UK National Screening Committee

# Screening for chronic obstructive pulmonary disease (COPD) in the general adult population

# External review against programme appraisal criteria for the UK National Screening Committee

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**The UK National Screening Committee secretariat is hosted by Public Health England.**

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The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.
Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

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# Plain English summary

Chronic obstructive pulmonary disease (COPD) causes breathing difficulties. The name covers a group of lung conditions that get worse with time. There are an estimated 3 million people with COPD in the UK. About 2 million of these will not know that they have the disease. Smoking tobacco causes most COPD cases.

Some people with COPD have symptoms such as breathlessness and persistent cough. In the early stages people may not have symptoms. Without treatment the quality of life of people with COPD will worsen.

This document looks at new evidence about population screening for COPD in adults. It includes evidences published between February 2012 and November 2017. It considers whether a national population screening programme should be set up. Such a programme would:

- identify people with COPD before they have symptoms
- offer treatments or interventions to reduce future worsening of their lung function

The UK National Screening Committee (UK NSC) published its last review in 2012. This recommended against introducing a screening programme for COPD in the UK. The current review looked at some key questions.

1. what is the accuracy of screening tests to detect COPD in adults without symptoms?
2. what is the impact of screening for COPD on people giving up smoking?
3. what is the effectiveness of drug treatment in adults who have COPD but no symptoms?
4. does screening for COPD in adults without symptoms reduce deaths and improve people's health?

This review of the evidence found that the UK NSC still cannot recommend population screening for COPD. This is because no new evidence has been published to change the conclusions of the previous UK NSC review.

# Executive summary

## Purpose of the review

This document reviews the evidence on systematic population screening for chronic obstructive pulmonary disease in the general adult population.

## Background

Chronic obstructive pulmonary disease (COPD) is a group of progressive lung conditions in which air flow to the lungs is gradually reduced by inflammation and irreversible damage to pulmonary air passages.

COPD is a leading cause of death and important cause of healthcare expenditure in the UK. About 2 million of the estimated 3 million people with COPD in the UK will be undiagnosed. Tobacco smoking is responsible for 80% to 90% of COPD cases and 15% of smokers will develop COPD. Key COPD symptoms include increasing breathlessness when active and persistent cough with phlegm. In the early stages many people appear ‘asymptomatic’, however they may be affected in ways that are difficult to perceive or measure and which could be dismissed as attributable to ageing. Untreated, COPD will progressively impair quality of life, increasing morbidity and mortality.

## Focus of the review

The function of a national population screening programme would be to identify adults with COPD when the disease is in an asymptomatic or unrecognised stage, and to offer treatments and interventions to reduce the rate of lung function deterioration.

This evidence summary includes studies published between February 2012 and November 2017. It considers 4 key questions relating to the test, the intervention and the screening programme:

1. what is the accuracy of screening tests at detecting COPD in an asymptomatic population?
2. what is the impact of screening for COPD on smoking cessation rates?
3. what is the clinical effectiveness of pharmacological treatment on screen-detected patients with COPD?

4. does screening for COPD in asymptomatic adults reduce morbidity or mortality or improve health-related quality of life?

## Recommendation under review

The current UK NSC policy is that systematic population screening for COPD in adults is not recommended. The previous UK NSC external review was published in 2012 and concluded that there were challenges around the test options for a population-wide screening programme; limited evidence on the effectiveness of intervention for early stage COPD; limited evidence on whether spirometry prompts people to quit smoking and no RCTs had been conducted on screening for COPD. The 2012 UK NSC review noted that evidence of cost-effectiveness existed for case finding symptomatic individuals with more developed COPD*.

## Findings and gaps in the evidence of this review

The current review found that the volume, quality and direction of new evidence published since February 2012 does not indicate that there have been any significant changes in the evidence base since the previous review. Areas of concern relate to:

- there are still concerns about the high number of false positives from risk assessment questionnaires
- there are uncertainties about the performance of screening tests using risk assessment questionnaires, pulmonary function based tests or a combination of both
- there are still uncertainties about the impact of screening on smoking cessation rates
- there is a lack of evidence for the effectiveness of pharmacological treatment in asymptomatic adults or adults with mild disease
- there is a lack of evidence that screening for COPD reduces mortality and morbidity.

* In case finding, people who present at their GP for other health problems are tested if they are either symptomatic or thought to be at risk of COPD

## Recommendations on screening

The current recommendation not to introduce a UK systematic population screening programme for COPD should be retained.

## Limitations

A limitation for this review is the lack of evidence specific to the population of interest for population-based screening for COPD, particularly relating to the treatment of ‘asymptomatic’ individuals with undetected mild to moderate symptoms or the effectiveness of screening.

# Introduction and approach

This evidence summary reviews systematic population screening for chronic obstructive pulmonary disease in the general adult population against selected UK National Screening Committee Criteria. The function of a national screening programme would be to identify adults with COPD when the disease is in an asymptomatic or unrecognised stage, and to offer treatments and interventions to reduce the rate of lung function deterioration.

## Background

Chronic obstructive pulmonary disease (COPD) is a group of progressive lung conditions, the most common of which are chronic bronchitis and emphysema[1]. Air flow to the lungs is gradually reduced by inflammation and irreversible damage to pulmonary air passages[1].

COPD is a leading cause of death and important cause of healthcare expenditure in the UK[2]. There are an estimated 3 million people with COPD in the UK, of which about 2 million will be undiagnosed[3]. Studies have estimated the prevalence of undiagnosed COPD in general populations as 7.4% and 8.4%[3]. In at-risk populations, prevalence estimates range from 18.9% to 27.9%[3]. Studies have found that smoking tobacco is responsible for 80% to 90% of COPD cases and that 15% of smokers will develop COPD[1]. Other at-risk individuals include people exposed to inhaled dusts and gases in the workplace, people with a previous diagnosis of asthma or people with a genetic problem leading to the onset of emphysema[3].

Key symptoms of COPD include increasing breathlessness when active and persistent cough with phlegm[1]. However, airflow obstruction without symptoms is also common[1]. In the early stages many people appear ‘asymptomatic’, however these individuals may be affected in ways that are difficult to perceive or measure and which could be dismissed as attributable to ageing[3]. Many COPD cases are not diagnosed until later in the disease[3]. Untreated, COPD will progressively impair quality of life, increasing morbidity and mortality[1].

Standardised classifications for airflow limitation severity in COPD were developed by the Global Initiative for COPD (GOLD). These classifications are also used by NICE[4]. Severity is measured post-bronchodilator using measures

of lung function (forced expired volume in 1 second ($FEV_1$) / forced vital capacity (FVC) ratio and $FEV_1$ percent predicted of normal)[4].

- stage 1 – mild - $FEV_1$/FVC <0.7; $FEV_1$% predicted ≥80%
- stage 2 – moderate - $FEV_1$/FVC <0.7; $FEV_1$% predicted 50%-79%
- stage 3 – severe - $FEV_1$/FVC <0.7; $FEV_1$% predicted 30%-49%
- stage 4 – very severe $FEV_1$/FVC <0.7; $FEV_1$% predicted <30% or $FEV_1$% predicted <50% with respiratory failure.

The NICE guideline specifies that symptoms should be present to diagnose COPD in people with mild airflow obstruction[4].

Severity assessment has implications for the treatment and prognosis of COPD. However, due to the heterogeneous nature of COPD, there is no single measure that can give an adequate assessment of the true severity in an individual patient[1].

The 2012 UK NSC external review considered the evidence for population screening for COPD against the UK NSC programme appraisal criteria[3]. This identified a number of studies exploring the natural history of COPD including a large population study[5] which found that there was no significant difference between asymptomatic subjects with stage 1 COPD and subjects with normal lung function on measures of lung function, respiratory care utilization and quality of life[3]. The 2012 UK NSC review also highlighted the limited evidence base for treatment outcomes in asymptomatic, mild or moderate disease[3].

The 2012 UK NSC review assessed different approaches for screening for COPD[3]. Risk assessment questionnaires were considered to potentially have some usefulness in ruling out COPD in the first step of a screening programme, but would include a high number of false positives[3]. Spirometry (measuring air flow) is used to diagnose COPD, but the review concluded that there were challenges in using spirometry as a screening test and in maintaining the quality of spirometric screening tests in primary care[3]. The 2012 review also highlighted issues around agreed cut-off levels for screening and cited the 2008 US Preventative Services Task Force (USPSTF) review which found evidence of high numbers of false positives in healthy asymptomatic individuals, particularly older people, when the GOLD stages were used[3].

With regards to treatments and interventions, the 2012 UK NSC review acknowledged the evidence for the benefit of stopping smoking after a COPD

diagnosis[3]. However, the evidence for whether a spirometric result or a diagnosis of COPD motivated individuals to stop smoking was inconsistent[3]. A number of pharmacotherapy treatments were considered in the 2012 review with the conclusion that although there was a strong evidence base for the treatment of COPD, there was limited evidence available on treatment outcomes for people with asymptomatic or mild disease[3]. The review did identify some large trials (TORCH[6] and UPLIFT[7]) which showed the benefit of pharmacological treatment for moderate stage 2 COPD[3]. The 2012 review acknowledged existing advice and guidelines on other interventions for COPD such as vaccinations, nutrition, education and self-management.

The 2012 UK NSC review did not identify any randomised controlled trials on screening for COPD[3].

## Current policy context and previous reviews

The current UK NSC policy is that systematic population screening for COPD in adults is not recommended. This policy is based on the previous UK NSC external review of screening for COPD which considered literature published up to February 2012[3]. This concluded that[3]:

- no RCTs had been conducted on screening for COPD
- the evidence on outcomes of treatments and interventions for early stage COPD was still limited
- the evidence regarding whether spirometry [or a diagnosis of COPD] prompted people to quit smoking was inconclusive
- challenges still existed with the test options for a population-wide screening programme
- prevention activity including the national COPD and tobacco strategies were yet to be fully implemented
- cost-effective evidence existed for case finding† symptomatic individuals with more developed COPD..

The USPSTF updated their evidence review for screening for COPD in adults in 2016[8]. They retained their decision not to recommend screening for COPD in adults due to a lack of evidence that screening for COPD in asymptomatic people alters the course of disease or improves patient outcomes[8].

† In case finding, people who present at their GP for other health problems are tested if they are either symptomatic or thought to be at risk of COPD[3]

## Objectives

The aim of the current review is to update the evidence in key areas identified in the previous review. The key questions addressed in the current review were developed by the UK NSC with input from Solutions for Public Health.

The key questions and the UK NSC criteria that they relate to are presented in Table 1 below.

**Table 1. Key questions for the evidence summary, and relationship to UK NSC screening criteria**

| | Criterion | Key questions | Studies Included |
|---|---|---|---|
| | **THE TEST** | | |
| **4** | There should be a simple, safe, precise and validated screening test. | 1. What is the accuracy of screening tests at detecting COPD in an 'asymptomatic' population? | 8 |
| **5** | The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed. | | |
| | **THE INTERVENTION** | | |
| **9** | There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered. | 2. What is the impact of screening for COPD on smoking cessation rates? | 4 |
| | | 3. What is the clinical effectiveness of pharmacological treatment on screen-detected patients with COPD? | 1 |
| | **THE SCREENING PROGRAMME** | | |
| **11** | There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence | 4. Does screening for COPD in 'asymptomatic' adults reduce morbidity or mortality, or improve health-related quality of life? | 2 |

| | Criterion | Key questions | Studies Included |
|---|---|---|---|
| | from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened. | | |

# Methods

The current review was conducted by Solutions for Public Health (SPH), in keeping with the UK National Screening Committee evidence review process. Database searches were conducted on 14th November 2017 to identify studies relevant to the questions detailed in Table 1.

## Eligibility for inclusion in the review

The following review process was followed:

1. each abstract was reviewed against the inclusion/ exclusion criteria by 1 reviewer. Where the applicability of the inclusion criteria was unclear from the abstract, the article was included at this stage in order to ensure that all potentially relevant studies were captured.
2. full text articles required for the full text review stage were acquired.
3. any queries at the abstract or full text stage were resolved through discussion with a second reviewer.
4. the review was quality assured by a second senior reviewer, not involved with the writing of the review in accordance with SPH's quality assurance process.

Eligibility criteria for each key question are presented in Table 2 below. Only peer-reviewed studies published in English between February 2012 and November 2017 were eligible for consideration in the review.

A total of 1,165 unique references were identified and sifted by an information scientist by title and abstract for potential relevance to the review. 155 titles and abstracts were reviewed by an SPH reviewer for further appraisal and possible inclusion in the final review.

Overall, 47 studies were identified as possibly relevant during title and abstract sifting and further assessed at full text.

**Table 2. Inclusion and exclusion criteria for the key questions.**

| Key question | Inclusion criteria: | | | | | | Exclusion criteria: |
|---|---|---|---|---|---|---|---|
| | **Population** | **Target condition** | **Intervention** | **Comparator** | **Outcomes** | **Study type** | |
| 1. What is the accuracy of screening tests at detecting COPD in an 'asymptomatic' population? | Asymptomatic adults (this could include people with undetected mild to moderate symptoms) | COPD | • Risk assessment questionnaire<br>• Screening spirometry without bronchodilator<br>• Combination of the above two tests | Index test and reference standard GOLD/ NICE classification | • COPD stage detected at screen (using GOLD/NICE classifications)<br>• Sensitivity, specificity<br>• PPV, NPV | Studies in randomly assigned or consecutively enrolled populations and systematic reviews of these should be prioritised | Case reports<br>Commentary<br>Conference abstracts |
| 2. What is the impact of screening for COPD on smoking cessation rates? | Asymptomatic adult smokers (this could include people with undetected mild to moderate symptoms) | COPD | Screening test positive + smoking cessation intervention | • Screening test negative +smoking cessation intervention<br>• Smokers in the general population without COPD screen | Smoking cessation uptake and adherence/ quit rate | RCTs, cohort studies and systematic reviews of these | Case reports<br>Commentary<br>Conference abstracts |
| 3. What is the clinical effectiveness of pharmacological treatment on screen-detected | Screen-detected COPD patients | COPD | • Bronchodilators<br>• Inhaled corticosteroids<br>• Theophylline<br>• Oral mucolytics | • No treatment<br>• Placebo | Improvement of morbidity/ quality of life<br>•Rate of FEV1 decline<br>•Breathing | RCTs, cohort studies and systematic reviews of these | Case reports<br>Commentary<br>Conference abstracts |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| patients with COPD? | | | • Combination therapy<br>• Other forms of pharmacological treatment | | improvements<br>• Improvement of cough symptoms<br>• Fewer chest infections<br>• Fewer exacerbations | | |
| 4. Does screening for COPD in 'asymptomatic' adults reduce morbidity or mortality, or improve health-related quality of life? | Asymptomatic adults (this could include people with undetected mild to moderate symptoms) | COPD | Screening using any combination of:<br>• Risk assessment questionnaire<br>• Screening spirometry without bronchodilator<br>• Combination of the above two tests | No screening | • Test uptake<br>• Physical health measures<br>• Speed of progression of disease through the 4 GOLD clinical stages<br>• Fewer exacerbations<br>• Quality of life<br>• Mortality<br>• Lung cancer | Systematic reviews and RCTs prioritised | Case reports<br>Commentary<br>Conference abstracts |

## Appraisal for quality/risk of bias tool

The following tools were used to assess the quality and risk of bias of each study included in the review:

- systematic reviews: Critical Appraisal Skills Programme (CASP) Systematic Review Checklist.
- diagnostic accuracy studies: Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool
- RCTs: Cochrane Collaboration's "Risk of Bias" Tool
- cohort studies: Critical Appraisal Skills Programme (CASP) Cohort Study Checklist.

Results of the quality assessments are presented in the summary and appraisal of individual studies in Appendix 3.

## Databases/sources searched

A systematic search of 3 databases (Medline, Embase and Cochrane) was conducted on 14th November 2017 for evidence published since February 2012. The search strategy is presented in Appendix 1.

# Question level synthesis

## *Criterion 4 – There should be a simple, safe, precise and validated screening test*

## *Criterion 5 – The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed*

*Question 1 – What is the accuracy of screening tests at detecting COPD in an 'asymptomatic' population?*

This question was considered by the 2012 UK NSC evidence review which concluded that:

- risk assessment questionnaires potentially had some usefulness in ruling out COPD in the first step of a screening programme, but included a high number of false positives
- there were challenges in using spirometry as a screening test and in maintaining the quality of spirometric screening tests in primary care
- there were issues around agreed cut-off levels for screening with evidence of high numbers of false positives in healthy asymptomatic individuals, particularly older people, when the GOLD stages were used3.

### Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population – 'asymptomatic' adults (this could include people with undetected mild to moderate symptoms)
- intervention – risk assessment questionnaire; screening spirometry without bronchodilator; combination of these tests
- comparator – index test and reference standard GOLD/NICE classification
- outcomes – COPD stage detected at screen (using GOLD/NICE classification); sensitivity; specificity; positive predictive value (PPV); negative predictive value (NPV)
- studies - studies in randomly assigned or consecutively enrolled populations and systematic reviews of these should be prioritised

## Description of the evidence

Database searches yielded 155 results, of which 111 were judged to be relevant to this question and 28 met the criteria for review at full text review. After review of the full texts, 8 studies were included in the review.

Reasons for excluding studies after review of the full text were:

- 1 review of assessment tests for people already diagnosed with COPD
- 1 review of strategies for finding COPD cases, not about screening test performance
- 1 review that covered similar studies to reviews already included and was less systematically conducted and less focused on screening test performance
- 1 descriptive overview (not a systematic review)
- 3 individual studies included in 1 of the included systematic reviews
- 6 studies that did not exclude people already diagnosed with COPD
- 2 studies about the feasibility of screening, not test performance
- 2 studies that recruited participants through advertisement (as studies with consecutively enrolled populations were available)
- 1 study with a population of patients referred for respiratory function tests
- 1 study on the development of a risk score for finding COPD cases from electronic patient records
- 1 duplicate study (returned twice by the search with different citations for online first and full publication).

## Summary of findings

A study-level summary of data extracted from each included publication is presented in the appraisal of individual studies in Appendix 3. In Appendix 3 publications are stratified by question.

Two reviews and 6 individual studies reported screening test performance in consecutively enrolled or random samples of ‘asymptomatic’ adults. The test performance scores are summarised in Table 3. All studies included post-bronchodilator spirometry as the reference standard.

Confidence intervals around the test performance scores, where reported, are provided in the Appendix 3 tables.

**Table 3. Screening test performance summary.**

| Screening test | Screening test cut-off | Sensitivity | Specificity | PPV | NPV | Study (the systematic reviews (SR) are indicated) |
|---|---|---|---|---|---|---|
| **Screening questionnaires** | | | | | | |
| CDQ | ≥16.5 | 80% to 93% | 24% to 49% | 17% to 45% | 76% to 98% | Guirguis-Blake et al (2016)[8] (SR) |
| | | 88% | 39% | 8% | 97% | Haroon et al (2015)[2] (SR) |
| | ≥19.5 | 63% to 72% | 54% to 77% | 23% to 50% | 69% to 96% | Guirguis-Blake et al (2016)[8] (SR) |
| | | 65% | 65% | 10% | 97% | Haroon et al (2015)[2] (SR) |
| COPD-PS | ≥4 | 67% | 73% | 15% | 97% | Guirguis-Blake et al (2016)[8] (SR) |
| | ≥5 | 35% | 79% | 10% | 95% | Guirguis-Blake et al (2016)[8] (SR) |
| | | 63% | 68% | --- | --- | Kobayashi et al (2017)[9] |
| LFQ | ≤18 | 88% | 25% | 21% | 90% | Guirguis-Blake et al (2016)[8] (SR) |
| CAT | >10 | 67% | 75% | 11% | 98% | Demirci et al (2017)[10] |
| SCSQ | ≥2 | 67% | 59% | 15% | 94% | Weiss et al (2017)[11] |
| EGARPOC | >13 | 73% | 58% | 38% | 86% | Llordés et al (2017)[12] |
| MARKO | >10 | 63% | 50% | 21% | 86% | Vrbica et al (2016)[13] |
| **Pulmonary function-based screening tools** | | | | | | |
| $FEV_1/FEV_6$ | <0.70 | 51% to 80% | 90% to 95% | 63% to 75% | 83% to 96% | Guirguis-Blake et al (2016)[8] (SR) |
| | | 33% | 100% | 100% | 86% | Labor et al (2016)[14] |
| | <0.70 to 0.75 | 80% | 84% | 23% | 99% | Haroon et al (2015)[2] (SR) |
| | <0.75 | 52% | 73% | --- | --- | Kobayashi et al (2017)[9] |
| | <0.78 | 79% | 72% | 53% | 94% | Llordés et al (2017)[12] |
| **Combined questionnaire and pulmonary function-based screening** | | | | | | |
| CDQ and $FEV_1/FEV_6$ | Not reported | 74% | 97% | 59% | 99% | Haroon et al (2015)[2] (SR) |
| COPD-PS and $FEV_1/FEV_6$ | ≥5 <0.75 | 41% | 96% | 79% | 84% | Kobayashi et al (2017)[9] |

CAT – COPD Assessment Test; CDQ – COPD Diagnostic Questionnaire; COPD-PS – COPD Population Screener; EGARPOC – COPD Screening Questionnaire from Terrassa; IPAG – International Primary Care Airways Group; LFQ- Lung Function Questionnaire; MARKO – MARKO questionnaire; SR – systematic review

Five of the 8 studies reported the GOLD staging of the people diagnosed with COPD. Almost all of the COPD cases detected by screening were at GOLD stage I (mild) or II (moderate).

- Kobayashi et al (2017)[9]: 27 COPD cases, 10 (37%) mild and 16 (59%) moderate
- Llordés et al 2017[12]: 107 COPD cases, 45 (42%) mild and 53 (49%) moderate
- Vrbica et al (2016)[13]: 42 COPD cases, 23 (55%) mild and 19 (45%) moderate
- Labor et al (2016)[14]: 43 COPD cases, 24 (56%) mild and 19 (44%) moderate.

Two COPD screening questionnaires were considered in more than 1 study, the COPD Diagnostic questionnaire (CDQ) using a cut-off level of either 16.5 or 19.5 and the COPD Population Screener (COPD-PS) using a cut-off level of 4 or 5. Remaining studies considered different, often new, screening questionnaires. As shown in Table 3, there is considerable variation in the reported sensitivity and specificity in different studies, even when the same questionnaire and cut-off level is used. NPV's were generally high but PPVs were generally low, with the highest PPV reported being 50%. This suggests that COPD screening questionnaires would generate a high number of false positives in 'asymptomatic' populations.

The same pattern of variable results is seen for pulmonary function-based screening tests. The PPVs are higher for these tests compared to screening questionnaires but still vary, ranging from 23% to 100%. Different cut-off levels were used in different studies.

Two studies reported the performance of a combination of screening questionnaire and pulmonary function-based screening test. These focused on different combinations of questionnaire and test. The results were still variable. One study reported a higher PPV, but with a lower NPV which would increase the chance that COPD cases could be missed.

The quality of the 2 reviews was assessed using the CASP checklist for systematic reviews. There were no areas of concern.

The quality of the 6 individual studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) framework. The QUADAS-2 framework is used to assess the quality of primary test accuracy studies and includes 5 domains on patient selection, the index test, the reference standard, test strategy flow and timing and applicability. The questions included in these domains and the responses for the 6 studies are summarised in Table 4.

The main areas of concern across the studies came from the unclear risk of bias around the blinding used in the interpretation of the index test and reference standard and the interval between testing. Generally the studies did not report this information. Areas where there was a high risk of bias included the absence of a pre-specified cut-off threshold for a positive screening test and the exclusion of patients from the analysis, usually due to failure to perform spirometry. There were applicability issues for some studies, eg, in studies about the development of a new screening test for a non-UK population and it is notable that in 3 studies the populations were confined to smokers and former smokers. Another limitation is in the small sample size of some of the studies. Further details on the QUADAS-2 scores are provided in the Appendix 3 tables.

**Table 4. QUADAS-2 scores summary.**

| | Weiss et al (2017)[11] | Kobayashi et al (2017)[9] | Demirci et al (2017)[10] | Llordés et al (2017)[12] | Vrbica et al (2016)[13] | Labor et al (2016)[14] |
|---|---|---|---|---|---|---|
| **Domain 1: Patient selection** | | | | | | |
| Consecutive or random sample of population enrolled? | Yes | Yes | Yes | Yes | Yes | Yes |
| Case-control design avoided? | Yes | Yes | Yes | Yes | Yes | Yes |
| Inappropriate exclusions avoided? | U | Yes | Yes | Yes | Yes | Yes |
| **Domain II: Index test** | | | | | | |
| Index test results interpreted without knowledge of reference standard results? | U | U | U | U | U | Yes |
| Threshold pre-specified? | No | No | Yes | No | U | Yes |
| **Domain III: Reference standard** | | | | | | |
| Reference standard likely to correctly classify condition? | U | Yes | Yes | Yes | Yes | Yes |
| Reference standard results interpreted without knowledge of index test results? | U | U | U | U | U | Yes |
| **Domain IV: Test strategy flow and timing** | | | | | | |
| Appropriate interval between index test and reference standard? | U | U | U | U | U | U |
| Did all participants receive same reference standard? | Yes | No | Yes | Yes | Yes | Yes |
| All patients included in analysis? | U | No | Yes | No | Yes | Yes |
| **Domain V: Applicability** | | | | | | |
| Applicable to UK screening population of interest? | Yes | Yes | Yes | Yes | Yes | Yes |
| Applicable to UK screening test of interest? | U | Yes | Yes | U | No | Yes |
| Target condition measured by reference test applicable to UK screening condition of interest? | U | Yes | Yes | Yes | Yes | Yes |
| **Total number of 'yes' (out of 13 )** | **4** | **7** | **10** | **7** | **8** | **12** |

A 'yes' score indicates a low risk of bias and a 'no' score indicates a high risk of bias. Unclear (U) is used when the relevant information was not reported in the study paper.

## Summary of Findings Relevant to Criteria 4 and 5: Criteria not met

Studies considering the performance of a number of different individual or combinations of screening tests in 'asymptomatic' populations were identified. The 2012 UK NSC review concluded that risk assessment questionnaires potentially had some usefulness in ruling out COPD but included a high number of false positives. This update review suggests that this is still the case.

The use of pulmonary function-based tests alone or in combination with a screening test may reduce the number of false positives. However the evidence base comes from fairly small studies with considerable variation in the populations, the tests used, the cut-off levels applied and the results. The evidence base is therefore insufficient to conclude that there is a simple, safe, precise and validated screening test with known distribution of test values and agreed suitable cut-off levels.

As a result, these criteria are not met.

*Criterion 9 –There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is not prospect of benefit to the individual screened then the screening programme shouldn't be further considered.*

*Question 2 – What is the impact of screening for COPD on smoking cessation rates?*

This question was considered by the 2012 UK NSC evidence review which acknowledged the evidence for the benefit of stopping smoking after a COPD diagnosis, but found that the evidence for whether a spirometric result or a diagnosis of COPD motivated individuals to stop smoking was inconsistent[3].

## Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population - asymptomatic adult smokers (this could include people with undetected mild to moderate symptoms)
- intervention - screening test positive + smoking cessation intervention
- comparator – screening test negative + smoking cessation intervention; smokers in the general population without COPD screen
- outcomes - smoking cessation uptake and adherence/ quit rate
- studies - RCTs, cohort studies and systematic reviews of these.

## Description of the evidence

Database searches yielded 155 results, of which 25 were judged to be relevant to this question and 9 met the criteria for review at full text. After review of the full texts, 4 studies were included in the review.

Reasons for excluding studies after review of the full text were:

- a systematic review in which all participants receiving an intervention were smokers with a diagnosis of COPD ie a study about the effectiveness of different smoking cessation interventions, not about the impact of screening
- a systematic review in which all 5 of the included studies were published between 1990 and 2009 and were therefore eligible for inclusion in previous UK NSC reviews and are not reconsidered here
- 1 randomised study focusing on different ways of presenting spirometry results. Results did not compare screen positive and screen negative or screening versus no screening
- 1 RCT on training and management of COPD patients identified through case finding. Smoking cessation not reported as an outcome
- 1 cohort study with a population of smokers and non-smokers screened and asked about motivation to quit smoking but no intervention offered and no smoking cessation outcomes reported.

## Summary of findings

A study-level summary of data extracted from each included publication is presented in Appendix 3.

The 4 included studies consisted of 1 RCT (Foulds et al 2015[15]) and 3 cohort studies (Salepci et al 2016[16]; Fuller et al 2012[17]; Riegels-Jakobsen et al 2012[18]). The RCT was assessed using Cochrane Collaboration's risk of bias tool. The cohort studies were assessed using the CASP cohort study checklist.

Foulds et al (2015)[15] assessed the impact of spirometry based feedback on treatment compliance and tobacco abstinence in 225 smokers who were ready to make a quit attempt in the next month. All participants received a 6-week smoking cessation intervention. The tobacco abstinence rate for the population as a whole was 52%, however there were no significant differences between the group who received motivational lung age feedback and those who received minimal feedback. The study was assessed as being at low risk of bias. The main area of concern was around applicability as all study participants were willing to quit smoking at the study outset. In addition, participants in both groups with $FEV_1$ <80% predicted were told their score was lower than expected and advised to see their doctor, which may have contributed to the lack of difference in the results for the intervention and control groups.

Salepci et al (2016)[16] assessed the effect of identifying airway obstruction via spirometry on smoking cessation rates in 563 smokers who applied to a smoking cessation out-patient clinic. Overall, 11% quit smoking, with significantly more people with obstruction on pulmonary function tests quitting (23%) compared to people without obstruction (8%). Smokers who did not attend follow-up visits were considered as non-quitters. Of the 162 people who completed 3-months of follow-up visits, 40% quit smoking. The study was generally at low risk of bias, however, less than one third of the population completed 3-months of follow-up and the population were seeking assistance to stop smoking which may limit the applicability.

Fuller et al (2012)[17] assessed the effectiveness of COPD screening in 185 people attending 4 community pharmacies or screening events, of which 20 were current smokers. Participants completed the COPD-PS

questionnaire and spirometry. Of the 9 current smokers who participated in a follow-up interview at 6-months, 2 reported that they had quit smoking and 5 reported some attempt to quit smoking. The overall proportion of patients in this population who had air-flow limitation was low (9%). There were a number of areas where this study was at risk of bias, eg, smoking cessation behaviours were self-reported and less than half of the smokers completed follow-up. Smoking cessation counselling was provided following screening but no specific smoking cessation intervention was offered. The screening test result of the 7 people who quit or attempted to quit smoking was not reported.

Riegels-Jakobsen et al (2012)[18] included an assessment of smoking cessation in their study on the effectiveness of early detection of COPD in current or former smokers with at least 1 respiratory symptom. 152 people were screened using spirometry without bronchodilator of which 51% were current smokers. The study authors reported that there were 40% fewer smokers at 3-month follow up but did not provide a figure for the number who quit smoking. The authors also reported that 57% of people diagnosed with COPD (n=78) were undergoing smoking cessation at follow-up compared to 8% at screening. There were a number of areas where this study was at risk of bias. Smoking cessation behaviours were self-reported and no specific smoking cessation intervention was offered. The authors did not compare smoking outcomes in participants with a positive or negative screening result. The population all had at least 1 respiratory symptom at recruitment which may limit the applicability to a screening programme for asymptomatic adults.

Overall, these studies provide limited evidence for the impact of screening for COPD on smoking cessation rates due to the applicability of the population included, the small sample size and/or the limited details provided on self-reported smoking cessation rates.

*Question 3 – What is the clinical effectiveness of pharmacological treatment on screen-detected patents with COPD?*

This question was considered by the 2012 UK NSC evidence review which concluded that there was a strong evidence base for the treatment of COPD, but there was limited evidence available on treatment outcomes for people with asymptomatic or mild disease. There was

evidence for the benefit of pharmacological treatment for moderate stage 2 COPD. The 2012 review also acknowledged existing advice and guidelines on other interventions for COPD such as vaccinations, nutrition, education and self-management[3].

The National Institute for Health and Care Excellence have published guidance on the diagnosis and management of COPD[4]. This review is specifically looking for evidence on the treatment of screen-detected patients with COPD.

## Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population - screen-detected COPD patients
- intervention – bronchodilators; inhaled corticosteroids; theophylline; oral mucolytics; combination therapy; other forms of pharmacological treatment
- comparator – no treatment; placebo
- outcomes – Improvement of morbidity/ quality of life; rate of $FEV_1$ decline; breathing improvements; improvement of cough symptoms; fewer chest infections; fewer exacerbations
- studies – RCTs, cohort studies and systematic reviews of these.

## Description of the evidence

Database searches yielded 155 results, of which 12 were judged to be relevant to this question and 6 met the criteria for review at full text. After review of the full texts, 1 study was included in the review.

Reasons for excluding studies after review of the full text were:

- 2 studies about the management of people diagnosed with COPD, not about the effectiveness of any treatment received
- a study comparing 4 treatments (ie no placebo or no treatment group) in patients admitted to hospital with respiratory symptoms
- a cohort study looking at the natural history of patients (not screen-detected) with COPD
- a study included in a systematic review.

## Summary of findings

A study-level summary of data extracted from each included publication is presented in the appraisal of individual studies in Appendix 3. In Appendix 3 publications are stratified by question.

No studies on the clinical effectiveness of pharmacological treatment on screen-detected patents with COPD were identified. A systematic review that included studies on patients with mild to moderate COPD was identified and included in the absence of any studies on screen-detected patients.

Guirguis-Blake et al 2016[8], in a systematic review for the USPSTF, did not identify any treatment trials for screen-detected patients and therefore extended their search to patients with mild to moderate COPD. Twenty studies of 14 RCTs were identified. The overall conclusion of the review authors was that there was no benefit in all-cause mortality, but that there was evidence for a modest decrease in annual rates of exacerbations[3] with pharmacological treatments.

The CASP checklist for systematic reviews was used to assess the quality of this review and identified no areas of concern. The review authors noted that the literature identified was largely based on patients at the more severe end of moderate COPD with implications for the applicability of the evidence identified to a screen-detected population. Other areas of potential bias identified by the review authors included the use of post-hoc sub-group analysis from trials that were powered to detect change in the whole population, not a sub-group and inconsistency in reported outcomes across the studies.

## Summary of Findings Relevant to Criterion 9: Criterion not met

Two questions were considered for this criterion, relating to the impact of screening on smoking cessation rates and the effectiveness of pharmacological treatment on screen-detected patients.

[3] Most studies in this systematic review defined an exacerbation as requiring treatment with an antibiotic or systemic corticosteroid. However, there were inconsistencies between studies with some including a patient-reported increase in symptoms as an exacerbation

The 2012 UK NSC review found that the evidence for whether a spirometric result or a diagnosis of COPD motivated individuals to stop smoking was inconsistent. The 4 studies identified for this review still do not provide a clear answer to this question due to limitations in the applicability or reporting of the studies.

The 2012 UK NSC review concluded that there was limited evidence available on treatment outcomes for people with asymptomatic or mild disease, although it did identify evidence for the benefit of pharmacological treatment for moderate stage 2 COPD. This update review did not find any new studies on the clinical effectiveness of pharmacological treatment on screen-detected patents with COPD. A systematic review that included studies on treatment efficacy in patients with mild to moderate COPD concluded that there is some evidence for a modest improvement in exacerbations with pharmacological treatments. However, the review authors noted that most of the evidence was from patients at the more severe end of moderate COPD, with limited applicability to a screen-detected population.

In the absence of evidence for the effectiveness of intervention for patients identified through screening this criterion is not met.

*Criterion 11 – There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.*

*Question 4 – Does screening for COPD in 'asymptomatic' adults reduce morbidity or mortality or improve health-related quality of life?*

The 2012 UK NSC review did not identify any randomised controlled trials on screening for COPD[3].

## Eligibility for inclusion in the review

The inclusion criteria for this question are summarised briefly below:

- population - asymptomatic adults (this could include people with undetected mild to moderate symptoms)
- intervention - screening using any combination of: risk assessment questionnaire; screening spirometry without bronchodilator; combination of these tests
- comparator – no screening
- outcomes – test uptake; physical health measures; speed of progression of disease through the 4 GOLD clinical stages; fewer exacerbations; quality of life; mortality; lung cancer
- studies – systematic reviews and RCTs prioritised.

## Description of the evidence

Database searches yielded 155 results, of which 9 were judged to be relevant to this question and 8 met the criteria for review at full text. After review of the full texts, 2 studies were included in the review.

Reasons for excluding studies after review of the full text were:

- 6 studies looking at the natural history of COPD, including in patients with previously undetected COPD at study entry. These studies did not did not compare screening with no screening and therefore did not address the question of whether screening reduces morbidity or mortality or improves health-related quality of life.

## Summary of findings

A study-level summary of data extracted from each included publication is presented in the appraisal of individual studies in Appendix 3. In Appendix 3 publications are stratified by question.

A systematic review for the USPSTF (Guirguis-Blake et al 2016[8]) searched for but identified no studies comparing the effectiveness of COPD screening with no screening on patient health outcomes. An appendix table has not been produced for this question, however further details of this systematic review are provided in the Appendix 3 tables for key questions 1 and 3.

Bertens et al (2014)[19] analysed data from a cluster RCT to assess the effectiveness of screening elderly people (≥65 years) for COPD and heart failure. The population included community-dwelling people with the assessment for the screening group (n=386) including a standardised questionnaire (name not specified) and pre and post-bronchodilator spirometry. The comparator group (n=443) received usual care, with complaints communicated to the treating physician. Six and 12-month follow-up data were collected from GP electronic records. New COPD cases were diagnosed in 84 (22%) of the screening group and 13 (3%) of the usual care group.

No significance tests comparing the screening and usual care groups were reported. The authors reported that mortality and hospitalisations after 12-month follow-up did not differ between the screening and usual care group, but only reported figures for the screening group according to COPD status (for patients with newly detected COPD all-cause mortality was 2.4% and hospitalisations 32%). The number of exacerbations[4] and/or pneumonia was 11.9% in the screening group and 6.5% for usual care (significance test not reported). The use of pulmonary drugs for patients with newly detected COPD increased in both groups at 6-months follow-up (significance tests not reported). In the screening group, none of the 10 smokers with newly detected COPD had quit smoking at 6-months follow-up.

The study was assessed using the Cochrane Collaboration's risk of bias tool. As this was an analysis of a cluster RCT sub-group, some information eg on randomisation method was not reported in this publication. The main areas of concern were the lack of statistical analysis in the reporting and the applicability of the frail elderly population to a wider UK screening population.

This study does not provide any evidence that screening for COPD in a frail elderly, community dwelling population reduces morbidity or mortality.

[4] Exacerbations of COPD were defined as symptomatic deterioration requiring oral corticosteroids or hospitalisation.

## Summary of Findings Relevant to Criterion 11: Criterion not met

The 2012 UK NSC review did not identify any randomised controlled trials on screening for COPD. This review identified 1 study that presented data from an RCT on screening versus usual care in a frail elderly population which may not be applicable to screening in the adult population as a whole. However this did not demonstrate an advantage for screening in this population.

This criterion is not met.

# Review summary

## Conclusions and implications for policy

This report is an update review on systematic population screening for COPD in the general adult population against select UK NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme. This review assessed key questions to determine if new evidence published since 2012 suggests that reconsideration of the current recommendation for screening for COPD in the UK is required. The volume, quality and direction of new evidence published since February 2012 does not indicate that there have been any significant changes in the evidence base since the previous review. Areas of concern relate to:

- there are still concerns about the high number of false positives from risk assessment questionnaires
- there are uncertainties about the performance of screening tests using risk assessment questionnaires, pulmonary function based tests or a combination of both
- there are still uncertainties about the impact of screening on smoking cessation rates
- there is a lack of evidence for the effectiveness of pharmacological treatment in asymptomatic adults or adults with mild disease
- there is a lack of evidence that screening for COPD reduces mortality and morbidity.

The current recommendation not to introduce a UK systematic population screening programme for COPD should be retained.

## Limitations

A limitation for this review is the lack of evidence specific to the population of interest for population-based screening for COPD, particularly relating to the treatment of ‘asymptomatic’ individuals with undetected mild to moderate symptoms or the effectiveness of screening.

This rapid review process was conducted over a condensed period of time (approximately 12 weeks). Searching was limited to 3 bibliographic databases and did not include grey literature sources. The review was guided by a protocol developed a priori. The literature search and first appraisal of search results were undertaken by 1 information scientist, and further appraisal and study selection by 1 reviewer. Any queries at both stages were resolved through discussion with a second reviewer. Studies not available in the English language, abstracts and poster presentations, were not included. Studies that were not published in peer-reviewed journals were not reviewed.

# Appendix 1 — Search strategy

## Electronic databases

The search strategy included searches of the databases shown in Table 5.

**Table 5. Summary of electronic database searches and dates.**

| Database | Platform | Searched on date | Date range of search |
|---|---|---|---|
| MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print | Ovid SP | 14th November 2017 | 2012 to Present |
| Embase | Ovid SP | 14th November 2017 | 2012 to Present |
| The Cochrane Library, including:<br>- Cochrane Database of Systematic Reviews (CDSR)<br>- Cochrane Central Register of Controlled Trials (CENTRAL)<br>- Database of Abstracts of Reviews of Effects (DARE) | Wiley Online | 14th November 2017 | 2012 to Present |

## Search Terms

Search terms for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase are shown in Table 6, and search terms for the Cochrane Library databases are shown in Table 7.

**Table 6. Search strategy for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase.**

| # | Search terms | Results |
|---|---|---|
| 1 | *chronic obstructive lung disease/ | 56851 |
| 2 | (copd or chronic obstructive pulmonary disease).tw. | 87314 |
| 3 | ((airflow or airway) adj (obstruction or limitation)).tw. | 28846 |
| 4 | 1 or 2 or 3 | 121567 |
| 5 | *spirometry/ | 4741 |
| 6 | (spiromet* or bronchospiromet*).tw. | 32406 |
| 7 | *lung function test/ | 9055 |
| 8 | ((respiratory or lung or pulmonary) adj function test*).tw. | 24529 |
| 9 | (((respiratory or lung or pulmonary) adj5 (screen* or assess* or evaluat* or function)) and questionnaire?).tw. | 10283 |
| 10 | 5 or 6 or 7 or 8 or 9 | 65501 |
| 11 | mass screening/ | 53722 |

| | | |
|---|---|---|
| 12 | screen*.tw. | 848821 |
| 13 | detect*.tw. | 2536531 |
| 14 | chronic obstructive lung disease/di [Diagnosis] | 8338 |
| 15 | 11 or 12 or 13 or 14 | 3203207 |
| 16 | 4 and 10 and 15 | 4258 |
| 17 | (screen* or detect*).ti. | 558476 |
| 18 | 4 and 17 | 1660 |
| 19 | 16 or 18 | 5331 |
| 20 | conference*.pt. | 3533781 |
| 21 | 19 not 20 | 3810 |
| 22 | limit 21 to (english language and yr="2012 -Current") | 1253 |
| 23 | smoking cessation/ | 50469 |
| 24 | ((smok* or "tobacco use") adj2 (cessation or quit* or stop or "give up")).ti,ab. | 35886 |
| 25 | 23 or 24 | 58953 |
| 26 | 10 and 25 | 1269 |
| 27 | 4 and 17 and 25 | 132 |
| 28 | 26 or 27 | 1331 |
| 29 | conference*.pt. | 3533781 |
| 30 | 28 not 29 | 876 |
| 31 | limit 30 to (english language and yr="2012 -Current") | 289 |
| 32 | ((long or short) adj acting beta$ agonist$).ti,ab. | 4897 |
| 33 | selective beta$ agonist$.ti,ab. | 274 |
| 34 | *beta adrenergic receptor stimulating agent/ | 7302 |
| 35 | exp *bronchodilating agent/ | 92021 |
| 36 | (albuterol or salbutamol or terbutaline or formoterol or salmeterol or indacterol).ti,ab. | 21732 |
| 37 | ((long or short) adj acting muscarinic antagonist$).ti,ab. | 922 |
| 38 | (antimuscarinic adj (bronchodilator$ or antagonist$)).ti,ab. | 29 |
| 39 | exp *cholinergic receptor blocking agent/ | 72820 |
| 40 | exp *muscarinic receptor blocking agent/ | 28531 |
| 41 | (ipratropium or tiptropium).ti,ab. | 2767 |
| 42 | inhaled corticosteroid$.ti,ab. | 13465 |
| 43 | exp *glucocorticoid/ | 227252 |
| 44 | (beclomethasone or budesonide or fluticasone).ti,ab. | 14838 |
| 45 | 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 | 393139 |
| 46 | 16 and 45 | 439 |
| 47 | 17 and 45 | 2079 |
| 48 | 46 or 47 | 2490 |
| 49 | conference*.pt. | 3533781 |
| 50 | 48 not 49 | 2171 |
| 51 | limit 50 to (english language and yr="2012 -Current") | 362 |
| 52 | exp mortality/ | 909840 |
| 53 | *disease course/ or *adverse outcome/ or *chronicity/ or *disease exacerbation/ or *illness trajectory/ or exp *prognosis/ or exp *survival/ | 161916 |

| | | |
|---|---|---|
| 54 | *"quality of life"/ | 83241 |
| 55 | (mortality or survival or morbidity).ti,ab. | 2019113 |
| 56 | ((copd or chronic obstructive pulmonary disease) adj5 (prognos* or progress* or sever* or exacerbat* or "quality of life" or qol)).ti,ab. | 25077 |
| 57 | (prognos* or progress* or sever* or exacerbat* or "quality of life" or qol).ti. | 677866 |
| 58 | 52 or 53 or 54 or 55 or 56 or 57 | 2845891 |
| 59 | 16 and 58 | 1438 |
| 60 | 4 and 17 and 58 | 448 |
| 61 | 59 or 60 | 1741 |
| 62 | conference*.pt. | 3533781 |
| 63 | 61 not 62 | 1165 |
| 64 | limit 63 to (english language and yr="2012 -Current") | |

**Table 7. Search strategy for the Cochrane Library Databases (Searched via the Wiley Online platform).**

| # | Search terms |
|---|---|
| #1 | MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] this term only |
| #2 | copd or "chronic obstructive pulmonary disease" or ((airflow or airway) next (obstruction or limitation)):ti,ab,kw (Word variations have been searched) |
| #3 | #1 or #2 |
| #4 | screen* or detect* or diagnos* or test*:ti (Word variations have been searched) |
| #5 | screen*:ti,ab,kw |
| #6 | #4 or #5 |
| #7 | #3 and #6 |

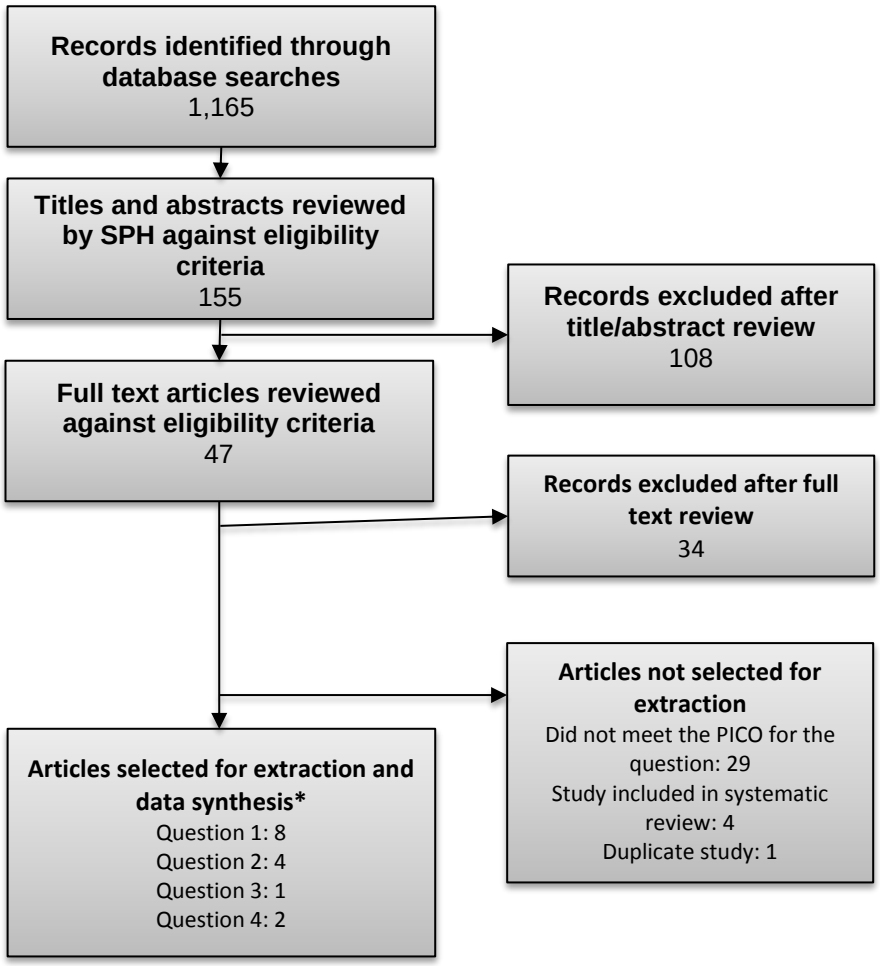
Duplicate references were removed.

# Appendix 2 — Included and excluded studies

## PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. 47 publications were ultimately judged to be relevant to one or more review questions and were considered for extraction. Publications that were included or excluded after the review of full text articles are detailed below.

**Figure 1. Summary of publications included and excluded at each stage of the review.**




*NB: 1 systematic review was included in multiple questions

## Publications included after review of full text articles

The 13 publications included after review of full texts are summarised in Table 8. Studies meeting the PICO inclusion/ exclusion criteria for each individual question were included. In questions 1 and 3 individual studies that were included in 1 of the systematic reviews identified were not considered separately.

**Table 8. Summary of publications included after review of full text articles, and the criteria each publication was identified as being relevant to.**

| Study | The test | The intervention | The screening programme | Comments |
|---|---|---|---|---|
| Guirguis-Blake et al (2016) | x | x | x | |
| Haroon et al (2015) | x | | | |
| Weiss et al (2017) | x | | | |
| Kobayashi et al (2017) | x | | | |
| Demirci et al (2017) | x | | | |
| Llordés et al (2017) | x | | | |
| Vrbica et al (2016) | x | | | |
| Labor et al (2016) | x | | | |
| Salepci et al (2016) | | x | | |
| Foulds et al (2015) | | x | | |
| Fuller et al (2012) | | x | | |
| Riegels-Jakobsen et al (2012) | | x | | |
| Berterns et al (2014) | | | x | |

# Appendix 3 — Summary and appraisal of individual studies

## Data extraction and quality assessment for studies relevant to criteria 4 and 5

### Key question 1: What is the accuracy of screening tests at detecting COPD in an 'asymptomatic' population?

### *Systematic reviews*

**Table 9: Guirguis-Blake et al (2016)**[8]

| | |
|---|---|
| Publication | Guirguis-Blake JM. Senger CA. Webber EM. Mularski RA. Whitlock EP. Screening for chronic obstructive pulmonary disease: evidence report and systematic review for the US Preventative Services Task Force. JAMA 2016, 315(13):1378-93 |
| Study details | Systematic review |
| Study objectives | To review the literature on the accuracy of screening questionnaires and office-based screening pulmonary function testing<br>NB evidence relating to the efficacy and harms of treatment of screen-detected COPD is considered under the appropriate key questions |
| Inclusions | Asymptomatic adults aged ≥40 years |
| Exclusions | Non stated |
| Population | 33 studies published up to January 2015 |
| Test | Screening questionnaires and primary case-feasible screening pulmonary function tests (eg handheld devices) |
| Comparator / reference standard | Post-bronchodilator spirometry $FEV_1/FVC$ <0.7 |
| Outcomes | **Screening questionnaires**<br>The COPD Diagnostic Questionnaire (CDQ) was the most extensively studied (5 studies; n=3,048). The range of test performance results from the included studies at a cut-off of ≥16.5 were:<br>• sensitivity 80% to 93%<br>• specificity 24% to 49%<br>• PPV 17% to 45%<br>• NPV 76% to 98%<br>Range of test performance results from the included studies at a cut-off of ≥19.5:<br>• sensitivity 63% to 72%<br>• specificity 54% to 77%<br>• PPV 23% to 50%<br>• NPV 69% to 96%<br><br>The Lung Function Questionnaire, using a cut-off of ≤18 (1 study):<br>• sensitivity 88% (95%CI 75 to 94)<br>• specificity 25% (95%CI 22 to 28)<br>• PPV 21% (95%CI 18 to 24)<br>• NPV 90% (95%CI 78 to 97)<br>NB: quality concerns reported included 31% incomplete or invalid spirometry and only a sub-set of screen negative patients received spirometry<br><br>The COPD Population Screener using a cut-off of ≥4 (1 study):<br>• sensitivity 67% (95%CI 60 to 74)<br>• specificity 73% (95%CI 71 to 75)<br>• PPV 15% (95%CI 12 to 17)<br>• NPV 97% (95%CI 96 to 98) |

| | |
|---|---|
| | Using a cut-off of ≥5:<br>• sensitivity 35% (95%CI 27 to 42)<br>• specificity 79% (95%CI 78 to 81)<br>• PPV 10% (95%CI 8 to 13)<br>• NPV 95% (95%CI 93 to 96)<br><br>**Pulmonary-function based screening tools**<br>$FEV_1/FEV_6$ <0.70 was the most extensively studied (3 studies; n=1,587). The range of test performance results from the included studies were:<br>• sensitivity 51% to 80%<br>• specificity 90% to 95%<br>• PPV 63% to 75%<br>• NPV 83% to 96% |
| Quality appraisal | The CASP checklist for systematic reviews was used to assess the quality of this review. There were no areas of concern.<br><br>The study authors appraised the quality of the included studies using the USPSTF quality rating standards. |

## Table 10: Haroon et al (2015)[2]

| | |
|---|---|
| Publication | Haroon S. Jordan R. Takwoingi Y. Adab P. Diagnostic accuracy of screening tests for COPD: a systematic review and meta-analysis. BMJ Open 2015, 5: e008133 |
| Study details | Systematic review and meta-analysis |
| Study objectives | To review the literature on the diagnostic accuracy of screening tests for COPD in primary care |
| Inclusions | Diagnostic accuracy studies evaluating ≥1 index tests in primary care in people aged ≥35 years with no prior diagnosis of COPD |
| Exclusions | See inclusion criteria |
| Population | 10 studies published up to December 2013 |
| Test | Screening questionnaires and handheld flow meters |
| Comparator / reference standard | Post-bronchodilator or pre-bronchodilator spirometry |
| Outcomes | **Screening questionnaires**<br>Four screening questionnaires were evaluated (n=9,472), including the COPD Diagnostic Questionnaire (CDQ) (4 studies), the Lung Function Questionnaire (2 studies) and 2 unnamed questionnaires<br><br>The CDQ studies were used in a meta-analysis. At a cut-off of ≥19.5 and a prevalence of 5.5%:<br>• sensitivity 64.5% (95%CI 59.5 to 68.8)<br>• specificity 65.2% (95%CI 52.9 to 75.8)<br>• PPV 9.7% (95%CI 6.9 to 14.2)<br>• NPV 96.9% (95%CI 95.8 to 97.7)<br>29 individuals would need to be screened, and 11 diagnostically assessed to identify 1 COPD case<br><br>At a cut-off of ≥16.5 and a prevalence of 5.5%:<br>• sensitivity 87.5% (95%CI 83.1 to 90.9)<br>• specificity 38.8% (95%CI 27.7 to 51.3)<br>• PPV 7.7% (95%CI 6.3 to 9.8)<br>• NPV 98.2% (95%CI 96.6 to 99.0)<br>21 individuals would need to be screened, and 13 diagnostically assessed to identify 1 COPD case<br><br>The remaining studies were unsuitable for meta-analysis due to heterogeneity in the design of the questionnaires. The range of results in these studies were:<br>• sensitivity 57% to 93%<br>• specificity 24% to 80%<br><br>**Handheld flow meters**<br>Four studies assessing handheld flow meters were included (n=1,400). Three studies were similar enough for meta-analysis. Using a cut-off of $FEV_1/FEV_6$ <0.70 to 0.75:<br>• sensitivity 79.9% (95%CI 74.2 to 84.7)<br>• PPV 23.0% (95%CI 12.2 to 41.3) |

| | |
|---|---|
| | • specificity 84.4% (95%CI 68.9 to 93.0) • NPV 98.6% (95%CI 97.9 to 99.1)<br>23 individuals would need to be screened, and 5 diagnostically assessed to identify 1 COPD case<br><br>**Combined CDQ and handheld meter (1 study)**<br>• sensitivity 74.4% (95%CI 64.2 to 83.1) • PPV 59.1% (95%CI 43.8 to 74.0)<br>• specificity 97.0% (95%CI 95.2 to 98.3) • NPV 98.5% (95%CI 97.9 to 99.0)<br>25 individuals would need to be screened, and 2 diagnostically assessed to identify 1 COPD case |
| Quality appraisal | The CASP checklist for systematic reviews was used to assess the quality of this review. There were no areas of concern.<br><br>The study authors appraised the quality of the included studies using the QUADAS-2 tool. The main areas of high or unclear risk were around the reporting of withdrawals, indeterminate results and blinding which may had led to overestimation of test accuracy |

## *Individual test performance studies*

### Table 11: Weiss et al (2017)[11]

| | |
|---|---|
| Publication | Weiss G. Steinacher I. Lamprecht B. Kaiser B. Mikes R. Sator L. Hartl S. Wagner H. Studnicka M. Development and validation of the Salzburg COPD-screening questionnaire (SCSQ): a questionnaire development and validation study |
| Study details | Screening test performance study |
| Study objectives | Validation of a new self-administered screening questionnaire to pre-select patients for spirometry |
| Inclusions | Age >40 years<br>Participants with complete questionnaire and spirometry data |
| Exclusions | Non stated in this publication |
| Population | 775 primary care patients who had participated in the Salzburg Burden of Obstructive Lung Disease (BOLD) study |
| Test | Salzburg COPD-screening questionnaire (SCSQ) |
| Comparator / reference standard | Post-bronchodilator spirometry |
| Outcomes | $FEV_1$/FVC <lower limit of normal (LLN) was considered a positive spirometry test<br><br>Prevalence for positive spirometry test was 9.8%. GOLD staging not reported<br><br>Using a cut-off score of ≥2 on the SCSQ:<br>• sensitivity 67.1% (95%CI 55.3 to 77.2)<br>• specificity 58.9% (95%CI 55.2 to 62.6)<br>• PPV 15.1% (95%CI 11.5 to 19.5)<br>• NPV 94.3% (95%CI 91.6 to 96.2)<br><br>The number of spirometry's needed to detect a new case was 6.6 |

| **Quality appraisal using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool** | | | |
|---|---|---|---|
| **Question** | **Assessment (Y, N, unclear)** | **Risk of Bias (low, high, unclear)** | **Supporting info** |
| **Domain I: Patient selection** | | | |
| Consecutive or random sample of population enrolled? | Y | Low | Random sample |
| Case-control design avoided? | Y | Low | |
| Inappropriate exclusions avoided? | Unclear | Unclear | No information on exclusions provided |
| **Domain II: Index Test** | | | |
| Index test results interpreted without knowledge of reference standard results? | Unclear | Unclear | No details of blinding reported |
| Threshold pre-specified? | N | High | Multiple thresholds considered |
| **Domain III: Reference standard** | | | |
| Reference standard likely to correctly classify condition? | Unclear | Unclear | GOLD/ NICE stages for COPD not used for the reference standard |
| Reference standard results interpreted without knowledge of index test results? | Unclear | Unclear | No details of blinding reported |
| **Domain IV: Test strategy flow and timing** | | | |
| Appropriate interval between index test and reference standard? | Unclear | Unclear | Interval not reported |
| Did all participants receive same reference standard? | Y | Low | |
| All patients included in analysis? | Unclear | Unclear | Analysis based on retrospective data from a sub-group of patients from a prior study |
| **Domain V: Applicability** | | | |
| Applicable to UK screening population of interest? | Y | Low | Random primary care population in Austria |
| Applicable to UK screening test of interest? | Unclear | Unclear | New questionnaire |
| Target condition measured by reference test applicable to UK screening condition of interest? | Unclear | Unclear | Test applicable but GOLD/ NICE classification not applied |
| **Other comments** | Population included never smokers | | |

## Table 12: Kobayashi et al (2017)[9]

| | |
|---|---|
| Publication | Kobayashi S. Masakazu H. Yanai M. for the Ishinomaki COPD Network (ICON) Investigators. Early Detection of Chronic Obstructive Pulmonary Disease in Primary Care. Internal Medicine Advance Publication, 2017, 8717-16 |
| Study details | Screening test performance study |
| Study objectives | To evaluate the effectiveness of an early detection programme using a self-administered questionnaire and handheld spirometric device for the early detection of COPD |
| Inclusions | Age ≥40 years |
| Exclusions | Patients with known chronic respiratory disease including asthma and COPD |
| Population | 482 primary care patients with chronic diseases recruited through primary care clinics and hospitals in Japan |
| Test | COPD Population Screener (COPD-PS)<br>Handheld spirometric device |
| Comparator / reference standard | Assessment by a respiratory specialist including post-bronchodilator spirometry and chest radiography |
| Outcomes | $FEV_1$/FVC <0.7 was considered a positive spirometry test<br><br>482 patients screened; 274 identified with possible COPD; 111 referred for further assessment (1 excluded due to inability to perform tests)<br><br>27 patients (5.6%) were newly diagnosed with COPD:<br>• GOLD stage 1 = 10<br>• GOLD stage II = 16<br>• GOLD stage III = 1<br><br>For a cut-off score of ≥5 on the COPD-PS:<br>• sensitivity 63.0%<br>• specificity 67.9%<br><br>For a cut-off level of $FEV_1$/FEV in 6 seconds <0.75 for a spirometric handheld device:<br>• sensitivity 51.9%<br>• specificity 73.0%<br><br>Using the combined COPD-PS and handheld spirometric device:<br>• sensitivity 40.7%<br>• specificity 96.4%<br>• PPV 78.6%<br>• NPV 83.5% |

| **Quality appraisal using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool** | | | |
|---|---|---|---|
| **Question** | **Assessment (Y, N, unclear)** | **Risk of Bias (low, high, unclear)** | **Supporting info** |
| **Domain I: Patient selection** | | | |
| Consecutive or random sample of population enrolled? | Y | Low | Consecutive sample |
| Case-control design avoided? | Y | Low | |

| | | | |
|---|---|---|---|
| Inappropriate exclusions avoided? | Y | Low | |
| **Domain II: Index Test** | | | |
| Index test results interpreted without knowledge of reference standard results? | Unclear | Unclear | No details reported |
| Threshold pre-specified? | N | High | Multiple thresholds considered |
| **Domain III: Reference standard** | | | |
| Reference standard likely to correctly classify condition? | Y | Low | Respiratory assessment including post-bronchodilator spirometry |
| Reference standard results interpreted without knowledge of index test results? | Unclear | Unclear | No details reported |
| **Domain IV: Test strategy flow and timing** | | | |
| Appropriate interval between index test and reference standard? | Unclear | Unclear | No details reported |
| Did all participants receive same reference standard? | N | High | 23% of the population received the reference standard |
| All patients included in analysis? | N | High | Not all patients received the reference standard; 1 patient excluded from the analysis due to inability to perform pulmonary function tests |
| **Domain V: Applicability** | | | |
| Applicable to UK screening population of interest? | Y | Low | Primary care population |
| Applicable to UK screening test of interest? | Y | Low | Internationally used questionnaire and device |
| Target condition measured by reference test applicable to UK screening condition of interest? | Y | Low | Spirometry with GOLD staging |
| **Other comments** | The study had a fairly small sample size. | | |

## Table 13: Demirci et al (2017)[10]

| | |
|---|---|
| Publication | Demirci H. Eniste K. Basaran EO. Ocakoglu G. Yilmaz Z. Tuna S. A multicentre family practitioners' research on Chronic Obstructive Pulmonary Disease screening using the COPD assessment test. Primary Health Care Research and Development 2017, 18: 603-607 |
| Study details | Screening test performance study |
| Study objectives | Evaluating the COPD Assessment Test (CAT) as a screening tool |
| Inclusions | 40-65 years old |
| Exclusions | Contraindications for spirometry<br>Inability to use the spirometer<br>Pregnancy |

| | |
|---|---|
| | High fever<br>Lung cancer<br>Previous history of obstructive lung disease<br>Use of corticosteroids, bronchodilators, theophyllines or other medications that may interfere with pulmonary function |
| Population | 357 people registered to 3 family physicians in Turkey |
| Test | CAT |
| Comparator / reference standard | Post-bronchodilator spirometry |
| Outcomes | $FEV_1$/FVC <0.7 was considered a positive spirometry test<br><br>15 people were diagnosed with COPD (4.2%). GOLD staging not reported<br><br>Using a cut-off score of >10 on the CAT:<br>• sensitivity 66.7% (95%CI 38.4 to 88.2)<br>• specificity 75% (95%CI 70 to 80)<br>• PPV 10.5% (95%CI 7.3 to 15.0)<br>• NPV 98.1% (95%CI 96.2 to 99.1) |

**Quality appraisal using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool**

| Question | Assessment (Y, N, unclear) | Risk of Bias (low, high, unclear) | Supporting info |
|---|---|---|---|
| **Domain I: Patient selection** | | | |
| Consecutive or random sample of population enrolled? | Y | Low | Random sample |
| Case-control design avoided? | Y | Low | |
| Inappropriate exclusions avoided? | Y | Low | |
| **Domain II: Index Test** | | | |
| Index test results interpreted without knowledge of reference standard results? | Unclear | Unclear | No details reported |
| Threshold pre-specified? | Y | Low | |
| **Domain III: Reference standard** | | | |
| Reference standard likely to correctly classify condition? | Y | Low | Post-bronchodilator spirometry |
| Reference standard results interpreted without knowledge of index test results? | Unclear | Unclear | No details reported |
| **Domain IV: Test strategy flow and timing** | | | |
| Appropriate interval between index test and reference standard? | Unclear | Unclear | No details reported |
| Did all participants receive same reference standard? | Y | Low | |
| All patients included in | Y | Low | |

| | | | |
|---|---|---|---|
| analysis? | | | |
| **Domain V: Applicability** | | | |
| Applicable to UK screening population of interest? | Y | Low | Primary care population |
| Applicable to UK screening test of interest? | Y | Low | Internationally used screening test |
| Target condition measured by reference test applicable to UK screening condition of interest? | Y | Low | |
| **Other comments** | The study had a fairly small sample size. | | |

## Table 14: Llordés et al (2017)[12]

| | |
|---|---|
| Publication | Llordés M. Zurdo E. Jaén A. Vázquez I. Pastrana L. Miravitlles M. Which is the best screening strategy for COPD among smokers in primary care? COPD: Journal of Chronic Obstructive Pulmonary Disease 2017, 14 (1): 43-51 |
| Study details | Screening test performance study |
| Study objectives | To develop and test a new screening questionnaire and determine the best cut-off point for a portable spirometer |
| Inclusions | Smokers or ex-smokers of at least 1 pack-year[**]<br>Aged over 40 years old |
| Exclusions | Previous diagnosis of COPD |
| Population | 417 smokers recruited via 8 primary care centres in Spain (who attended primary care for any reason) |
| Test | COPD screening questionnaire from Terrassa (EGARPOC)<br>Portable spirometer (Vitalograph COPD-6®) |
| Comparator / reference standard | Post-bronchodilator spirometry |
| Outcomes | $FEV_1/FVC$ <0.7 was considered a positive spirometry test<br><br>10 patients were excluded due to incorrect spirometry<br><br>107 people were diagnosed with COPD (26.3%). GOLD staging:<br>• Mild 45 (42.1%)<br>• Moderate 53 (49.1%)<br>• Severe 9 (8.4%)<br>• Very severe 0 (0%)<br><br>Using a cut-off score of >13 on the EGARPOC:<br>• sensitivity 72.9%<br>• specificity 58.3%<br>• PPV 38.4%<br>• NPV 85.8%<br><br>Using a cut-off score of 0.78 $FEV_1/FEV_6$ (%) on the COPD-6: |

[**] The number of cigarettes smoked per day multiplied by the number of years smoking divided by 20

- sensitivity 78.9%
- specificity 72.3%
- PPV 53.1%
- NPV 94.3%

| **Quality appraisal using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool** | | | |
|---|---|---|---|
| **Question** | **Assessment (Y, N, unclear)** | **Risk of Bias (low, high, unclear)** | **Supporting info** |
| **Domain I: Patient selection** | | | |
| Consecutive or random sample of population enrolled? | Y | Low | Random sample |
| Case-control design avoided? | Y | Low | |
| Inappropriate exclusions avoided? | Y | Low | |
| **Domain II: Index Test** | | | |
| Index test results interpreted without knowledge of reference standard results? | Unclear | Unclear | Not stated |
| Threshold pre-specified? | N | High | Optimal cut-off explored |
| **Domain III: Reference standard** | | | |
| Reference standard likely to correctly classify condition? | Y | Low | Post-bronchodilator spirometry with GOLD staging |
| Reference standard results interpreted without knowledge of index test results? | Unclear | Unclear | Not stated |
| **Domain IV: Test strategy flow and timing** | | | |
| Appropriate interval between index test and reference standard? | Unclear | Unclear | Interval not stated |
| Did all participants receive same reference standard? | Y | Low | |
| All patients included in analysis? | N | High | 10 patients excluded due to incorrect spirometry |
| **Domain V: Applicability** | | | |
| Applicable to UK screening population of interest? | Y | Low | Primary care population |
| Applicable to UK screening test of interest? | Unclear | Unclear | New questionnaire developed for a Spanish population. COPD-6 internationally used |
| Target condition measured by reference test applicable to UK screening condition of interest? | Y | Low | |

| | |
|---|---|
| **Other comments** | The study had a fairly small sample size. |

## Table 15: Vrbica et al (2016)[13]

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|---|---|
| Publication | Vrbica Z. Labor M. Košćec Đuknić A. Radošević-Vidaček B. gudelj I. Labor S. Jurić I. Calverley PMA. Plavec D. for the MARKO study group. Development and the initial validation of a new self-administered questionnaire for an early detection of health status changes in smokers at risk for chronic obstructive pulmonary disease (MARKO questionnaire). Croat Med J 2016, 57: 425-33 |
| Study details | Screening test performance study |
| Study objectives | Validation of a new self-administered questionnaire to detect early changes in smokers that could lead to the future development of COPD |
| Inclusions | Smokers or ex-smokers<br>Aged 40 to 65 years<br>Smoking history of at least 20 pack-years<br>No previous diagnosis of COPD |
| Exclusions | Any clinically relevant chronic disease significantly affecting quality of life<br>Immunosuppressive therapy<br>Preceding acute respiratory disease 4 weeks before the visit<br>Hospitalisation for any reason during past 3 months<br>Myocardial infarction, cerebrovascular infarction or transient ischemic attack during past 6 months<br>Diagnosis of asthma<br>Inability to perform diagnosis protocol |
| Population | 224 participants, consecutively recruited at 15 GP practices in Croatian cities during a visit not related to respiratory symptoms |
| Test | MARKO questionnaire |
| Comparator / reference standard | Pulmonologist assessment for COPD including:<br>• COPD Assessment Test (CAT)<br>• St George's Respiratory Questionnaire (SGRQ)<br>• history-taking<br>• physical examination<br>• lung function with bronchodilator test<br>• 6-minute walk test<br>• laboratory tests |
| Outcomes | After diagnostic work-up participants were divided into 4 sub-groups:<br>• healthy smokers (no respiratory symptoms and $FEV_1/FVC \geq 0.7$) (n=72)<br>• symptomatic smokers (chronic respiratory symptoms as dyspnea, cough and/or sputum production and $FEV_1/FVC \geq 0.7$) (n=110)<br>• COPD GOLD stage I (n=23)<br>• COPD GOLD stage II (n=19)<br><br>42 (18.8%) patients diagnosed with COPD<br><br>Test performance to distinguish COPD from non-COPD, using a MARKO cut-off score of >10:<br>• Sensitivity 62.5%<br>• Specificity 49.5%<br>• PPV 21.4%<br>• NPV 85.7%<br><br>Correlation scores between the MARKO, CAT and SGRO questionnaires |

not included as not of interest in this review

| **Quality appraisal using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool** | | | |
|---|---|---|---|
| **Question** | **Assessment (Y, N, unclear)** | **Risk of Bias (low, high, unclear)** | **Supporting info** |
| **Domain I: Patient selection** | | | |
| Consecutive or random sample of population enrolled? | Y | Low | Consecutive sample |
| Case-control design avoided? | Y | Low | |
| Inappropriate exclusions avoided? | Y | Low | |
| **Domain II: Index Test** | | | |
| Index test results interpreted without knowledge of reference standard results? | Unclear | Unclear | MARKO questionnaire completed twice 2-4 weeks apart. Not clear which occasion used as the index test for test performance analysis or if blinding used |
| Threshold pre-specified? | Unclear | Unclear | One cut-off value reported but not clear if this was pre-specified |
| **Domain III: Reference standard** | | | |
| Reference standard likely to correctly classify condition? | Y | Low | Pulmonologist assessment including lung function tests using GOLD classification |
| Reference standard results interpreted without knowledge of index test results? | Unclear | Unclear | Participants and assessors blinded to results from first completion of MARKO questionnaire. However it is not clear if blinding was used in the second completion or which test result was used to calculate test performance |
| **Domain IV: Test strategy flow and timing** | | | |
| Appropriate interval between index test and reference standard? | Unclear | Unclear | MARKO questionnaire completed twice. The first occasion was 2-4 weeks before the reference standard, the second occasion concurrently with the reference standard. Not clear which occasion used for analysing test performance |
| Did all participants receive same reference standard? | Y | Low | |
| All patients included in analysis? | Y | Low | |
| **Domain V: Applicability** | | | |
| Applicable to UK | Y | Low | Primary care population of |

| | | | |
|---|---|---|---|
| screening population of interest? | | | smokers and ex-smokers |
| Applicable to UK screening test of interest? | N | High | Questionnaire is in the Croatian language |
| Target condition measured by reference test applicable to UK screening condition of interest? | Y | Low | Pulmonologist assessment used as the reference standard |
| **Other comments** | The study had a small sample size. | | |

## Table 16: Labor et al (2016)[14]

| | |
|---|---|
| Publication | Labor M. Vrbica Z. Gudelj I. Labor S. Plavec D. Diagnostic accuracy of a pocket screening spirometer in diagnosing chronic obstructive pulmonary disease in general practice: a cross sectional validation study using tertiary care as a reference. BMC Family Practice 2016, 17: 112 |
| Study details | Screening test performance study |
| Study objectives | To validate COPD-6™ lung function testing in general practice |
| Inclusions | Smokers or ex-smokers<br>Aged 40 to 65 years<br>Smoking history of at least 20 pack-years<br>No previous diagnosis of COPD |
| Exclusions | Any clinically relevant chronic disease significantly affecting quality of life<br>Immunosuppressive therapy<br>Preceding acute respiratory disease 4 weeks before the visit<br>Hospitalisation for any reason during past 3 months<br>Myocardial infarction, cerebrovascular infarction or transient ischemic attack during past 6 months<br>Diagnosis of asthma<br>Inability to perform diagnosis protocol |
| Population | 227 participants, consecutively recruited at 26 GP practices in Croatia during a visit not related to respiratory symptoms |
| Test | COPD-6™ lung function test (index test) |
| Comparator / reference standard | Pulmonologist assessment for COPD including:<br>• Repeat COPD-6™ lung function test<br>• Lung function testing followed by post bronchodilator spirometry<br>• history-taking<br>• physical examination |
| Outcomes | 43 (18.9%) patients diagnosed with COPD<br>• 24 GOLD stage I<br>• 19 GOLD stage II<br><br>At a cut-off level of $FEV_1/FEV_6$ <0.7:<br>• sensitivity 32.6% (95%CI 20.5 to 47.5)<br>• specificity 100% (95%CI 98.0 to 100)<br>• PPV 100% (95%CI 78.5 to 100)<br>• NPV 86.4% (95%CI 81.1 to 90.4) |

| **Quality appraisal using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool** | | | |
|---|---|---|---|
| **Question** | **Assessment (Y, N, unclear)** | **Risk of Bias (low, high, unclear)** | **Supporting info** |

| | | | |
|---|---|---|---|
| **Domain I: Patient selection** | | | |
| Consecutive or random sample of population enrolled? | Y | Low | Consecutive population |
| Case-control design avoided? | Y | Low | |
| Inappropriate exclusions avoided? | Y | Low | |
| **Domain II: Index Test** | | | |
| Index test results interpreted without knowledge of reference standard results? | Y | Low | Index test performed 2-4 weeks before reference standard |
| Threshold pre-specified? | Y | Low | |
| **Domain III: Reference standard** | | | |
| Reference standard likely to correctly classify condition? | Y | Low | |
| Reference standard results interpreted without knowledge of index test results? | Y | Low | Assessor blinded to index test result |
| **Domain IV: Test strategy flow and timing** | | | |
| Appropriate interval between index test and reference standard? | Unclear | Unclear | Reference standard completed 2-4 weeks after index test |
| Did all participants receive same reference standard? | Y | Low | |
| All patients included in analysis? | Y | Low | |
| **Domain V: Applicability** | | | |
| Applicable to UK screening population of interest? | Y | Low | Primary care population |
| Applicable to UK screening test of interest? | Y | Low | Internationally used test |
| Target condition measured by reference test applicable to UK screening condition of interest? | Y | Low | |
| **Other comments** | The study had a small sample size. | | |

## Data extraction and quality assessment for studies relevant to criterion 9

### Key question 2: What is the impact of screening for COPD on smoking cessation rates?

### Table 17: Salepci et al 2016[16]

| | |
|---|---|
| Publication | Salepci B. Caglayan B. Fidan A. Parmaksiz ET. Kiral N. Comert SS. Dogan C. Coskun E. The effect of pulmonary function testing on the success of smoking cessation. Respiratory Care 2016, 61(8): 1073-1080 |
| Study details | Cohort study |
| Study objectives | To determine the effect of identifying airway obstruction via spirometry on smoking cessation rates |
| Inclusions | People who attended a smoking cessation clinic between 2012 and 2014 and who performed pulmonary function tests |
| Exclusions | Patients who failed to perform pulmonary function tests |
| Population | 563 smokers who applied to a smoking cessation out-patient clinic |
| Group 1 | Patients with obstruction or small airway obstruction who received a smoking cessation intervention |
| Group 2 | Patients with normal pulmonary function tests who received a smoking cessation intervention |
| Key findings | 563 people performed pulmonary function tests (PFT). Of these:<br>• 114 (20.2%) had obstructive disease (94 (82.4%) with GOLD stage I-II; 20 (7.6%) with GOLD stage III-IV)<br>• 270 (47.9%) had comorbid disease (including 36 (6.3%) with COPD)<br>• 162 (28.8%) attended follow-up visits for 3 months (people who did not attend follow-up visits were considered non-quitters)<br><br>After 3 months:<br>• 64 (11.3%) quit smoking<br>• significantly more quitters had obstruction on PFT (40.6%) compared to non-quitters (17.6%) (p<0.001)<br>• significantly more people with obstruction on PFT quit smoking (22.8%) compared to people without obstruction (8.4%) (p<0.001)<br>• there was no significant difference in the number quitting between people with GOLD stage I-II (22.3%) and GOLD stage III-IV (25%) (p=0.79)<br>• presence of obstruction on PFT was significantly higher in people who attended follow-up visits (p<0.01; percentages not reported)<br><br>In 162 people who completed 3 months of follow-up visits:<br>• 64 (39.5%) quit smoking<br>• significantly more quitters had obstruction on PFT (41.6%) compared to non-quitters (22.5%) (p<0.01) |
| Quality appraisal | The CASP cohort study checklist was used to assess the quality of this study. Generally the study was at low risk of bias. However, the study was limited by the retrospective design and there are some limitations in the applicability of the results.<br><br>The study addressed a clearly focused issue and the cohort was recruited in an acceptable way. Objective measures were used to assess pulmonary function in all participants and carbon monoxide levels were assessed to determine quit status, in people who attended follow-up visits. The authors considered appropriate confounding factors in their analysis. |

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|---|---|
| | Less than one-third of the population completed at least 3 months of follow-up visits, however results were reported separately for people who did and did not complete follow-up.<br><br>This was a retrospective study at a single smoking cessation centre in Turkey with a population of people seeking assistance to stop smoking. People who did not attend follow-up appointments were assumed to be non-quitters, but there may have been people who quit smoking within this group. Financial support to cover the costs of pharmacological treatments to support smoking cessation was not provided which may have affected the proportion of people who attended follow-up appointments. |

## Table 28: Foulds et al (2015)[15]

| | |
|---|---|
| Publication | Foulds J. Veldheer S. Hrabovsky S. Yingst J. Sciamanna C. Chen G. Maccani JZJ. Berg A. The effect of motivational lung age feedback on short-term quit rates in smokers seeking intensive group treatment: a randomized controlled pilot study. Drug Alcohol Depend. 2015, 153: 271-277 |
| Study details | Randomised controlled trial |
| Study objectives | To assess the impact of spirometry based feedback on 'lung age' on treatment compliance and tobacco abstinence<br><br>'Lung age' is lung function test results demonstrating lung function in relation to expected performance by age |
| Inclusions | People who smoked ≥5 cigarettes per day, were ready to make a quit attempt in the next month, ≥21 years old and willing to attend study visits |
| Exclusions | Contraindications for nicotine patch or lung function testing, current use of smoking cessation medicines, uncontrolled mental illness or substance misuse in past 6 months, life expectancy <1 year or unwillingness to quit all tobacco products |
| Population | 225 smokers willing to attend tobacco dependence treatment recruited via posters and clinician referral |
| Intervention | Motivational 'lung age' feedback with explanation of the results and the beneficial effects of quitting smoking and 6-week smoking cessation intervention (n=120) |
| Comparator | Minimal 'lung age' feedback (results without additional explanation) and 6-week smoking cessation intervention (n=105) |
| Key findings | At baseline:<br>• 41% had an $FEV_1$ <80% predicted<br><br>28-day follow-up (intent-to-treat analysis):<br>• the overall tobacco abstinence rate was 52%<br>• no significant difference in 7-day biochemically confirmed tobacco abstinence rates between the intervention (50.8%) and control groups (52.4%) (p=0.65)<br>• no significant difference in attendance of the last smoking cessation session between the intervention (70%) and control groups (76%) (p=0.30) |
| Quality appraisal | The Cochrane Collaboration's risk of bias tool was used to assess the quality of this study. Generally the study was at low risk of bias with some concern about applicability.<br><br>A computerized block randomisation sequence was used and the clinician was blind to study group until after baseline lung measurements had been taken. As this was a behavioural study blinding was not used during the intervention. An objective measure (carbon monoxide levels) was used to determine tobacco abstinence.<br><br>An intention-to-treat analysis was completed. More than 70% of participants attended the final assessment with no significant difference between the groups. People who did |

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|---|---|
| | not attend the 28-day follow-up were assumed to have continued smoking.<br><br>The applicability of the study is limited by the fact that all study participants were willing to quit smoking at the study outset. In addition, participants in both groups with $FEV_1$ <80% predicted were told that their score was lower than expected and advised to see their doctor, which may have diluted the difference in the information received by the intervention and control groups. |

## Table 19: Fuller et al (2012)[17]

| | |
|---|---|
| Publication | Fuller L. Conrad WF. Heaton PC. Panos R. Eschenbacher W. Frede SM. Pharmacist-managed chronic obstructive pulmonary disease screening in a community setting. Journal of the American Pharmacists Association 2012, 52(5): e59-e66 |
| Study details | Cohort study |
| Study objectives | To determine the effectiveness of COPD screening in community pharmacy and the impact on enrolment in smoking cessation programmes |
| Inclusions | Age >35 years |
| Exclusions | • pregnancy at the time of screening<br>• history of lung cancer<br>• diagnosis of COPD<br>• lung surgery or resection<br>• recent abdominal or thoracic surgery<br>• respiratory infection within the previous 3 weeks<br>• uncontrolled hypertension<br>• inability to produce 3 acceptable tracings during spirometry |
| Population | 185 people attending 4 pharmacies or off-site screening events (for hypertension, diabetes, dyslipidemia and depression)) in a US city |
| Intervention | COPD screening questionnaire (COPD PS) and spirometry. Current smokers were offered smoking cessation counselling (regardless of screening result) |
| Comparator | No comparator |
| Outcomes | • 10 (5.4%) patients were excluded due to inability to perform spirometry<br>• 16 patients (9%) had airflow limitation ($FEV_1$/FVC <lower limit of normal)<br>• 20 patients were current smokers<br>• 12 ‘test positive’ patients were former or current smokers<br><br>9 of the 20 current smokers (45%) participated in a 6-month follow-up interview. Of these:<br>• 2 had successfully quit smoking<br>• 5 reported some attempt to quit smoking<br><br>It is not reported if these individuals had a positive or negative screening test |
| Quality appraisal | The CASP cohort study checklist was used to assess the quality of this study. Generally there were a number of areas where the study was at risk of bias.<br><br>The study addressed a clearly focused issue and the cohort was recruited in an acceptable way. Objective measures were used to assess pulmonary function in all participants however, smoking cessation behaviours were self-reported. The authors did not consider confounding factors in their analysis.<br><br>The number of current smokers identified was small (n=20) and less than half of those screened completed a six-month follow-up interview. The study authors did not state the screening test result of the 7 patients who quit or attempted to quit smoking. The results therefore do not contribute much information to assess the impact of screening on smoking cessation rates. |

| | |
|---|---|
| | Smoking cessation counselling was provided following screening but no specific smoking cessation intervention was offered.<br><br>This study was performed in pharmacies in the US. |

## Table 20: Riegels-Jakobsen et al (2012)[18]

| | |
|---|---|
| Publication | Riegels-Jakobsen T. Skouboe M. Dollerup J. Andersen CB. Staal LB. Jakobsen RB. Poulsen PB. Municipality screening of citizens with suspicion of chronic obstructive pulmonary disease. International Journal of COPD 2012, 7:35-41 |
| Study details | Cohort study |
| Study objectives | To determine the effectiveness of early detection of COPD |
| Inclusions | • age >35 years<br>• smoker or ex-smoker<br>• presence of ≥1 respiratory symptom eg dyspnea, cough, wheeze, phlegm |
| Exclusions | Previous diagnosis of COPD |
| Population | 152 people at risk of COPD recruited from advertisements, existing courses and training and screening at market places In Denmark |
| Intervention | Spirometry screening without bronchodilator |
| Comparator | No comparator |
| Outcomes | 78 (51.3%) had evidence of airway obstruction and were advised to see their GP:<br>• 24 mild (32%)<br>• 42 moderate (55%)<br>• 8 severe (10%)<br>• 2 very severe (3%)<br><br>51% were current smokers<br><br>All participants were contacted by telephone 3 months after screening with a 92% response rate<br>• 40 of 47 people (85%) who visited their GP were diagnosed with COPD<br>• 57% of people diagnosed with COPD were undergoing smoking cessation at follow-up compared with 8% at screening<br>• there were 40% fewer smokers at follow-up compared to at screening |
| Quality appraisal | The CASP cohort study checklist was used to assess the quality of this study. Generally there were a number of areas where the study was at risk of bias.<br><br>The study addressed a clearly focused issue and the cohort was recruited in an acceptable way. Objective measures were used to assess pulmonary function in all participants however, smoking cessation behaviours were self-reported. The authors did not consider confounding factors in their analysis.<br><br>Follow-up was relatively short at 3-months, however the response rate was high. The number of current smokers was reduced at follow-up and more than half of people diagnosed with COPD reported that they were undergoing smoking cessation. Although smoking appeared to be reduced there is no figure comparing smoking outcomes in people who had a positive or negative screening result.<br><br>No specific smoking cessation intervention was offered with the screening, although people may have received support through their GP. This study was performed in a community sample of smokers and ex-smokers with at least one self-reported respiratory symptom in Denmark. |

## Key question 3: What is the clinical effectiveness of pharmacological treatment on screen-detected patients with COPD?

### Table 21: Guirguis-Blake et al (2016)[8]

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| Publication | Guirguis-Blake JM. Senger CA. Webber EM. Mularski RA. Whitlock EP. Screening for chronic obstructive pulmonary disease: evidence report and systematic review for the US Preventative Services Task Force. JAMA 2016, 315(13):1378-93 |
| Study details | Systematic review |
| Study objectives | To review evidence on the efficacy and harms of treatment of screen-detected COPD<br>NB Evidence relating to the literature on the accuracy of screening questionnaires and office-based screening pulmonary function testing is considered under the appropriate key question |
| Inclusions | Treatment efficacy RCTs on the following COPD drug classes or combinations of:<br>• long-acting ß-agonists (LABAs)<br>• long-acting anticholinergics<br>• inhaled corticosteroids |
| Exclusions | Non stated |
| Population | 20 studies of 14 RCTs published up to January 2015 |
| Intervention | COPD treatments |
| Comparator | No treatment/ placebo |
| Outcomes | No studies on screen-detected or asymptomatic populations were identified. The search was expanded to include people diagnosed with mild or moderate COPD. The review authors noted that the literature identified was largely based on patients at the more severe end of moderate COPD.<br><br>Overall, the review concluded that treatment RCTs and sub-group analysis of populations with mild to moderate symptoms showed no benefit in all-cause mortality but supported a modest reduction in exacerbation frequency.<br><br>**LABAs**<br>• studies identified: 1 post-hoc sub-analysis from 1 RCT and 1 post-hoc pooled analysis from 3 RCTs<br>• outcomes: LABAs appeared to reduce exacerbations and dyspnea scores; health-related quality of life results were mixed<br>• safety: few differences between treated and untreated groups for a variety of individual adverse events<br><br>**Inhaled corticosteroids**<br>• studies identified: 1 RCT of patients with mild to moderate COPD; 2 post-hoc sub-analysis from RCTs and 2 RCTs of patients with a mean $FEV_1$ ≥60%<br>• outcomes: results seemed to indicate a reduction in exacerbations, but exacerbations were variably defined and annual rates varied widely; insufficient data to draw conclusions about dyspnea or health-related quality of life<br>• safety: generally few differences between treated and untreated groups<br><br>**LABAs and inhaled corticosteroids**<br>• studies identified: 1 post-hoc sub-analysis from 1 RCT of patients with moderate COPD and 2 RCTs on the harms of treating patients with mild to moderate COPD<br>• outcomes: the sub-analysis suggested a possible all-cause mortality benefit, a statistically significant, but probably not clinically meaningful improvement in health-related quality of life and a reduction in exacerbations |

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| | • safety: similar rates of adverse events between treated and control groups, but with a possible higher risk of pneumonia with treatment<br><br>**Long-acting muscarinic antagonist tiotropium (a bronchodilator)**<br>• studies identified: 1 RCT in patients with moderate COPD naïve to maintenance treatment and 4 sub-group analyses<br>• outcomes: the majority of evidence showed beneficial outcomes for exacerbations and health-related quality of life<br>• safety: limited data on harms with one study reporting more adverse events with treatment, but another study reporting no difference in serious events |
| Quality appraisal | The CASP checklist for systematic reviews was used to assess the quality of this review. There were no areas of concern about the quality of the review.<br><br>The study authors appraised the quality of the included studies using the USPSTF quality rating standards. The study authors appraised the quality of the included studies using the USPSTF quality rating standards. Areas of concern in the RCTs considered included the use of post-hoc sub-group analysis from trials that were powered to detect change in the whole population, not a sub-group and inconsistency in reported outcomes across the studies.<br><br>The review authors raised questions about the applicability of the evidence identified to a screen-detected population. |

## Data extraction and quality assessment for studies relevant to criterion 11

### Key question 4: Does screening for COPD in 'asymptomatic' adults reduce morbidity or mortality or improve health-related quality of life?

**Table 22: Berterns et al (2014)**[19]

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| Publication | Berterns LCM. Reitsma JB. van Mourik Y. Lammers JWJ. Moons KGM. Hoes AW. Rutten FH. COPD detected with screening: impact on patient management and prognosis. Eur Respir J 2014, 44: 1571-1578 |
| Study details | Analysis of data from a cluster RCT |
| Study objectives | The effectiveness of screening elderly people for COPD and heart failure |
| Inclusions | Aged ≥65 years<br>Dyspnoea and/or reduced exercise tolerance |
| Exclusions | People with both COPD and heart failure at study entry (people with 1 of these conditions were included) |
| Population | Community-dwelling frail elderly people in The Netherlands |
| Intervention | Screening including history taking using a standardised questionnaire (name not stated), physical examination, ECG, pre and post-bronchodilator spirometry, blood tests and echocardiography |
| Comparator | Usual care. Complaints of dyspnoea and exercise tolerance were communicated to the treating physician |
| Outcomes | **For the screening group (n=386):**<br>Diagnosis of COPD was made by a consensus panel. Patients either had:<br>• no COPD (n=236; 61.1%)<br>• new COPD (n=84; 21.8%) (1 (1.2%) GOLD stage I; 77 (91.6%) GOLD stage II) |

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| | • confirmed COPD (n=50; 13.0%) (40 (80.0%) GOLD stage II; 9 (18.0%) GOLD stage III)<br>• former COPD (previous diagnosis could not be confirmed) (n=16; 4.1%)<br><br>6 and 12-month follow-up data was collected from GP electronic records.<br><br>For the 236 people with no COPD:<br>• use of pulmonary drugs decreased from 41 (17.4%) at baseline to 31 (13.1%) at 6-months (significance test not reported)<br>• all-cause mortality at 12-months follow-up was 7 (3.0%)<br>• all hospitalisations at 12-months follow-up was 54 (22.9%)<br>• pneumonia or exacerbations at 12-months follow-up was 9 (3.8%)<br><br>For the 84 people newly diagnosed with COPD:<br>• use of pulmonary drugs increased from 24 (28.6%) at baseline to 32 (38.1%) at 6-months (significance test not reported)<br>• none of the 10 smokers had quit smoking at 6-months follow-up<br>• all-cause mortality at 12-months follow-up was 2 (2.4%)<br>• all hospitalisations at 12-months follow-up was 27 (32.1%)<br>• pneumonia or exacerbations at 12-months follow-up was 8 (9.5%)<br><br>For the 50 people with confirmed COPD:<br>• use of pulmonary drugs decreased from 40 (80.0%) at baseline to 39 (78.0%) at 6-months (significance test not reported)<br>• all-cause mortality at 12-months follow-up was 4 (8.0%)<br>• all hospitalisations at 12-months follow-up was 14 (28.0%)<br>• pneumonia or exacerbations at 12-months follow-up was 26 (52.0%)<br><br>For the 16 people with former COPD:<br>• use of pulmonary drugs decreased from 13 (81.3%) at baseline to 12 (75.0%) at 6-months (significance test not reported)<br>• all-cause mortality at 12-months follow-up was 1 (6.3%)<br>• all hospitalisations at 12-months follow-up was 5 (31.3%)<br>• pneumonia or exacerbations at 12-months follow-up was 3 (18.8%)<br><br>**For the usual care group (n=443):**<br>• 13 (2.9%) had a new diagnosis of COPD; 66 (14.9%) had a diagnosis of COPD at baseline<br>• use of pulmonary drugs increased from 6 (46.2%) at baseline to 9 (69.2%) at 6-months (significance test not reported)<br>• mortality and hospitalisations after 12-months follow-up did not differ from the screening arm (figures not reported)<br>• fewer patients experienced an episode of pneumonia and/or exacerbations 29 (6.5%) than in the screening group 46 (11.9%)<br><br>No significance tests comparing the screening and usual care groups reported |
| Quality appraisal | The Cochrane Collaboration's risk of bias tool was used to assess the quality of this study. As this study was an analysis of a cluster RCT sub-group some information (eg details of randomisation method) was not available in the publication assessed.<br><br>No blinding was reported in this study. Details of the numbers of patients completing the study and reasons for withdrawal were reported. Follow-up data was taken from electronic patient records. A low value for missing values in the dataset was reported |

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| | (0.4%).<br><br>Outcome measures included objective measures of medication use, smoking status, hospitalization and survival. However no statistical analysis was reported.<br><br>The study population for this study was frail elderly people living in the community and may have limited generalisability to a wider UK screening population. |

# Appendix 4 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 2.

**Table 23. UK NSC reporting checklist for evidence summaries**

| | Section | Item | Page no. |
|---|---|---|---|
| **1.** | TITLE AND SUMMARIES | | |
| **1.1** | Title sheet | Identify the review as a UK NSC evidence summary. | Title page |
| **1.2** | Plain English summary | Plain English description of the executive summary. | 5 |
| **1.3** | Executive summary | Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review. | 6 |
| **2.** | INTRODUCTION AND APPROACH | | |
| **2.1** | Background and objectives | Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews<br><br>Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, | 9 |

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| | | criteria they address, and number of studies included per question, description of the overall results of the literature search.<br><br>Method – briefly outline the rapid review methods used. | | |
| **2.2** | Eligibility for inclusion in the review | State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*. | | 14 |
| **2.3** | Appraisal for quality/risk of bias tool | Details of tool/checklist used to assess quality, eg QUADAS 2, CASP, SIGN, AMSTAR. | | 17 |
| **3.** | SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION) | | | |
| **3.1** | Databases/ sources searched | Give details of all databases searched (including platform/interface and coverage dates) and date of final search. | | 17 |
| **3.2** | Search strategy and results | Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used.<br><br>Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion. | | 36 |
| **3.3** | Study selection | State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out. | | 14 |
| **4.** | STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION) | | | |
| **4.1** | Study level reporting, results and risk of bias | For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up | Study level reporting: Appendix 3<br><br>Quality assessment: Appendix 3 | |

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| | assessment | period, outcomes reported, statistical analyses etc.).<br>Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available.<br>For each study, present the results of any assessment of quality/risk of bias. | |
| **5.** | QUESTION LEVEL SYNTHESIS | | |
| **5.1** | Description of the evidence | For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion. | 18,24,27,30 |
| **5.2** | Combining and presenting the findings | Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency. | 18,25,28,30 |
| **5.3** | Summary of findings | Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion.<br>Summarise the main findings including the quality/risk of bias issues for each question.<br>Have the criteria addressed been 'met', 'not met' or 'uncertain'? | 24,29,33 |
| **6.** | REVIEW SUMMARY | | |
| **6.1** | Conclusions and implications for policy | Do findings indicate whether screening should be recommended?<br>Is further work warranted?<br>Are there gaps in the evidence highlighted by the review? | 34 |
| **6.2** | Limitations | Discuss limitations of the available evidence and of the review methodology if relevant. | 34 |

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