitation (GINA criteria)	<u>Inclusion criteria:</u> Outpatient referral for asthma symptoms <u>Exclusion criteria:</u> Extensive atopic dermatitis Acute infection within 4 weeks of study Treatment with topical or oral steroids and/or chromones within 4 weeks of study	185	Asthma Serum ECP (µg/L) (95%CI)	Non-asthma 8.2 (4.7, 13.7)	P value <i>n.s.</i>	<ul style="list-style-type: none"> Female 57% 70% of participants atopic 99 participants classified with asthma (using GINA criteria) Some concern the GINA criteria lacked specificity for the reference standard No comment about blinding between the measurement of the screening and reference standards Reference standard was measured after the screening tests Participation rate not documented Sensitivity and specificity not documented
(Alvarez et al. 2000) Grade 2- Case control Country: Spain	<u>Tests:</u> Serum and sputum eosinophil and ECP <u>Reference:</u> Asthma: Recurrent attacks of wheezing, cough, breathlessness and chest tightness	<u>Inclusion criteria:</u> Asthma, rhinitis and healthy controls. Conducted in a hospital setting. History of respiratory symptoms lasting 12-24 months required in the asthma and rhinitis groups <u>Exclusion criteria:</u> Smoking Respiratory infection during the past 2 months Treated with corticosteroids within 2 months	56	Serum ECP (ug/L) Asthma Rhinitis Healthy controls	16.8 11.8 10.2	P value (versus asthma) <i>n.s.</i> <i>P < 0.003</i>	<ul style="list-style-type: none"> Mean age 22 and female 43% Mean FEV₁ 100%PV in asthma group 31 patients classified with asthma Reference: based on clinical history only so may lack specificity Screening and reference standards were measured blind Sensitivity and specificity not calculated Study also presented under sputum eosinophils, sputum ECP and blood eosinophils

Blood eosinophils

Table 17: Validity of blood eosinophilia as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Hsu et al. 1997) Cross-sectional Grade 2- Country: Taiwan	<u>Tests:</u> Sputum diff. count Blood diff. Serum IgE <u>Reference:</u> Episodic wheezing + SOB + positive bronchodilator and/or positive PC ₂₀	<u>Inclusion criteria:</u> Episodic dyspnoea, wheezing or cough for > 3 weeks <u>Exclusion criteria:</u> Recent MI Pregnancy Recent systemic infection	114	Blood eosinophils (≥ 300/cm ³) Number tested 114 Sensitivity (%) 70 Specificity (%) 92 PPV ¹ (%) 75 NPV ¹ (%) 90 PPV ² (%) 49 NPV ² (%) 97	<ul style="list-style-type: none"> Mean age 53 Mean FEV₁ 66%PV including 63%PV in asthma group 52 patients classified with asthma, 25 COPD, 25 cough and 12 CHF Potential for overlap between asthma and COPD groups suggesting the specificity should be higher than indicated in the presented results Unclear whether investigators were blind to the reference diagnosis ¹Based on asthma prevalence of 25% ²Based on asthma prevalence of 10% Study also presented under PC₂₀, sputum eosinophils and serum IgE
(Alvarez et al. 2000) Grade 2- Case control Country: Spain	<u>Tests:</u> Serum and sputum eosinophil and ECP <u>Reference:</u> Asthma: Recurrent attacks of wheezing, cough, breathlessness and chest tightness	<u>Inclusion criteria:</u> Asthma, rhinitis and healthy controls. Conducted in a hospital setting. History of respiratory symptoms lasting 12-24 months required in the asthma and rhinitis groups <u>Exclusion criteria:</u> Smoking Respiratory infection during the past 2 months Treated with corticosteroids within 2 months	56	Blood eosinophil (cells/mm ³) Asthma 359 Rhinitis 255 Healthy controls 100 <i>P</i> value (versus asthma) <i>n.s.</i> <i>P</i> < 0.0001	<ul style="list-style-type: none"> Mean age 22 and female 43% Mean FEV₁ 100%PV in asthma group 31 patients classified with asthma Reference: based on clinical history only so may lack specificity Screening and reference standards were measured blind Sensitivity and specificity not calculated Study also presented under sputum eosinophils, sputum ECP and serum ECP

Serum IgE

Table 18: Validity of serum IgE as a diagnostic indicator of asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Hsu et al. 1997) Cross-sectional Grade 2- Country: Taiwan	<u>Tests:</u> Sputum diff. count Blood diff. Serum IgE <u>Reference:</u> Episodic wheezing + SOB + positive bronchodilator and/or positive PC ₂₀	<u>Inclusion criteria:</u> Episodic dyspnoea, wheezing or cough for > 3 weeks <u>Exclusion criteria:</u> Recent MI Pregnancy Recent systemic infection	114	Serum IgE (≥ 300 IU/ml) Number tested 114 Sensitivity (%) 31 Specificity (%) 86 PPV ¹ (%) 42 NPV ¹ (%) 79 PPV ² (%) 20 NPV ² (%) 92	<ul style="list-style-type: none"> ▪ Mean age 53 ▪ Mean FEV₁ 66%PV including 63%PV in asthma group ▪ 52 patients classified with asthma, 25 COPD, 25 cough and 12 CHF ▪ Potential for overlap between asthma and COPD groups ▪ Unclear whether investigators were blind to the reference diagnosis ▪ ¹Based on asthma prevalence of 25% ▪ ²Based on asthma prevalence of 10% ▪ Study also presented under PC₂₀, sputum eosinophils and blood eosinophils

Nasal ASA

Table 19: Validity of nasal acetylsalicylic acid as a diagnostic indicator of aspirin intolerant asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Milewski et al. 1998) Case control Grade 2+ Country: Poland	<u>Tests:</u> Response to nasal lysine ASA (measured by rhino-manometry) <u>Reference:</u> Oral ASA challenge	<u>Inclusion criteria:</u> AIA: nonsmokers, chronic nasal symptoms, confirmed by oral challenge test ATA: negative oral challenge Healthy controls: healthy, non-smoking, no adverse response to ASA (taken in the past year) <u>Exclusion criteria:</u> Large nasal polyps	64	Nasal provocation (nasal flow decreased >40% compared with baseline) Sensitivity (%) 78 Specificity (%) 96 PPV* (%) 87 NPV* (%) 93	<ul style="list-style-type: none"> ▪ Mean age 43 and female 77% ▪ Mean FEV₁ 88%PV in AIA group, 92%PV in ATA group ▪ 41 patients classified with AIA, 13 with ATA and 10 healthy controls ▪ Blinding between measurement of screening and reference standard not stated ▪ No baseline statistical comparison between study groups but eyeball differences in age with healthy volunteers averaging 37 years ▪ 20% of AIA cases excluded due to nasal flow issues ▪ *PPV and NPV based on in-study prevalence of AIA
(Nizankowska et al. 2000) Case control Grade 2+ Country: Poland	<u>Tests:</u> Response to: oral ASA (Maximum cumulative dose 500 mg) Nasal lysine ASA (maximum cumulative dose 182 mg) <u>Reference:</u> Oral challenge test	<u>Inclusion criteria:</u> AIA: History of adverse reaction following ingestion of ASA and decrease in FEV ₁ ≥ 20% post oral challenge ATA: Used aspirin and other NSAIDs without adverse reaction	50	Fall in FEV ₁ >20% and/or extra bronchial symptoms Sensitivity (%) 77 Specificity (%) 93 PPV* (%) 96 NPV* (%) 64	<ul style="list-style-type: none"> ▪ Mean age 42 and female 70% ▪ 35 patients classified with AIA and 15 with ATA ▪ Screen and reference standards measured single blind ▪ Participation rate not stated ▪ No baseline comparison for statistically significant difference in age (AIA mean age 44, ATA mean age 37) ▪ Study also presented under oral ASA ▪ *PPV and NPV based on in-study prevalence of AIA

Table 19: Validity of nasal acetylsalicylic acid as a diagnostic indicator of aspirin intolerant asthma (*continued*)

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Casadevall et al. 2000) Case control Grade 2- Country: Spain	<u>Tests:</u> Response to nasal ASA based on: clinical symptoms, acoustic rhinometry <u>Reference:</u> ASA challenge testing: Positive if FEV ₁ decreased > 30% (maximum cumulative dose 740 mg).	<u>Inclusion criteria:</u> Aspirin intolerant asthma (AIA): Single attack only – positive challenge test, > 1 attack – no confirmatory test Aspirin tolerant asthma (ATA) – negative challenge test Healthy controls – no challenge	31	Decrease in nasal volume ¹ Sensitivity (%) 73 Specificity (%) 94 PPV* (%) 92 NPV* (%) 79	<ul style="list-style-type: none"> ▪ Mean age 48 and female 45% ▪ Mean FEV₁ 64%PV in ASA, 81%PV in ATA ▪ 15 patients classified with AIA, 8 with ATA and 8 healthy controls ▪ Significant difference in clinical symptoms between groups (ASA had most symptoms) but data not further presented ▪ Significant difference in age between the three groups ▪ Participation rate not documented ▪ Not formally assessing all participants with a challenge test reduces confidence in classification ▪ ¹Measured using acoustic rhinometry – 25% decrease was the cut-off used ▪ *PPV and NPV based on in study prevalence of AIA

Oral AIA

Table 20: Validity of oral acetylsalicylic acid as a diagnostic indicator of aspirin intolerant asthma

Study source, design and evidence grading	Diagnostic Tests/ Reference	Criteria for Inclusion/ Exclusion	N	Results/outcomes	Comments
(Nizankowska et al. 2000) Case control Grade 2+ Country: Poland	<u>Tests:</u> Response to: oral ASA (Maximum cumulative dose 500 mg) Nasal lysine ASA (maximum cumulative dose 182 mg) <u>Reference:</u> Oral challenge test	<u>Inclusion criteria:</u> AIA: History of adverse reaction following ingestion of ASA and decrease in FEV ₁ ≥ 20% post oral challenge ATA: Used aspirin and other NSAIDs without adverse reaction	50	Fall in FEV ₁ >20% and/or extra bronchial symptoms Sensitivity (%) 89 Specificity (%) 93 PPV (%) 97 NPV (%) 77	<ul style="list-style-type: none"> ▪ Mean age 42 and female 70% ▪ 35 patients with AIA and 15 with ATA ▪ Screen and reference standards measured single blind ▪ Participation rate not stated ▪ No baseline comparison for statistically significant difference in age (AIA mean age 44 and ATA mean age 37) ▪ Study also presented under nasal ASA ▪ *PPV and NPV based on in-study prevalence of AIA

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Appendix 1

SEARCH STRATEGIES

Medline

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1      exp asthma/ (9422)
2      exp asthma/di (1369)
3      di.fs. (157722)
4      1 and 3 (1669)
5      "Sensitivity and Specificity"/ or "sensitivity and
specifcity".mp. (34102)
6      du.fs. (25150)
7      1 and 5 (226)
8      1 and 6 (463)
9      2 or 4 or 7 or 8 (2008)
10     DIAGNOSIS/ (294)
11     1 and 10 (0)
12     2 and 10 (0)
13     (asthma: and diagnos:).ti. (147)
14     9 or 13 (2020)
15     (news or letter).pt. (100252)
16     case report/ (143192)
17     diagnosis, differential/ (34475)
18     (child: or infan: or paediatric: or pediatric:).ti. (52761)
19     (child: or infan: or paediatric: or pediatric:).jw. (38633)
20     (chronic obstructive or copd or coad).ti. (1466)
21     exp asthma/ci (330)
22     1 and 17 (247)
23     14 or 22 (2035)
24     15 or 16 or 18 or 19 or 20 or 21 (285705)
25     23 not 24 (1233)
26     limit 25 to english (1026)
27     forced expiratory volume/ or peak expiratory flow rate/ (2616)
28     (cough or wheeze).mp. (2982)
29     ((short: adj breath:) or (dyspnea or dyspnoea)).mp. (3649)
30     (tight: adj2 chest).mp. (106)
31     (atop: or allerg: or eczema: or hay fever or rhinitis).mp.
(15793)
32     or/27-31 (23325)
33     26 and 32 (609)
34     from 33 keep (SELECTED REFERENCES)

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Embase

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1      exp ASTHMA/di [Diagnosis] (4574)
2      DIAGNOSIS/ (35450)
3      differential diagnosis/ (34093)
4      2 or 3 (69280)
5      1 and 4 (261)
6      (asthma and diagnos:).ti. (368)
7      (news or letter).pt. (194445)
8      case report/ (433740)
9      (child: or infan: or paediatric: or pediatric:).ti. (148231)
10     (child: or infan: or paediatric: or pediatric:).jw. (107476)

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11 (chronic obstructive or copd or coad).ti. (3867)
 12 forced expiratory volume/ or peak expiratory flow rate/ (8810)
 13 (cough or wheeze).mp. (7571)
 14 ((short: adj breath:) or (dyspnea or dyspnoea)).mp. (12705)
 15 (tight: adj2 chest).mp. (338)
 16 (atop: or allerg: or eczema: or hay fever or rhinitis).mp.
 (59795)
 17 or/7-11 (757124)
 18 or/12-16 (83634)
 19 1 or 5 or 6 (4641)
 20 19 not 17 (3166)
 21 18 and 20 (1917)
 22 limit 21 to yr=1997-2000 (907)
 23 limit 22 to english (775)
 24 animal/ or cat/ or dog/ or rat/ or mouse/ or monkey/ (717899)
 25 23 not 24 (752)
 26 from 25 keep (SELECTED REFERENCES)

Current Contents

1 asthma.mp. (22395)
 2 diagnos:.ti. (51355)
 3 diagnosis.kw. (13024)
 4 2 or 3 (59223)
 5 1 and 4 (427)
 6 differential diagnosis.mp. (11865)
 7 (forced expiratory volume or fev1).mp. (4930)
 8 (peak expiratory flow or peak flow).mp. (2645)
 9 (cough or wheeze).mp. (4509)
 10 ((short: adj breath:) or (dyspnea or dyspnoea)).mp. (4742)
 11 (atop: or allerg: or eczema: or hay fever or rhinitis).mp.
 (32732)
 12 (tight: adj2 chest).mp. (193)
 13 or/6-12 (57040)
 14 (child: or infan: or paediatric: or pediatric:).ti. (113740)
 15 (chronic obstructive or copd or coad).ti. (2030)
 16 (child: or paediatric: or pediatric: or infan:).jw. (77816)
 17 or/14-16 (161435)
 18 diagnosis.mp. (169424)
 19 1 and 18 and 13 (1091)
 20 19 not 17 (841)
 21 limit 20 to yr=1997-2000 (506)
 22 5 and 13 (275)
 23 22 not 17 (216)
 24 limit 23 to yr=1997-2000 (130)
 25 21 or 24 (524)
 26 limit 25 to english (455)
 27 from 26 keep (SELECTED REFERENCES)

Cinahl

1 exp ASTHMA/di [Diagnosis] (381)
 2 Diagnosis, Differential/ (2681)
 3 exp asthma/ (3574)
 4 2 and 3 (46)
 5 (asthma and diagnos:).ti. (86)
 6 di.fs. (32089)
 7 exp asthma/ (3574)

- 8 6 and 7 (475)
- 9 1 or 4 or 5 or 8 (504)
- 10 du.fs. (683)
- 11 DIAGNOSIS/ (339)
- 12 (news or letter).pt. (10362)
- 13 case report/ (1604)
- 14 (child: or infan: or paediatric: or pediatric:).ti. (29508)
- 15 (child: or infan: or paediatric: or pediatric:).jw. (16448)
- 16 (chronic obstructive or copd or coad).ti. (931)
- 17 forced expiratory volume/ or peak expiratory flow rate/ (376)
- 18 (cough or wheeze).mp. (646)
- 19 ((short: adj breath:) or (dyspnea or dyspnoea)).mp. (1015)
- 20 (tight: adj2 chest).mp. (28)
- 21 (atop: or allerg: or eczema: or hay fever or rhinitis).mp.
(2466)
- 22 10 or 11 (1021)
- 23 3 and 22 (40)
- 24 9 or 23 (524)
- 25 or/12-16 (50767)
- 26 24 not 25 (424)
- 27 or/17-21 (4288)
- 28 26 and 27 (125)
- 29 limit 28 to yr=1997-2000 (71)
- 30 "Sensitivity and Specificity"/ or "sensitivity and
specificity".mp. (2000)
- 31 3 and 30 (19)
- 32 31 not 25 (12)
- 33 32 and 27 (6)
- 34 limit 33 to yr=1997-2000 (6)
- 35 29 or 34 (76)
- 36 from 35 keep (SELECTED REFERENCES)

Science Citation Index

Search One:

Asthma

AND

Diagnosis

AND

Peak flow OR peak expiratory flow OR forced expiratory volume OR fecl
OR cough OR wheeze OR dyspoea OR dyspnea OR atop* OR allerg* OR hay
fever OR rhinitis OR eczema

NOT

Child* OR infan* OR pediatric* OR paediatric* OR copd OR coad

Search Two

Asthma

AND

Diagnosis

AND

Short*

AND

Breath

NOT

Child OR infan* OR pediatric* OR paediatric* OR copd OR coad

Search Three

Asthma

AND

Diagnosis

AND
Tight*
AND
Chest
NOT
child OR infan* OR pediatric* OR paediatric* OR copd OR coad

Other databases

Other databases without index terms and additional sources were searched using combinations of the keywords used in the Current Contents and Science Citation Index search.

Appendix 2

CALCULATION OF TEST CHARACTERISTICS

		Reference standard	
		Positive	Negative
Screening test	Positive	a	b
	Negative	c	d

$$\text{Sensitivity \%} = \frac{a \times 100}{a + c}$$

$$\text{Specificity \%} = \frac{d \times 100}{b + d}$$

$$\text{PPV \%} = \frac{a \times 100}{a + b}$$

$$\text{NPV \%} = \frac{d \times 100}{c + d}$$

Appendix 3

DIAGNOSTIC CHECKLIST

Study identification		
<i>Include author, title, reference, year of publication</i>		
Checklist completed by:		
SECTION 1: INTERNAL VALIDITY		
Evaluation criterion		<i>How well is this criterion addressed?</i>
1.1	Does the study address an appropriate and clearly focused question?	
SELECTION OF SUBJECTS		
1.2	Are the cases and controls taken from comparable populations?	
1.3	Are the same exclusion criteria used for both cases and controls?	
1.4	What percentage of each group (cases and controls) participated in the study?	
1.5	Is there any comparison of participants and non-participants to establish their similarities or differences?	
1.6	Are cases clearly defined and differentiated from controls? Is it clearly established that controls are non-cases?	
ASSESSMENT		
1.7	Have measures been taken to prevent knowledge of primary exposure influencing case ascertainment?	
1.8	Is exposure to the intervention measured in a standard, valid and reliable way?	
CONFOUNDING		
1.9	Are the main potential confounders identified and taken into account adequately in the design and analysis?	
STATISTICAL ANALYSIS		
1.10	Are the same data processing methods used for cases and controls?	
1.11	Have sensitivity and specificity been provided? PPV NPV?	
1.12	Is a measure of goodness-of-fit provided for any multivariate model used?	
1.13	Was a statistical analysis of results undertaken?	

SECTION 2: REFERENCE STANDARD AND TESTS		
2.1	Was the test compared with a valid reference standard?	
2.2	Were the test and reference standards measured independently (blind) of each other?	
2.3	Was the choice of patients for assessment by the reference standard independent of the test's results?	
2.4	Was the reference standard measured before any interventions were started with knowledge of test results?	
2.5	Were tests compared in a valid design? i.e. all tests done independently (blind to the results of the other tests) on each person or different tests done on randomly allocated individuals? (<i>For studies comparing tests only</i>)	
SECTION 3: DESCRIPTION OF THE STUDY		
3.1	What diagnoses and diagnostic tests are evaluated in this study?	
3.2	What outcomes are assessed?	
3.3	How many patients participated in the study? <i>Overall number, and in each group within the study.</i>	
3.4	What are the characteristics of the study population? <i>e.g. age, sex, disease characteristics of the population, disease prevalence.</i>	
3.5	What are the characteristics of the study setting? <i>e.g. rural, urban, hospital inpatient or outpatient, general practice, community.</i>	
3.6	Are there any specific issues raised by this study? <i>Make any general comments on the study results and their implications</i>	