

Diagnostic accuracy of screening tools for chronic obstructive pulmonary disease in primary health care: Rapid evidence synthesis

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) contributed significantly to burden of diseases in India, with missed, incorrect, and delayed diagnosis in primary care. We conducted a rapid evidence synthesis, to summarize the evidence on accuracy of the screening tests for COPD in primary health care on request from State Health Resource Centre, Chhattisgarh. **Methods:** Considering the rapid nature of decision making, our approach was to first search for existing systematic reviews. We identified one existing systematic review on the topic with the search conducted until 2014. We updated the review by searching in two major databases screened, title/abstracts, and full texts of studies as per eligibility criteria and extracted relevant data. A narrative synthesis was conducted. **Results:** We retrieved 7,007 and included five new studies, to add to 10 studies of the existing systematic review. Overall, 13 studies assessed diagnostic accuracy of screening questionnaires [e.g., COPD Diagnostic Questionnaire (CDQ)], five assessed handheld flow meters (COPD6 and PICO-6), and four assessed the combination of both the tests. The CDQ questionnaire using a score threshold ≥ 16.5 or >17 demonstrated comparatively a higher sensitivity both in pooled result for ever-smokers [87.5% (95% CI 83.1--90.9%)] and among the adults >35 years [73.8--93% (95% CI 69--98%)] when compared to a different score threshold of CDQ and other questionnaires. Handheld flow meters reported a pooled high sensitivity of 79.9% (95% CI 74.2--84.7%) in ever-smokers and 87.9% in adults with age >35 years. **Conclusions:** The need for better diagnosis of COPD in primary healthcare can be addressed by using of COPD Diagnostic Questionnaire alone or in combination with hand-held flow meters. There is scope for more implementation research on the domain.

Keywords: Chronic obstructive pulmonary disease, diagnostic test accuracy, primary health care, screening, sensitivity, specificity, spirometry

Introduction

Chronic obstructive pulmonary disease (COPD) is a major contributor to disease burden globally in spite of being preventable and treatable.^[1] Globally, 261 million cases of COPD were reported in 2016, with an estimated 3.17 million deaths in 2015.^[2,3] The burden of COPD in low-and middle-income

countries (LMICs) is continually increasing, posing a substantial public health burden.^[1] Smoking cessation and early detection of this disease can prevent its development and limit its mortality and morbidity.^[1] The Global Burden of Disease study reported that the prevalence of COPD in India increased by 39.4% in 2017 posing a significant public health threat.^[3,4]

The requester [State Health Resource Centre (SHRC)] in Chhattisgarh had identified the high burden of COPD in Chhattisgarh and the need to improve identification of COPD patients and subsequent care of COPD patients in the primary

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care. Globally it is known that primary care providers often missed early diagnosis of COPD, when symptoms are mild and the disease is often diagnosed at an advanced stage, when lung changes are no longer fully reversible.^[5]

We received a request from SHRC to conduct a review of the evidence (within 6 weeks) on screening tests for diagnosing COPD in primary healthcare facilities.

Methods

Approach for the study

Based on an initial scoping of literature, we identified a systematic review^[6] published in 2015 which address the review question of interest. It provided relevant details from included studies (published until 2014) on diagnostic accuracy of screening tests for identifying undiagnosed COPD. Hence, our approach was updating the systematic review^[6] by searching for studies of any quantitative design that evaluated screening tests conducted in PHC.

Ethical approval

The article is a review of published literature and did not involve any living participant. As such, no ethical approval was necessary.

Eligibility criteria

We included studies which met the following criteria.:

1. Population: Studied which included individuals aged ≥ 35 years with no prior diagnosis of COPD.
2. Index test: Screening questionnaires (any), handheld flow meters/handheld spirometer (e.g., Piko-6 or COPD-6), peak flow meters/micro spirometry, risk prediction models, decision aids, and chest radiography, either used alone or in combination with any of the aforementioned tests.
3. Reference Standard Presence of airflow obstruction measured by prebronchodilator or postbronchodilator spirometry.
4. Diagnosis of interest: Identification of COPD.
5. Study designs: Studies of any quantitative design.
6. Setting: Studies conducted in PHC context (including general practices and community pharmacies) were considered.

Information sources

We searched two electronic databases (Medline and EMBASE) from January 2014 to March 2020 [Appendix 1]. The search was restricted to studies published in the English language.

Study selection and data collection process:

The primary reviewer independently applied the inclusion criteria to the retrieved publications. The titles and abstracts of studies for inclusion were screened. For the studies deemed relevant, full texts were retrieved and screened for eligibility as per the eligibility criteria. We included studies which specifically mentioned the target condition as COPD, identified by the use of airflow obstruction, with prebronchodilator or postbronchodilator spirometry as the reference standard. No assessment of methodological quality of the studies was conducted.

Data collection process

A pre-designed template for data extraction was developed. The primary reviewer independently extracted all relevant outcome data. We extracted data on several key parameters including: 1) Study type, 2) Countries where studies were conducted, 3) Participants (number) and details of setting, 4) Index and reference tests, 5) Outcome measures (sensitivity and specificity).

Synthesis of results

Relevant outcome data were extracted and tabulated from selected reviews. A narrative synthesis was presented that addressed the review question documenting the relevant data and findings from all^[7-21] the included studies. The findings of meta-analyses conducted in the existing systematic review^[6] were presented, wherever relevant. On account of considerable heterogeneity, additional five^[17-21] studies were precluded from meta-analyses.

We used the PRISMA extension for Diagnostic Test Accuracy (DTA) [Appendix 2] for reporting the study.

Results

Study selection

We retrieved 7,007 articles after electronic databases search. Following the removal of one duplicate, the titles/abstracts of 7,006 studies were screened based on the pre-set eligibility criteria. Full texts of 44 potentially eligible articles were obtained and were reviewed for further examination. Only five of the 44 studies were included in the final report.

We thus added five new studies^[17-21] to the existing 10 studies^[7-16] of the systematic review by Haroon *et al.*^[6] Figure 1 depicts the study selection process in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Study characteristics

The review reported 10 studies^[7-16] from existing systematic review^[6] and additional five studies^[17-21] were supplemented with updated search. Overall, 15 studies^[7-21] accounting for 35,429 participants were included in the review. The review examined evidence on diagnostic accuracy of screening tests mainly measured by sensitivity and specificity of the test for detecting COPD. Majority of the studies were of cross-sectional diagnostic test accuracy design. The mean age of the participants ranged from 49 years to 69.5 years. Most of the studies were conducted in developed countries like UK, US, Australia, European countries, except one^[8] which was conducted in Vietnam. Four studies^[10,15,18,19] used a paired design and compared two screening tests (screening questionnaires and handheld flow meters), while the remaining studies used single screening method followed by spirometry as reference test. Meta-analyses were conducted in five^[10,12,14-16] studies from the systematic review by Haroon *et al.*^[6] Rest of the studies were excluded from the meta-analyses on the account of heterogeneity in the studies. The methodological quality of 10 studies from the systematic review was assessed

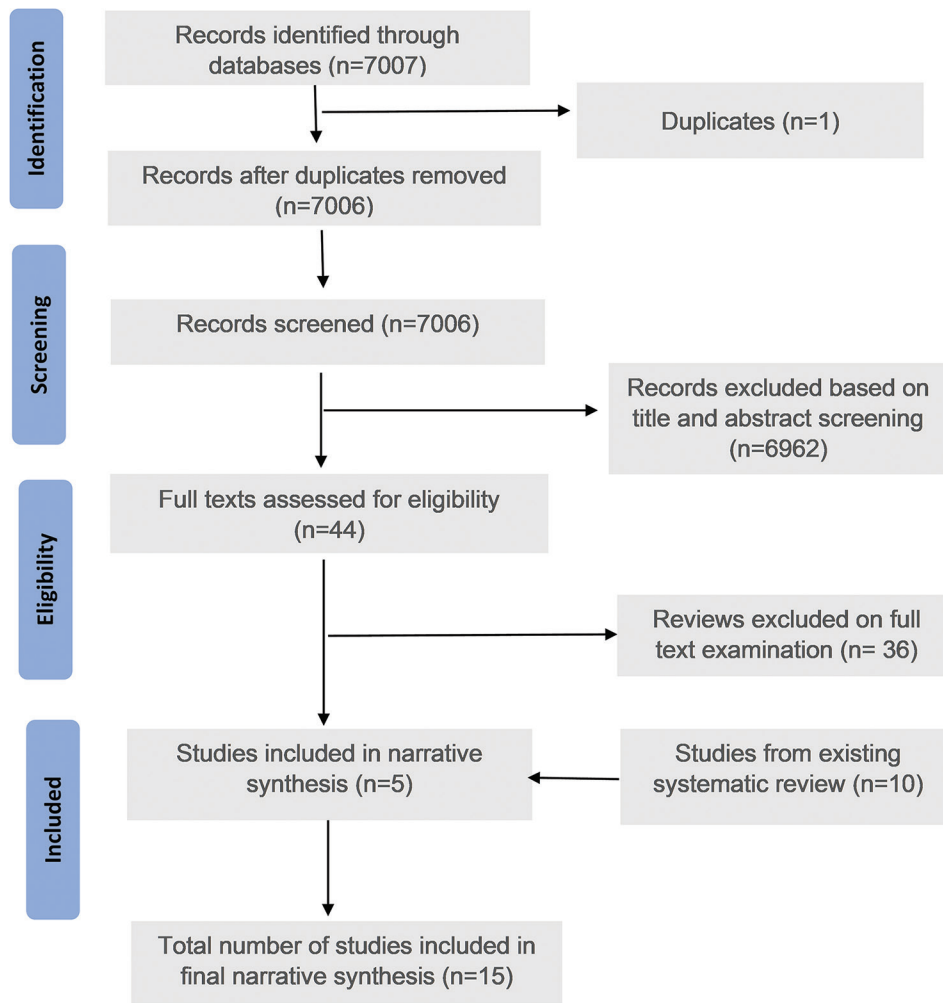


Figure 1: The study selection process in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

using QUADAS-2 tool,^[7-16] however, the additional five studies were not appraised.^[17-21] Key characteristics of all the included studies are presented in Appendix 3.

Index and reference tests

Index tests included screening questionnaires ($n = 13$)^[7,9-15,17-21] handheld flow meters ($n = 6$).^[8,10,15,16,18,19] Prebronchodilator spirometry was used as the reference standard test in two^[7,11] studies while 13^[8-10,12-21] studies used both pre and postbronchodilator spirometry.

Screening questionnaires

Thirteen studies^[7,9-15,17-21] assessed four screening questionnaires on 15,182 participants. Among all the questionnaires, the CDQ was the most widely used screening tool ($n = 8$)^[10,12,14,15,17,18,20,21] followed by other screening questionnaires. The CDQ is also referred to as the Respiratory Health Screening Questionnaire (RHSQ) or International Primary Care Airways Group (IPAG) questionnaire. Few studies reported using more than one questionnaire as their screening tool.^[17,18,20]

No new studies were found which had evaluated CDQ as screening tool (using a threshold of ≥ 19.5 , ≥ 16.5 or > 17) in ever-smokers and the meta-analysis of four studies^[10,12,14,15] was done by the Haroon *et al.*^[6]. Remaining studies^[17,18,20,21] were precluded from conducting meta-analysis as a result of the heterogeneity in their threshold of score and the participants. The pooled sensitivity and specificity reported for the score threshold of ≥ 19.5 was 64.5% [95% Confidence Interval (CI) 59.9--68.8%] and 65.2% (95% CI 52.9--75.8%), respectively. While the pooled sensitivity reported for the score threshold of ≥ 16.5 was higher at 87.5% (83.1 to 90.9), the specificity was quite low at 38.8% (27.7 to 51.3).

The un-pooled sensitivities and specificities in adults > 35 years and ever-smokers for different threshold score were reported separately [Table 1]. At a score threshold of < 19.5 , the sensitivity and specificity reported was 36% (CI 11--61%) and 93% (CI 89--96%), respectively. The sensitivities and specificities using a score threshold ≥ 19.5 ranged from 59 to 73% and 54 to 77%, respectively. At a score threshold ≥ 16.5 or ≥ 17 , the sensitivities ranged from 73.8 to 93%, while specificities were reported in the range of 24--57%.

Table 1: Accuracy of Different Diagnostic Tests for COPD^[7-21]

Screening test	Sensitivity (95% CI)*	Specificity (95% CI)*	PPV (95% CI)*	NPV (95% CI)*	NNS OR NND* (95% CI)
Narrative Synthesis with Pre and Post bronchodilator spirometry as reference test in adults >35 years					
CDQ (using a score threshold <19.5) ^[17]	36 (11-61)	93 (89-96)	NR	NR	NR
CDQ (using a score threshold ≥19.5) ^[10,12,14,21]	59-73%	54-77%	NR	NR	NR
CDQ (using a score threshold ≥16.5 or ≥17) ^[10,12,14,15,18,20,21]	73.8-93%	24-57%	NR	NR	NR
COPD-PS (using a score threshold ≥4 or ≥5) ^[18-20]	20-80.4%	47.7-90%	5.3-41%	87.2-94.3%	NR
LFQ (using a score of ≤18) ^[11,13,15,20]	79-93%	25-71%	NR	NR	NR
Other unnamed questionnaires ^[7,9]	57-87%	71-80%	NR	NR	NR
Handheld flow meters ^[8,10,15,16,18,19]	79-87.9%	71-99%	NR	NR	NR
CDQ and handheld flow meter ^[15] , used together	74.4 (64.2-83.1)	97.0 (95.2-98.3)	59.1 (43.8-74.0)	98.5 (97.9-99.0)	NNS-25 (22-29); NND-2 (2-3)
COPD-PS and handheld flow meter ^[19] used together	20%	92.9%	14.3%	95.1%	NR
Meta-analysis (pooled result) [†] with Pre and Post bronchodilator spirometry as reference test for “ever smokers”					
CDQ (using a score threshold ≥19.5) ^[10,12,14]	64.5 (59.9-68.8)	65.2 (52.9-75.8)	9.7 (6.9-14.2)	96.9 (95.8-97.7)	NNS-29 (26-31); NND- 11 (7-15)
CDQ (using a score threshold ≥16.5 or >17) ^[10,12,14,15]	87.5 (83.1-90.9)	38.8 (27.7-51.3)	7.7 (6.3-9.8)	98.2 (96.6-99.0)	NNS-21 (20-22); NND- 13 (11-16)
Handheld flow meters ^[10,15,16]	79.9 (74.2-84.7)	84.4 (68.9-93.0)	23.0 (12.2-41.3)	98.6 (97.9-99.1)	NNS-23 (22-24); NND-13 (11-16)

NR- Not Reported. *Sensitivity -ability of a test to correctly identify those with the disease (true positive), Specificity - ability of the test to correctly identify those without the disease (true negative), PPV-Positive Predictive Value - Chances that participants with a positive test truly have the disease, NPV- Negative Predictive Value- Chances that participants with a negative test truly don't have the disease., NND- Number needed to diagnose- number of patients needing a diagnostic assessment to identify one patient with COPD (the lower the number better the yield), NNS- Number needed to screen - number of individuals who -needed-to be-screen to identify one patient with COPD (the lower the number better the yield), †The pooled results reported are from the studies of existing systematic review^[9], CDQ- COPD Diagnostic Questionnaire is also referred as the International Primary Airways Group (IPAG) Questionnaire or Respiratory Health Screening Questionnaire (RHSQ).It is an 8-item tool designed by the COPD Questionnaire Study Group from a cross-sectional study of primary care patients ≥40 years old from the United Kingdom and the United States with a history of smoking but no prior respiratory diagnosis. It could be used as a filtering tool to select patients at high risk of COPD to undergo spirometry.^[21] COPD-PS- COPD Population Screener developed by a clinician working group in the United States, is a five-item, self-administered questionnaire that was validated for screening individuals in the general population who are at high risk of COPD. It is composed of three COPD-related items (breathlessness, productive cough, and activity limitation) and one question, each regarding smoking history and age.^[22] LFQ The Lung Function Questionnaire (LFQ) is a simple, brief, self-administered instrument, being developed to address the need for a screening tool to identify patients appropriate for COPD spirometry-confirmed diagnosis evaluation. It is a five-item tool with a cut point score of ≤18.^[23]

The pooled^[10,12,14,15] result for ever-smokers and among the adults >35 years^[10,12,14,16,18,21] reported a comparative high sensitivity for COPD diagnostic questionnaire (CDQ) using a score threshold ≥16.5 or >17 as compared to a different score threshold of CDQ and other questionnaires signifying a lower percentage of missed positive cases [as summarized in Table 1]. Likewise, the pooled Negative Predictive Value (NPV) of CDQ reported at the same threshold score 98.2% probability that the subject with negative result is truly free of disease.

Studies using Lung Function Questionnaire (LFQ), COPD Population Screener (COPD-PS), and Two screening questions (2SQ) reported a significant heterogeneity in their design, and therefore were not eligible to be included in a meta-analysis.

The COPD-PS screening questionnaire across the three studies^[18-20] in adults >35 years reported (using a score threshold ≥4 or ≥5) sensitivities ranging from 20 to 80.4% and specificities from 47.7 to 90%, respectively.

Lung Function Questionnaire^[11,13,15,20] at a score of ≤18 reported sensitivity ranging from 79 to 93% which was again suggestive of a lower percentage of missed positive cases while the specificity reported was between the range of 25 and 71%.

Other screening questionnaires were assessed in = 2 studies^[7,9] which reported sensitivity range of 57--87% and specificity ranging between 71-80%.

Handheld flow meter

Handheld flowmeter is a device intended for measuring lung function. FEV1 and FEV6 is a measure of forced expiratory volume in 1 and 6 s, respectively. The test is repeated three times with the highest values recorded. Five studies evaluated the diagnostic accuracy of handheld flow meter in 2,052 participants.^[8,10,15,16,18,19] The mean age of the participants ranged from 52 to 65.3 years. Four studies used it without a bronchodilator.^[8,10,16,18,19] The handheld meter used were COPD6 and PICO-6. An FEV1/FEV6 cut off <0.7 provided a range of sensitivity from 79 to 87.9% and specificity from 71 to 99% for COPD screening.

Three studies^[10,15,16] enrolling ever-smokers from the existing systematic review^[6] were deemed eligible for conducting meta-analysis as a result of their homogeneity. Handheld flow meters^[10,15,16] when used under the supervision of trained nurses and health professionals reported a pooled high sensitivity of 79.9% (95% CI 74.2--84.7%) and a specificity of 84.4% (95% CI 68.9--93.0%), respectively [Table 1].

In adults with age >35 years and ever-smokers, the un-pooled^[8,10,15,16,18,19] sensitivities and specificities were reported in the range of 79--87.9% and 71--99%, respectively.

Combined screening tests

The combined diagnostic test accuracy of a handheld flow meter along with a questionnaire was assessed in four studies.^[10,15,18,19] However, the combined results for the diagnostic accuracy was reported by only two studies.^[15,19]

Sichletidis *et al.* found that the combined sensitivity of a screening questionnaire (CDQ) with a handheld flow meter was 74.4% (95% CI 64–83%), and specificity 97% (95% CI 95–98%). The NNV was reported as 98.5% for combined usage. This is suggestive of an improved diagnostic accuracy of screenings tests when used in combination, thereby potentially reducing number of diagnostic assessments required.

Likewise, Shirley *et al.* reported the combined results for screening questionnaire (COPD-PS) and handheld flow meter. The tests together yielded a sensitivity of 20% and specificity of 92.9%. The individual test accuracy of other two studies^[10,18] has been aforementioned in the above sections.

Discussion

The rapid evidence synthesis is an update of an existing systematic review^[6] examining the evidence on diagnostic accuracy of screening tests and overall we incorporated evidence from 15 studies. Of all the screening questionnaires, CDQ was the most extensively used screening tool and was found to have acceptable sensitivity and specificity. Combined usage of handheld flow meters and the CDQ questionnaire lead to higher sensitivity and specificity compared to the CDQ screening questionnaire alone when used under the supervision of trained nurses or general practitioners. A higher sensitivity and specificity of handheld flow meter (80% and 79.8%, respectively) alone when compared to COPD-PS questionnaire (20% and 78.6%, respectively) was also reported. These results indicate that the use of a simple, validated, easy to administer tool in primary healthcare context is an effective method to facilitate early diagnosis of patients at a risk of COPD. However, the use of handheld flow meter requires training, underlying the need for further investments on this regards, particularly in resource-scarce settings. However, it is expected that such an early diagnosis focused strategy would be more cost-effective than the current scenario wherein delayed diagnosis leads to high costs of treatment in the secondary and tertiary care sectors as well as high mortality and morbidity. Formal cost-effectiveness evaluations might be mandated. There are, however, implementation challenges expected, including but not limited to addressing demand-side barriers, human resource and technical capacity issues, and issues around governance and financing. There is need for implementation research in the domain. There is also need for understanding care pathways for COPD in different countries to enable better planning.

We acknowledge the limitation of searching only in electronic databases with no search for identifying grey/unpublished literature and the lack of conduct of risk of bias assessment in

this update but contend this would not change the findings of the study and its implications majorly.

Conclusion

The problem of misdiagnosis or underdiagnosis of COPD in primary care can be resolved through usage of handheld flow meters along with COPD questionnaires. There is need for more implementation research on this domain.

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Conflicts of interest

There are no conflicts of interest.

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APPENDICES

Appendix 1: Search strategies

Medline

No.	Search terms
#1	Chronic obstructive pulmonary disease [MeSH] OR Chronic obstructive lung disease [MESH] OR Chronic obstructive airways disease [MESH] OR COPD[tw] OR COAD[tw] OR Emphysema[tw] OR “Chronic bronchitis”[tw] OR “Airflow obstruction”[tw] OR “Airflow limitation”[tw]
#2	Secondary prevention [MESH] OR Spirometry [MESH] OR Design questionnaire [MESH] OR Decision aid [MESH] OR Algorithm [MESH] OR “Case finding”[tw] OR “Screening”[tw] OR “early detection”[tw] OR “Questionnaire”[tw] OR “Peak flow”[tw] OR “Chest X-ray”[tw] OR Sensitivity[tw] OR Specificity[tw]
#3	care, primary health[MeSH] OR primary health care*[tw] OR “primary health care”[tw]
#4	#1 AND #2 AND #3 Filters: English; Humans; Published in the 2014-2020

EMBASE

No.	Search terms
#1	Chronic obstructive pulmonary disease/de OR Chronic obstructive lung disease/de OR Chronic obstructive airways disease/de OR “COPD” OR “COAD” OR “Emphysema” OR “Chronic bronchitis” OR “Airflow obstruction” OR “Airflow limitation”
#2	Secondary prevention/de OR Spirometry/de OR Design questionnaire/de OR Decision aid/de OR Algorithm/de OR “Case finding” OR “Screening” OR “early detection” OR “Questionnaire” OR “Peak flow” OR “Chest X-ray” OR Sensitivity OR Specificity
#3	“Primary health care/de OR primary health care* OR “primary health care”
#4	#1 AND #2 AND #3 AND [embase]/lim NOT [medline]/lim AND [humans]/lim AND [2014-2020]/py AND [english]/lim

Appendix 2: PRISMA DTA CHECKLIST

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
TITLE/ABSTRACT			
Title	1	Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.	1
Abstract	2	Abstract: See PRISMA-DTA for abstracts.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).	2
Objectives	4	Provide an explicit statement of question (s) being addressed in terms of participants, index test (s), and target condition (s).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (participants, setting, index test (s), reference standard (s), target condition (s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2

Contd...

Section/topic	#	PRISMA-DTA Checklist Item	Reported on page #
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.	13
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target condition (s), index test (s), reference standard (s) and other characteristics (e.g. study design, clinical setting).	3
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	NA
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measure (s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).	NA
Synthesis of results	14	Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition. b) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards	4
Meta-analysis	D2	Report the statistical methods used for meta-analyses, if performed.	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources	5
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	NA
Results of individual studies	20	For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.	5,6
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	7,8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence.	9
Limitations	25	Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test).	9
FUNDING			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders	10

Adapted From: McInnes MDF, Moher D, Thoms BD, McGrath TA, Bossuyt PM, The PRISMA-DTA Group (2018). Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. *JAMA*. 2018 Jan 23;319 (4):388-396. doi: 10.1001/jama.2017.19163.

Appendix 3: Characteristics of included studies

Study	Country	Setting	Recruitment method	Eligibility criteria	Index and reference tests	Definition of COPD
Buffels ^[7] 2004	Belgium	20 general practitioners	Invited patients routinely attending general practice over a 12-week period in 1999.	Inclusion criteria: Age 35-70 years Exclusion criteria: Receiving bronchodilators and/or inhaled corticosteroids	Index test: Screening questionnaire Reference test: Pre-BD spirometry in all subjects with respiratory symptoms and 10% sample of asymptomatic subjects	Pre-BD FEV1/FVC <88.5% predicted for men & FEV1/FVC <89.3% for women
Duong-Quy ^[8] 2009	Vietnam	12 primary care medical centres in one city	Broadcast an advertisement on the local television daily for one week. A recruitment company was used to help with participant recruitment (details not reported). Eligible subjects expressing an interest in participating were advised to attend one of the 12 primary care centres from January 2007 to February 2008.	Inclusion criteria: Active and former smokers with >10 pack-years and aged >40 years Exclusion criteria: Previously diagnosed respiratory disease (asthma, COPD and tuberculosis)	Index test: Pre-BD handheld flow meter (Piko-6®) Reference test: Full medical assessment including clinical examination, pulmonary radiology, ECG, and post-BD spirometry for those who had an index FEV1/FEV6 <0.7 and a sample of those with FEV1/FEV6 ≥0.7	Post-BD FEV1/FVC <0.7 with <200 mL or 12% reversibility
Casado ^[7] 2015	Spain	Primary care centre	Random sampling of a general population	Inclusion criteria: Population aged between 40 to 75 years	Index test: Screening questionnaire Reference test: Pre-/Post BD Spirometry on all subjects	Post-BD Ratio of FEV1/FVC (forced expiratory volume in 1 second/forced vital capacity) of <0.7
Freeman ^[9] 2005	UK	One general practice	Postal invitation from October 1997 to April 2002.	Inclusion criteria: Age ≥40 years & current/ex-smoker & had either received respiratory medications in the preceding 2 years or had a history of asthma Exclusion criteria: None	Index test: Screening questions Reference test: Pre-/post-BD spirometry on all subjects	Post-BD FEV1/FVC <0.7 and lack of reversibility (reversibility defined as increase in FEV1 of 200mL and 15% from pre-BD FEV1 (not clear if all were post-BD)
Frith ^[10] 2011	Australia	4 primary care practices	Recruited during routine practice visits, invitation to study days, and local newspaper advertisement between August and December 2006.	Inclusion criteria: Age ≥50 years & current/ex- smoker & no prior diagnosis of obstructive lung disease (COPD, emphysema, chronic bronchitis, asthma) & no treatment for obstructive lung disease in past 12months Exclusion criteria: Refusal or inability to give consent, pre-existing non-obstructive lung disease, symptoms suggestive of unstable heart disease, and spirometry contraindications	Index test: Pre-BD handheld flow meter (Piko-6®) & screening questionnaire (COPD Diagnostic Questionnaire) Reference test: Pre-/post-BD spirometry on all patients	Post-BD FEV1/FVC <0.7
Hanania ^[11] 2010	US	Two family physician group offices	Invited patients aged ≥40 years visiting the practices from March-May 2008	Inclusion criteria: Age ≥40 years Exclusion criteria: None	Index test: Screening questionnaire (Lung Function Questionnaire) Reference test: Pre-BD spirometry	Pre-BD FEV1/FVC <0.7

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Study	Country	Setting	Recruitment method	Eligibility criteria	Index and reference tests	Definition of COPD
Kotz ^[12] 2008	Netherlands	General population and primary care practices	Advertisements in a local newspaper, flyers, posters and mailings to households and invitation during primary care consultations from Jan 2005-Dec 2006.	Inclusion criteria: Age 40-70 years & current smoker with ≥10 pack years & motivated to stop smoking & able to read and speak Dutch & reporting a respiratory symptom (cough, phlegm or dyspnoea) Exclusion criteria: Prior respiratory diagnosis, spirometry in previous 12 months or contraindications to smoking cessation therapy	Index test: Questionnaire (COPD Diagnostic Questionnaire) Reference test: Pre-/post-BD spirometry in all participants	Post-BD FEV1/FVC <0.7
Llorde ^s [18] 2016	Spain	8 primary care centres	Active, Patient who attended the primary care centre for any reason during the study period were invited to participate.	Inclusion criteria: Subjects over the age of 40 years who were smokers or ex-smokers of at least 1 pack-year with no previous diagnosis of COPD and who attended the Primary Care centres for any reason.	Index test: Screening questionnaire (CDQ/Respiratory Health Screening Questionnaire (RHSQ)) COPD-population screener (PS) Two screening questions (2SQ)); Handheld spirometer (Vitalograph COPD-6). Reference test: Pre and Post BD Spirometry	Post-bronchodilator FEV1/FVC <0.7
Mintz ^[13] 2011	US	36 primary care centres	NR	Inclusion criteria: Age ≥30 years old & current/ex-smoker with ≥10 pack years Exclusion criteria: Regular use of respiratory medications within 4 weeks of the study, known diagnosis of substantial lung conditions with regular use of respiratory medications.	Index test: Screening questionnaire (Lung Function Questionnaire) Reference test: Pre-/post-BD spirometry	LFQ ≤ 18 & post-BD FEV1/FVC <0.7
Price ¹ [4] 2006	UK & US	2 primary care practices	Postal invitation	Inclusion criteria: Age ≥40 years & current/ex-smoker Exclusion criteria: Refusal to consent, history of non-obstructive lung disease, use of respiratory medications in past year, acute symptoms of unstable heart disease	Index test: Screening questionnaire (COPD Diagnostic Questionnaire) Reference test: Pre-/post-BD spirometry	Post-BD FEV1/FVC <0.7
Shirley ^[9] 2015	Japan	2 HIV primary care clinics	Subjects were recruited via referral from clinic providers and staff, and via response to flyers posted in the waiting rooms.	Inclusion criteria: Patients who met inclusion criteria (age ≥ 35 years with documented HIV infection) were screened for entrance to the study.	Index test: Screening questionnaire (COPD-PS); Peak flow meter (Vitalograph asma-1 electronic peak flow meter) Reference test: Pre and Post BD Spirometry	Post-BD FEV1/FVC <0.7

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Study	Country	Setting	Recruitment method	Eligibility criteria	Index and reference tests	Definition of COPD
Sichletidis ^[15] 2011	Greece	25 general practices	Invited first 50 patients meeting the inclusion criteria who visited each participating GP from 1st March-31st May 2009.	Inclusion criteria: Age >40 years Exclusion criteria: Confirmed diagnosis of lung disease, thoracic surgery in previous 6 months, acute respiratory infection, uncontrolled cardiac disease, or could not perform acceptable spirometry	Index tests: 1. Screening questionnaire (International Primary Airways Group Questionnaire, also known as the COPD Diagnostic Questionnaire) 2. Post-BD handheld flow meter (Piko-6®) (Bronchodilator = 400µg salbutamol) Reference test: Pre-/post-BD spirometry	Post-BD FEV1/FVC <0.7
Spyratos ^[20] 2016	Greece	Primary care clinics	The general population were invited to participate in the present study by advertisement posters that had been distributed across a network of primary care practices in the city	Inclusion criteria: Participants eligible for this cross-sectional study were subjects aged >40 years, current and former smokers (≥10 pack-years). Exclusion criteria: A previous medical diagnosis of bronchial asthma or chronic pulmonary disease other than COPD (e.g, bronchiectasis, lung cancer, tuberculosis, and interstitial lung disease).	Index test: Screening questionnaire (CDQ/International Primary Care Airways Group (IPAG) questionnaire; COPD Population Screener (COPD-PS) questionnaire ; Lung Function Questionnaire (LFQ)) Reference test: Pre and Post BD Spirometry	Post-BD FEV 1/FVC <0.7
Stanley ^[21] 2014	Australia	36 general practices	Patients aged 40-85 years who were former or current smokers with no previous diagnosis of COPD or other obstructive lung disease were invited to a case-finding appointment with a practice nurse in one of the 36 study general practices.	Inclusion criteria: Patients aged 40-85 years who were former or current smokers with no previous diagnosis of COPD or other obstructive lung disease.	Index test: Screening questionnaire (COPD Diagnostic Questionnaire (CDQ)) Reference test: Pre and Post BD Spirometry	post-BD forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio <0.7,
Thorn ^[16] 2012	Sweden	21 primary healthcare centres	Invited patients attending participating primary healthcare centres over a 5-month period.	Inclusion criteria: Age 45-85 years & current/ex-smoker with ≥15 pack years Exclusion criteria: None	Index test: Pre-BD handheld flow meter (COPD-6) Reference test: Pre-/post-BD spirometry	Post-BD FEV1/FVC <0.7

BD, bronchodilator; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; CDQ, COPD Diagnostic Questionnaire; COPD-PS, COPD Population Screener questionnaire; LFQ, Lung Function Questionnaire; IPAG, International Primary Airways Group