CASE FINDING FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN PRIMARY CARE: FINDING THE OPTIMAL APPROACH

by

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Abstract

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality but widely underdiagnosed. This thesis explores methods to improve case finding for COPD in primary care. It includes two systematic reviews- the first evaluated the diagnostic accuracy of screening tests and showed that handheld flow meters are more accurate than the COPD Diagnostic Questionnaire. The second evaluated the comparative effectiveness of different case finding strategies and found that inviting symptomatic ever smokers for a screening assessment may be more efficient than inviting all ever smokers directly for diagnostic spirometry. The thesis then reports the development and external validation of two risk prediction models for COPD using data from electronic health records and a cluster randomised controlled trial. These models can be used to assess the risk of undiagnosed COPD to help target patients for case finding and can potentially be integrated with clinical information systems. Finally, primary care providers were interviewed to explore their views on case finding for COPD, including potential benefits and harms, as well as barriers and facilitators. This suggests that more training and support for community respiratory services may be needed in order to improve the timely diagnosis of COPD.

Dedication

This thesis is dedicated to my parents, my teachers, and to everyone who has supported my education. Thank you and thank you again for making this possible.

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LIST OF ABBREVIATIONS

AO	Airflow obstruction
ATS	American Thoracic Society
BD	Bronchodilator
BLF	British Lung Foundation
BLISS	Birmingham Lung Improvement Studies
BMI	Body mass index
CDQ	COPD Diagnostic Questionnaire
CI	Confidence interval
CMO	Chief Medical Officer
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in one second
FEV_6	Forced expiratory volume in six second
FVC	Forced vital capacity
GLI	Global Lung Initiative
GOLD	Global Initiative for Obstructive Lung Disease
GP	General practitioner
GPRD	General Practice Research Database
HSE	Health Survey for England
LR	Likelihood ratio
LRTI	Lower respiratory tract infection
MRC	Medical Research Council
NHANES	National Health And Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
NND	Number of diagnostic assessments needed per case detected
NNS	Number-needed-to-screen per case detected
NNT	Number-needed-to-target per case detected
NR	Not reported
OR	Odds ratio
NPV	Negative predictive value
PPV	Positive predictive value
RCT	Randomised controlled trial

S	Supplementary
SD	Standard deviation
URTI	Upper respiratory tract infection
USPSTF	United States Preventive Services Task Force

CHAPTER 1: INTRODUCTION

1.1 A personal perspective on a major public health challenge

Chronic obstructive pulmonary disease (COPD) represents a major public health challenge and is currently the third leading cause of death worldwide (Figure 1.1).(1) It has risen from being a relatively neglected condition to one that is now recognized as a major priority for health services and public health.(3, 4) As a junior doctor I personally found managing patients with COPD, both in primary and secondary care, challenging. COPD is a complex condition with a wide spectrum of disease severity

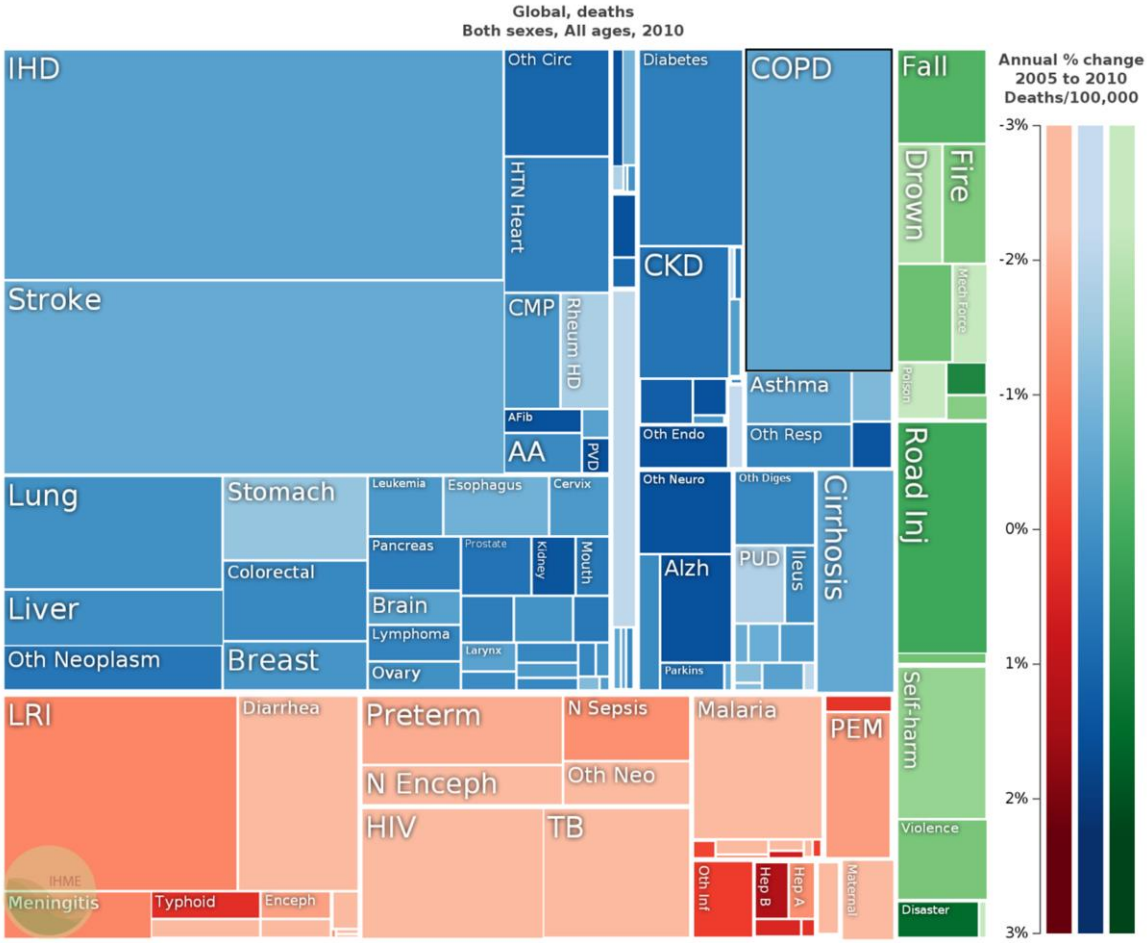

Figure 1.1 Causes of death estimated in the Global Burden of Diseases Study (2010)
(Reproduced with permission from the Institute for Health Metrics and Evaluation (2))

(5) and patients with more advanced disease often suffer with recurrent hospital admissions (6) and poor quality of life.(7) Seeing this first hand made me appreciate the vital importance of preventive medicine in the management of chronic respiratory disease. This has been recognised at a national and international level through the prioritisation of legislation to curb tobacco exposure (8) and improve air quality (9) but also by the recognition of the high prevalence of undiagnosed COPD (10) and a growing consensus on the importance of early diagnosis.(11)

While working as a specialty trainee in public health, I was introduced to my current academic supervisors Professor Peymane Adab and Dr Rachel Jordan who offered the opportunity to conduct a pilot randomised controlled trial (RCT) comparing two approaches to case finding for COPD in primary care.(12) During the course of this study it became apparent that primary care organizations in the UK and worldwide were actively involved in case finding for COPD. However, this was largely being undertaken in the absence of robust evidence or guidelines. This highlighted that there is a need for further research to improve our understanding of the optimal approach for identifying patients with undiagnosed COPD, and that this is highly relevant for policy makers, clinicians and above all, patients. This introduction to the epidemiology of COPD then led to the development of the body of work presented in this PhD thesis, which has been conducted in collaboration with the Birmingham Lung Improvement Studies (BLISS) programme.(13) I hope it goes some way to bridging gaps in the evidence on identifying patients with undiagnosed COPD in primary care.

1.2 Pathology

COPD is characterised by persistent, often progressive and not fully reversible airflow obstruction associated with chronic airway inflammation in response to noxious particles or gases.(14) However, the disease is highly heterogeneous with a number of overlapping clinical phenotypes and pathophysiological processes.(15) This mainly consists of varying degrees of small airways disease and destruction of the gas-exchanging surface of the lung (emphysema).(16) The small airways undergo structural changes and progressive narrowing while destruction of lung parenchyma reduces its elastic recoil, limiting the ability of airways to remain open during expiration.(17) COPD is often accompanied by chronic bronchitis which is characterised by airway mucociliary dysfunction and mucus hypersecretion.(18) In addition, COPD often overlaps with asthma and in older individuals with COPD, as many as half or more may have overlapping diagnoses, which has led to the recognition of the asthma-COPD overlap syndrome.(19) COPD is also characterised by multi-morbidity (20, 21) (Figure 1.2) which is related to the effects of ageing and

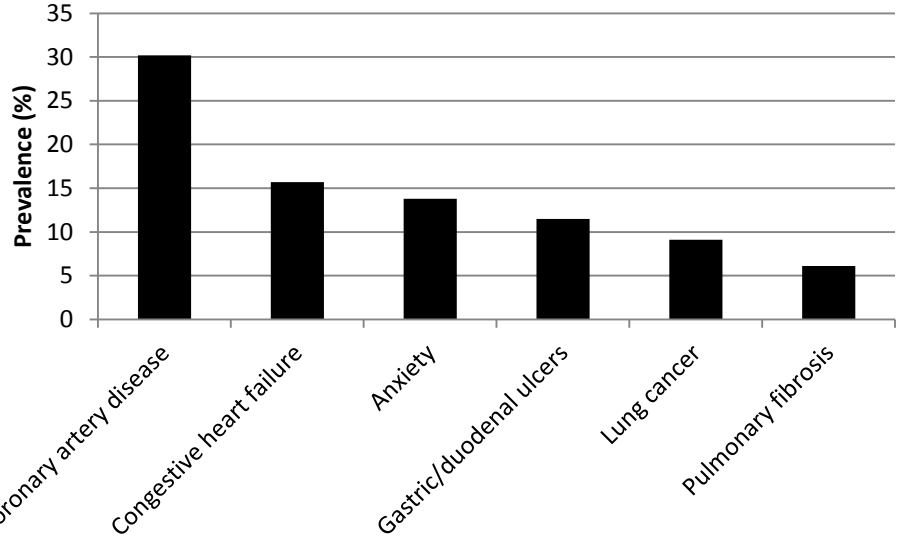

Figure 1.2 Prevalence of comorbidities associated with increased risk of death in patients with COPD (20)

other shared risk factors as well as systemic inflammation.(22)

1.3 Symptoms

People with COPD suffer with chronic respiratory symptoms such as cough, shortness of breath, wheeze and sputum production, and often experience recurrent exacerbations (although the latter may be more characteristic of a specific phenotype (23)), which are often triggered by both bacterial and viral respiratory infections.(24) They may also experience more systemic symptoms such as fatigue, weight loss, muscle weakness and anorexia,(25, 26) and can suffer with depression and anxiety.(27) Lung function decline, reduction in muscle strength, and reduced exercise capacity all contribute to increasing disability.(28)

1.4 Diagnosis

The most widely recommended diagnostic criteria for COPD used in clinical practice requires the presence of relevant symptoms (as described above) and a compatible clinical history (aged over 35 years with a history of smoking or other noxious exposures) together with objective measures of airflow obstruction as defined by a post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio of less than 0.7.(29)

However the approach and threshold used to define airflow obstruction remains in dispute because it may over-diagnose males aged >40 years and females >50 years (30) as well as asymptomatic older never smokers.(31) The European Respiratory Society and the American Thoracic Society as well as a large number of epidemiological studies have thus adopted a different criterion for airflow obstruction

Table 1.1 Global Initiative for Obstructive Lung Disease (GOLD) COPD severity staging classification

GOLD Stage	Criteria
1	$FEV_1 \geq 80\%$ predicted
2	$50\% \leq FEV_1 < 80\%$ predicted
3	$30\% \leq FEV_1 < 50\%$ predicted
4	$FEV_1 < 30\%$ predicted

FEV_1=forced expiratory volume in one second

which is an FEV_1/FVC less than the lower limit of normal (5^{th} percentile) after adjusting for age, sex, height, and ethnic group.(32, 33)

Disease severity has traditionally been graded according to the ratio of the observed FEV_1 to the predicted value (Table 1.1).(14) However a different classification for severity grading recently proposed by the GOLD committee, which incorporates information about symptoms and frequency of exacerbations, has been incorporated into their most recent guidance.(14) Other clinical investigations including chest radiography and a full blood count are also indicated for the diagnosis of COPD and to exclude differential diagnoses.(29)

1.5 Risk factors

The main risk factor for COPD is cigarette smoking which has an estimated population attributable risk (PAR) ranging from 48-76%.(34, 35) Other risk factors have also been implicated including exposure to industrial fumes and dust,(36) outdoor air pollution,(37) second hand smoke,(38) biomass smoke,(39) and chronic asthma.(40) Alpha-1 antitrypsin deficiency is a well-established genetic risk factor for COPD although other rare genetic syndromes such as cutis laxa (41) (caused by mutations in the elastin gene) may also cause COPD.(40) There is increasing evidence that lung function development is influenced both *in utero* and in the early years of life by factors such as maternal smoking, low birth weight, diet, and nutrition.(42) Factors such as parental and childhood asthma, maternal smoking and

childhood respiratory infections have been shown to permanently lower lung function and predispose to COPD in later life as much as heavy smoking.(43)

1.6 Public health impact

About one in four individuals are likely to be diagnosed with COPD during their lifetime (44) and COPD rose from being the fourth leading cause of death worldwide in 1990 to now being the third.(1) It is also the ninth leading cause of disability adjusted life years lost.(45) The incidence is approximately one case per 100 person years and ten times higher in smokers than nonsmokers.(46) Although COPD is almost twice as prevalent in males as females (47) the disease burden is rising among women as a consequence of increasing tobacco consumption over the last few decades.(48)

Diagnosis and management of the disease has significant resource implications for health services. In the UK, COPD is associated with over 100,000 emergency hospital attendances (2% of all emergency visits),(49) 1 million inpatient days, 1.4 million general practice consultations and costs the health service over £800 million per year.(50) Most of these costs are associated with inpatient hospitalisations.(51)

COPD also has wider societal implications. Lost productivity can account for roughly half the overall societal costs, which range from £641 to £3850 per patient in Western Europe and the USA.(51) People with COPD often have difficulty maintaining employment due to chronic symptoms and exacerbations. One international survey suggested that individuals with COPD in active employment incurred average lifetime losses of £4661 from time off work and that 40% of those of working age with COPD retire early because of their condition.(52)

People with COPD tend to have both poorer physical and mental health than those without COPD (53) and COPD even in its milder stages can significantly affect quality of life and limit activities of daily living.(54) COPD is also likely to have a significant impact on the quality of life of carers, particularly in the latter stages of the disease when access to specialist palliative care is often limited.(55)

1.7 Prevalence of COPD

A systematic review and meta-analysis by Halbert and colleagues (47) attempted to quantify the global prevalence of COPD in the population aged over 40 years, which they estimated at 9-10% for physiologically defined disease. Heterogeneity in population characteristics and diagnostic criteria make it difficult to produce precise estimates of COPD prevalence globally. However pooled estimates from the Burden of Obstructive Lung Disease (BOLD) study, which used a uniform methodology for assessing population-based prevalence of airflow obstruction (defined as post-bronchodilator FEV1/FVC<0.7) as a proxy for COPD across 12 international sites, suggested that the overall prevalence at GOLD stage II-IV is 10% (11.8% for men and 8.5% for women).(10) However, this varied significantly by country from 8.5-22.2% among men and from 1.3-16.7% among women. The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) similarly investigated the prevalence of COPD (again defined as post-bronchodilator FEV1/FVC<0.7) in five Latin American cities, with estimates ranging from 7.8-19.7% in adults aged over 40 years.(56) Among young adults with normal lung function and no history of asthma, the European Community Health Survey II (which defined airflow obstruction as pre-bronchodilator FEV_1/FVC<0.7) showed an incidence rate of 2.8 cases per

1000 person-years, with the presence of chronic cough and phlegm being associated with a nearly threefold increased risk.(57)

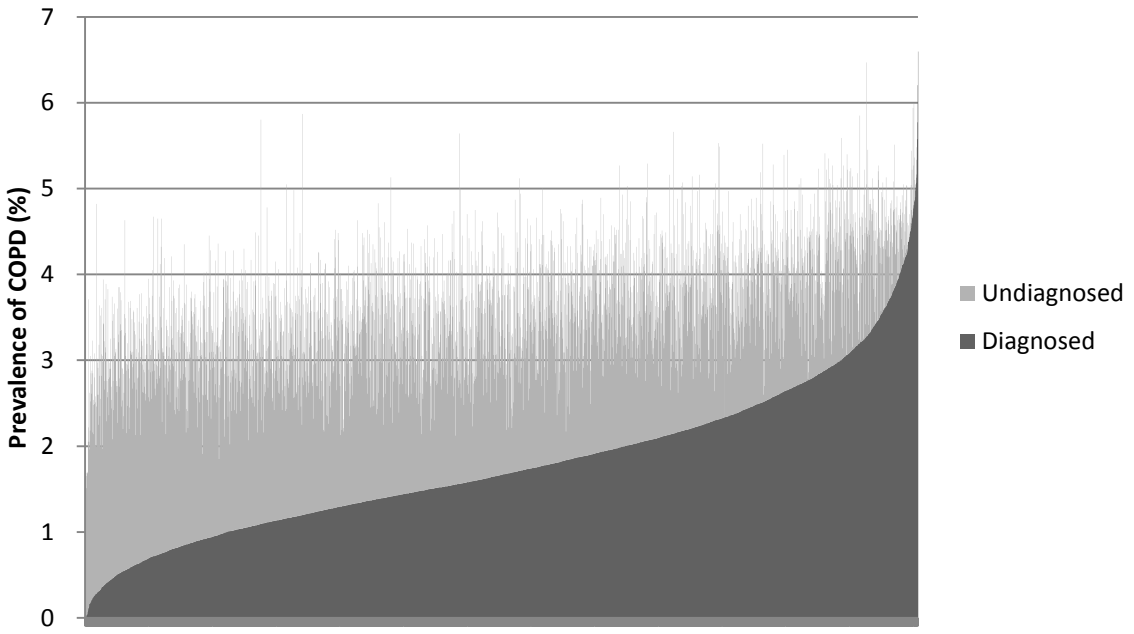

Figure 1.3 Estimated prevalence of diagnosed and undiagnosed COPD by general practice in England in 2012/2013 (58-60)

1.8 The burden of undiagnosed disease

Estimates of prevalence from population-based healthcare data are unreliable because COPD is largely underdiagnosed (Figure 1.3). For example in England the recorded prevalence of COPD in primary care registers in those aged over 35 years is 1.6% (58, 59) whereas model based estimates of predicted prevalence are closer to 5%.(60) The prevalence of airflow obstruction is even higher, with one analysis of the Health Survey for England estimating it at 13.3% (airflow obstruction defined as pre-bronchodilator $FEV_1/FVC<0.7$) among people aged over 35 years, 80% of whom had no respiratory diagnosis.(61) Overall estimates from large international prevalence surveys suggest that four out of five smokers aged over 40 years have

undiagnosed COPD.(62, 63) Although this varies by country and healthcare system it is now widely accepted that COPD remains universally underdiagnosed.

The reasons for this are multifactorial. Firstly, patients often do not recognise that their symptoms are due to an underlying disease and instead attribute them to, for example, a smoker's cough or simply old age.(64) Because of the progressive nature of COPD, patients often gradually adapt to their symptoms without necessarily consulting the health services. COPD still remains poorly understood by the general public (65) in stark contrast to conditions such as cardiovascular disease, stroke and cancer. Knowledge of COPD can often even be poor among patients with an established diagnosis.(66)

Secondly, clinicians often miss cues to the diagnosis such as presentation with recurrent respiratory symptoms and lower respiratory tract infections. A recent analysis of routine data from primary care health records in the UK by Jones and colleagues (67) suggested that opportunities to diagnose COPD were missed in 85% of patients with COPD in the five years preceding diagnosis. Missed cues included presentations to primary care with lower respiratory tract infections, and requirements for antibiotic prescriptions and chest radiography.(67) Knowledge of COPD and its management by clinicians in primary care in some areas has been poor.(68, 69)

Furthermore, limited access to high quality spirometry, which is essential for the diagnosis of COPD, has historically been highly variable (70, 71) and has resulted in both missed diagnoses as well as misdiagnosis.(72) However this is improving with increasing emphasis on training primary care staff to achieve good spirometry standards.(73) Historically there has also been a somewhat nihilistic attitude towards

COPD among clinicians.(74) This no longer justified with the current availability of evidence-based therapeutic options, particularly for improving symptoms and quality of life and potentially even reducing hospitalisations and mortality.(75) The views of clinicians in primary care on the underdiagnosis of COPD and factors influencing this have not been widely researched and will be addressed as part of this thesis.

1.9 Therapies for COPD

The UK National Institute for Health and Care Excellence (NICE) has produced comprehensive guidelines on the management of patients with COPD.(29) Below is a summary of some of the key components of care.

1.9.1 Smoking cessation

Although COPD is irreversible, there are a number of therapies that can improve symptom burden and quality of life and potentially slow disease progression. Chief among these is smoking cessation. As far back as the 1970s Fletcher and Peto demonstrated that smokers susceptible to the harmful effects of tobacco smoke who quit smoking can reduce the rate of lung function decline to that of a non-smoker.(76) Smoking cessation is also associated with a significant reduction in the risk of future hospitalisations (77) and mortality.(78)

15% of the world's population now has access to smoking cessation programmes (79) and smoking cessation services are widely available in the UK and shown to be effective at improving smoking quit rates with four week and one year quit rates of 53% and 15%, respectively.(80) Treatments for smoking cessation such as bupropion have been shown to be effective at improving quit rates in patients with

COPD.(81) The Lung Health Study which randomised 5,887 patients with mild COPD (airflow obstruction defined as pre-bronchodilator $FEV_1/FVC<0.7$ and FEV_1 55-90% of predicted) to either an intensive smoking cessation programme and inhaled anticholinergic or usual care showed a sustained smoking quit rate of 22% at 5 years and reduced age-related decline in FEV_1.(82)

A simulation modelling study based on a Dutch population estimated the cost-benefit of pharmacotherapy and intensive counselling for smoking cessation for patients with COPD to be £8490 per QALY gained,(83) which is well within the accepted incremental cost-effectiveness ratio threshold used by NICE.

1.9.2 Pulmonary rehabilitation

NICE guidelines for COPD recommend that patients who consider themselves functionally disabled by their condition, usually with MRC grade three dyspnoea or above, and those who have experienced a recent hospitalisation due to an exacerbation should be offered pulmonary rehabilitation.(29) A Cochrane review published in 2006 incorporated data from 31 RCTs that compared pulmonary rehabilitation against usual care among patients with COPD with an $FEV_1<70\%$ of predicted.(84) This concluded that pulmonary rehabilitation is significantly effective at relieving dyspnoea and fatigue, improving emotional function and enhancing patients' sense of control over their condition. Another systematic review of six RCTs for pulmonary rehabilitation following acute exacerbations of COPD suggested that it significantly reduces the risk of hospital admissions and mortality, improves disease-related quality of life and improves exercise capacity.(85) Furthermore, an economic evaluation of a multidisciplinary outpatient pulmonary rehabilitation programme showed it was likely to be cost-effective.(86) The cost-benefit of pulmonary

rehabilitation for moderate-to-severe COPD has been estimated at £13,515 per QALY gained over a ten year time horizon.(83)

1.9.3 Immunisations

Annual influenza vaccination is recommended for all patients with COPD irrespective of their severity.(29) Evidence from at least six RCTs suggest that influenza vaccination significantly reduces frequency of exacerbations compared with placebo while causing only mild and transient local adverse reactions.(87) A national cross-sectional study in England found a significant protective association between levels of influenza immunisation and COPD hospital admission rates.(88)

Pneumococcal vaccination is also recommended for all patients with COPD.(29) Streptococcus pneumoniae is a common bacterial pathogen implicated in the pathogenesis of COPD exacerbations.(89) However a Cochrane systematic review published in 2010 failed to find strong evidence from RCTs that pneumococcal vaccination protects against exacerbations, hospitalisations and mortality in patients with COPD (90) which suggests that current recommendations for pneumococcal vaccination in this patient group should re-evaluated.

1.9.4 Pharmacotherapy

A number of inhaled medications are available to treat the symptoms of COPD including short-acting beta agonists (e.g. salbutamol) and short-acting antimuscarinic antagonists (e.g. ipratropium) for treating breathless and/or exercise limitation, and long-acting beta agonists (e.g. salmeterol), long-acting antimuscarinic antagonists (e.g. tiotropium), corticosteroids (e.g. fluticasone) and combination inhalers (e.g. salmeterol and fluticasone) for treating exacerbations or persistent

breathlessness.(29) These may improve symptoms and quality of life and in some cases reduce lung function decline. For example, a large multi-centre RCT that compared a combination of inhaled fluticasone and salmeterol against either agent alone and placebo over a period of one year, among COPD patients with a baseline FEV_1 25-70% of predicted, demonstrated that those receiving the combination inhaler experienced a clinically significant improvement in health status as well as lung function and lower frequency of exacerbations relative to the comparison groups.(91, 92) Other RCTs have similarly shown clinical benefits for inhaled therapies in terms of improved symptoms and quality of life and reduced frequency of exacerbations.(93) However the evidence for the effectiveness of inhaled therapies for COPD is largely limited to patients with moderate-to-severe disease and there is little evidence for their effectiveness in patients with mild (GOLD stage I) COPD.

These treatments are likely to be cost-effective. A combination of inhaled corticosteroids and long-acting beta agonists are estimated to have an incremental cost-benefit ratio of £6519 per QALY gained.(83) Inhaled bronchodilators and corticosteroids are thus a cornerstone of COPD management in national and international guidelines.(14, 29) However pharmacotherapy for COPD is not without side effects. A recent observational analysis of an administrative health insurance database in Quebec of 163,514 patients suggested that current use of inhaled corticosteroids was associated with a 69% relative increase in the risk of serious pneumonia.(94) In addition, to-date clinical trials for inhaled therapies for COPD have failed to demonstrate reductions in mortality.

Patients with COPD may also be prescribed oral corticosteroids and antibiotics for exacerbations. Findings from three systematic reviews suggest that oral

corticosteroids improve FEV_1 and hypoxaemia as well as reduce the duration of hospitalisation following exacerbations.(95-97) Treatment with antibiotics has also been shown to reduce the risk of mortality, treatment failure and sputum purulence.(98) Finally, patients with severe COPD may be eligible for long-term oxygen therapy which has been shown to reduce the five-year relative risk of mortality by 58% in patients with severe hypoxaemia but few comorbidities.(99)

1.10 Rationale for early detection

There is a large burden of undiagnosed COPD and the majority of these individuals present with moderate-to-severe disease (GOLD stage II or worse) at the time of diagnosis.(100) They are likely to have experienced symptoms (such as breathlessness) for a considerable period of time without access to evidence-based healthcare interventions, such as pulmonary rehabilitation and inhaled therapy that would otherwise be indicated. An analysis of the Third National Health and Nutrition Examination Survey (NHANES III) in the USA showed that undiagnosed airflow obstruction (defined as pre-bronchodilator $FEV_1/FVC<0.7$ and $FEV_1<80\%$ predicted) was associated with impaired health and functional status.(101) Furthermore, patients with COPD often receive their diagnosis at the time of an emergency admission for an acute exacerbation,(102) which carries an overall inpatient mortality of 7.5%.(103) A national survey in England of COPD-related hospital admissions showed a positive association between the prevalence of undiagnosed COPD and the rate of hospitalisations.(88)

Early detection of COPD may enable timely access to appropriate care, which could help relieve symptoms, improve quality of life and reduce acute hospital admissions,

although this remains to be demonstrated empirically. Only limited evidence from a COPD-improvement programme in Finland suggested that efforts to improve the diagnosis and management of COPD may significantly reduce COPD-related hospital admissions.(104)

Smoking cessation has been shown to significantly improve the trajectory of lung function decline in smokers,(76, 105) reduce all-cause and cardiovascular mortality,(106) and reduce respiratory symptoms.(107) A diagnosis of COPD could plausibly encourage a decision to quit smoking and thus improve prognosis. However, the effect of diagnosing COPD or impaired lung function on smoking cessation has shown inconsistent results. In a COPD screening study in Poland,(108) smokers diagnosed with airflow limitation were slightly more likely to quit smoking at one year compared to smokers with normal lung function (10.1% versus 8.4%, respectively) although this difference was not statistically significant. A similar but much larger screening study that recruited over 4000 current smokers also found that subjects who were informed of their COPD diagnosis had higher smoking cessation rates at one year than those with normal lung function (16.3% versus 12.0%, $p<0.001$).(109) Similar findings were also shown in a screening study in Sweden that compared the effect of a combination of annual spirometry and brief smoking cessation advice on smoking cessation rates between smokers diagnosed with COPD and smokers without COPD (abstinence at three years 29% versus 14%, respectively).(110)

One RCT in the UK compared reporting lung age versus raw spirometry results (FEV_1) to current smokers in primary care.(111) While those who received their lung age were significantly more likely to quit smoking at 12 months (13.6% versus 6.4%,

p=0.005), subjects with worse spirometric lung age were no more likely to quit smoking than those with normal lung age. In Denmark Ulrik and colleagues (112) found that when screening patients (mostly smokers) with respiratory symptoms (dyspnoea, cough, wheeze, sputum, and/or recurrent chest infections), 50% of current smokers stated that they were not interested in quitting smoking, and this did not differ between those with and without airflow obstruction. In another RCT, Buffels and colleagues (113) randomised smokers in primary care receiving smoking cessation support to additionally receive a single spirometry assessment but found no significant difference in smoking cessation rates between both groups although this was from a relatively small sample (n=89).

While there are good intuitive reasons for detecting COPD early, it remains unclear whether doing so actually improves prognosis and reduces mortality. Prospective studies evaluating the effectiveness of early detection on reducing exacerbations, hospital admissions and mortality are currently underway (the Birmingham COPD Study), the findings of which must be reported before robust recommendations on case finding for COPD can be made.

1.11 Screening and case finding for COPD

The UK National Screening Committee (NSC) defines screening as a process of identifying apparently healthy people who may be at an increased risk of a disease or condition.(114) High risk individuals can then be offered information, diagnostic tests, and treatment to reduce risk and complications arising from the disease. Case finding is the active and systematic search for individuals at high risk of disease.(115) Both screening and case finding greatly overlap in the context of identifying undiagnosed

COPD in primary care. However they appear to have been interpreted differently in the literature with the term “screening” often being used to refer to the use of spirometry on a population-wide basis (116) and case finding to the identification of symptomatic patients for further clinical evaluation.(117) In this thesis, both terms are used synonymously since they both essentially refer to the systematic identification of high risk individuals for further diagnostic assessment (however the term “screening” will be used in the context of studies evaluating the test accuracy of screening tests such as questionnaires and handheld flow meters).

There has recently been an international drive to identify individuals with undiagnosed COPD. In the UK this was spearheaded first by the Chief Medical Officer’s annual report in 2004 (3) which emphasised the importance of early diagnosis, and later by the British Lung Foundation at the launch of its “missing millions” campaign.(118) This highlighted the huge burden of undiagnosed COPD and advocated for systematic case finding to improve patient outcomes. Case finding and early detection of COPD has been encouraged by NICE guidelines (29) and the GOLD strategy,(119) and was advocated by the UK Department of Health’s Outcomes Strategy for COPD and Asthma in England.(120)

To this end a large number of studies have evaluated the effectiveness of a variety of screening tests and approaches for COPD. In 2008 the US Preventive Service Task Force commissioned a review on screening for COPD with spirometry which concluded that this should not be recommended on the basis that hundreds of patients would need to be screened in order to prevent one exacerbation of COPD.(116) However there are a number of other approaches that could improve the efficiency of case finding such as the use of screening questionnaires,(121) a

number of which have been evaluated in prospective studies,(122-124) as well as handheld flow meters (e.g. COPD-6®).(125) The latter differ from diagnostic spirometers in that they only measure FEV_1 and FEV_6, are cheaper and quicker to administer, and are predominantly being marketed as screening devices. Other screening modalities have also been evaluated in primary care including use of peak flow meters (126) and chest radiography.(127) The efficiency of case finding may also be further enhanced through the use of risk prediction models using routine healthcare data.(128) This could potentially help to identify patients at the highest risk of undiagnosed disease based on the presence of risk factors and target those most likely to benefit from further clinical assessment. The latter approach has now been used widely for cardiovascular risk assessment (129) and is gradually being used for an increasing number of chronic conditions.(130-132)

The most efficient approach for identifying individuals with undiagnosed COPD remains unknown, which has partly formed the basis for a decision against screening made by the UK NSC.(133) In addition, it is important that case finding initiatives aim to diagnose patients with clinical disease and not those with asymptomatic airflow obstruction for whom there is uncertainty regarding treatment options.(116) NICE guidelines recommend that the diagnosis of COPD should be made in patients with relevant exposures who have respiratory symptoms and spirometric evidence of airflow limitation.(29) Current therapeutic interventions for COPD, such as inhaled bronchodilators and pulmonary rehabilitation, are largely aimed at relieving symptoms rather than improving lung function decline.(119) There have been no published RCTs evaluating interventions for patients with asymptomatic airflow obstruction. However the presence of symptoms may be difficult to elicit in the clinical

history since patients often adapt to their symptoms and therefore underestimate their impact on quality of life.(134)

In a time of increasing constraints on healthcare budgets,(135) addressing these questions will be important for developing a clinically relevant and economically sustainable pathway for timely diagnosis. Finding accurate methods for discriminating between patients with and without COPD is important to minimize harms from false positive and false negative screening tests. Evidence on which patients to target, how best to identify and reach them, and the effectiveness of using different screening and diagnostic tests is needed to provide guidance on the most efficient approach. Also, for it to be implemented in day-to-day clinical practice, the views of patients and healthcare professionals should be elicited to gain an insight into potential benefits, harms, barriers and facilitators to undertaking case finding for COPD as part of routine care. Answering these questions will be important for informing future updates of screening policy for COPD in primary care and forms the focus of this thesis.

1.12 Birmingham Lung Improvement Studies

Birmingham Lung Improvement Studies (BLISS) is an NIHR-funded research programme based at the University of Birmingham that aims to investigate COPD in primary care. One of its main studies is TargetCOPD, a cluster RCT based in the West Midlands, UK.(123) The trial recruited 54 general practices and aims to compare the effectiveness and cost-effectiveness of case finding for COPD against usual care. Within the case finding arm is an individually randomised RCT that compares opportunistic case finding by providing a respiratory questionnaire at

routine primary care visits with a more active approach in which questionnaires were additionally posted to patients. Patients reporting chronic respiratory symptoms (chronic cough or phlegm, wheeze or dyspnoea) were then invited for an assessment that included post-bronchodilator spirometry. As part of this trial, data from electronic health records were extracted to help characterise enrolled patients in terms of their demographic characteristics, comorbidities and health service use. Data from this trial has formed an important component of this thesis, which is described below.

1.13 Aims and objectives of this thesis

1. To evaluate the diagnostic accuracy of screening tests for COPD in primary care (Chapter 2).

2. To evaluate the effectiveness of alternative case finding strategies for COPD in primary care (Chapter 3).

3. To develop a prediction model to risk stratify patients for undiagnosed COPD using routine primary care data (Chapters 4 and 5).

4. To explore the views of primary healthcare providers on case finding for COPD, including the benefits, harms, barriers and facilitators (Chapter 6).

1.14 Thesis outline

Chapters 2 and 3 of this thesis consist of two linked systematic reviews. The first aims to determine the accuracy (sensitivity and specificity) of screening tests for COPD while the second addresses the effectiveness of alternative strategies for case finding in primary care. This should help policy makers, commissioners and clinicians determine how best to identify undiagnosed COPD with existing tools, help researchers identify gaps in the evidence base that should to be bridged, and help

inform the UK National Screening Committee for future policy recommendations on case finding or screening for COPD.

Chapter 4 describes the development of a prediction model and clinical score for assessing the risk of undiagnosed COPD in primary care using routine healthcare data from a large nationally representative dataset. Chapter 5 builds on this using data from a large cluster RCT of COPD case finding based in primary care (the TargetCOPD trial).(123) The objective of these prediction models is to provide primary care clinicians with tools that can help them target high risk patients for systematic case finding.

Chapter 6 explores the views of general practitioners, nurses and practice managers on case finding for COPD in order to gain an understanding of their current practices, their attitudes towards case finding, and identify barriers and facilitators that may affect its implementation in real life practice.

The findings of these chapters and their clinical implications are then summarised and discussed in Chapter 7.

1.15 References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
2. GBD Compare Washington: Institute for Health Metrics and Evaluation; 2014 [cited 2014 09/10/2014]. Available from: http://www.healthdata.org/results/data-visualizations.
3. Donaldson L. Annual report of the chief medical officer on the state of public health. London: Department of Health, 2004.
4. COPD Prevalence Estimates Dec 2011: Public Health England; 2011 [cited 2014 06.12.2014]. Available from: http://www.apho.org.uk/resource/item.aspx?RID=111122.
5. Bednarek M, Maciejewski J, Wozniak M, Kuca P, Zielinski J. Prevalence, severity and underdiagnosis of COPD in the primary care setting. Thorax. 2008;63(5):402-7.
6. Garcia-Aymerich J, Farrero E, Felez MA, Izquierdo J, Marrades RM, Anto JM, et al. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. Thorax. 2003;58(2):100-5.
7. Yohannes AM, Roomi J, Waters K, Connolly MJ. Quality of life in elderly patients with COPD: measurement and predictive factors. Resp Med. 1998;92(10):1231-6.
8. WHO framework convention on tobacco control. J Adv Nurs. 2004;48(5):541-.
9. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality - Extended follow-up of the Harvard six cities study. Am J Resp Crit Care. 2006;173(6):667-72.
10. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007;370(9589):741-50.
11. Global Strategy for the Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2011.
12. Haroon S, Adab P, Griffin C, Jordan R. Case finding for chronic obstructive pulmonary disease in primary care: a pilot randomised controlled trial. Brit J Gen Pract. 2013;63(606).
13. Birmingham Lung Improvement Studies Birmingham: University of Birmingham; 2014 [cited 2014 10/10/2014]. Available from: http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/BLISS/index.aspx.
14. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease, 2013.
15. Vestbo J, Agusti A, Wouters EFM, Bakke P, Calverley PMA, Celli B, et al. Should We View Chronic Obstructive Pulmonary Disease Differently after ECLIPSE? A Clinical Perspective from the Study Team. Am J Resp Crit Care. 2014;189(9):1022-30.
16. Hogg JC, Timens W. The Pathology of Chronic Obstructive Pulmonary Disease. Annu Rev Pathol-Mech. 2009;4:435-59.
17. Mclean KH. The Pathogenesis of Pulmonary Emphysema. Am J Med. 1958;25(1):62-74.
18. Thurlbeck WM, Angus GE. Relationship between Emphysema and Chronic Bronchitis as Assessed Morphologically. Am Rev Respir Dis. 1963;87(6):815-&.
19. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it? Thorax. 2009;64(8):728-35.
20. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and Risk of Mortality in Patients with Chronic Obstructive Pulmonary Disease. Am J Resp Crit Care. 2012;186(2):155-61.
21. Miller J, Edwards LD, Agusti A, Bakke P, Calverley PM, Celli B, et al. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. Respiratory medicine. 2013;107(9):1376-84.
22. Agusti AG, Noguera A, Sauleda J, Sala E, Pons J, Busquets X. Systemic effects of chronic obstructive pulmonary disease. Eur Respir J. 2003;21(2):347-60.
23. Wedzicha JA, Brill SE, Allinson JP, Donaldson GC. Mechanisms and impact of the frequent exacerbator phenotype in chronic obstructive pulmonary disease. BMC medicine. 2013;11:181.
24. Wedzicha JA, Donaldson GC. Exacerbations of chronic obstructive pulmonary disease. Respiratory care. 2003;48(12):1204-13; discussion 13-5.
25. Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. The American review of respiratory disease. 1993;147(5):1151-6.
26. Wust RC, Degens H. Factors contributing to muscle wasting and dysfunction in COPD patients. International journal of chronic obstructive pulmonary disease. 2007;2(3):289-300.

27. Hanania NA, Mullerova H, Locantore NW, Vestbo J, Watkins ML, Wouters EF, et al. Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort. American journal of respiratory and critical care medicine. 2011;183(5):604-11.
28. Eisner MD, Iribarren C, Blanc PD, Yelin EH, Ackerson L, Byl N, et al. Development of disability in chronic obstructive pulmonary disease: beyond lung function. Thorax. 2011;66(2):108-14.
29. Chronic obstructive pulmonary disease : management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Institute for Health and Clinical Excellence; 2010.
30. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. The American review of respiratory disease. 1991;144(5):1202-18.
31. Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Morkve O. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. Eur Respir J. 2002;20(5):1117-22.
32. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-68.
33. Bakke PS, Ronmark E, Eagan T, Pistelli F, Annesi-Maesano I, Maly M, et al. Recommendations for epidemiological studies on COPD. European Respiratory Journal. 2011;38(6):1261-77.
34. Lindberg A, Jonsson AC, Ronmark E, Lundgren R, Larsson LG, Lundback B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Chest. 2005;127(5):1544-52.
35. Lindberg A, Eriksson B, Larsson LG, Ronmark E, Sandstrom T, Lundback B. Seven-year cumulative incidence of COPD in an age-stratified general population sample. Chest. 2006;129(4):879-85.
36. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et al. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. American journal of respiratory and critical care medicine. 2003;167(5):787-97.
37. Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Loft S, Sorensen M, et al. Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study. American journal of respiratory and critical care medicine. 2011;183(4):455-61.
38. Berglund DJ, Abbey DE, Lebowitz MD, Knutsen SF, McDonnell WF. Respiratory symptoms and pulmonary function in an elderly nonsmoking population. Chest. 1999;115(1):49-59.
39. Hu G, Zhou Y, Tian J, Yao W, Li J, Li B, et al. Risk of COPD from exposure to biomass smoke: a metaanalysis. Chest. 2010;138(1):20-31.
40. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2010;182(5):693-718.
41. Turner-Stokes L, Turton C, Pope FM, Green M. Emphysema and cutis laxa. Thorax. 1983;38(10):790-2.
42. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. The lancet Respiratory medicine. 2013;1(9):728-42.
43. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D, et al. Early life origins of chronic obstructive pulmonary disease. Thorax. 2010;65(1):14-20.
44. Gershon AS, Warner L, Cascagnette P, Victor JC, To T. Lifetime risk of developing chronic obstructive pulmonary disease: a longitudinal population study. Lancet. 2011;378(9795):991-6.
45. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-223.
46. Johannessen A, Omenaas E, Bakke P, Gulsvik A. Incidence of GOLD-defined chronic obstructive pulmonary disease in a general adult population. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2005;9(8):926-32.
47. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J. 2006;28(3):523-32.
48. Han MK, Postma D, Mannino DM, Giardino ND, Buist S, Curtis JL, et al. Gender and chronic obstructive pulmonary disease: why it matters. American journal of respiratory and critical care medicine. 2007;176(12):1179-84.
49. HESonline: Hospital Episode Statistics: Health and Social Care Information Centre (HSCIC); 2012 [cited 2014 22/04/2014]. Available from: http://www.hscic.gov.uk/searchcatalogue?productid=9161&q=chronic+obstructive+pulmonary+disease&topics=1%2fHospital+care%2fAdmissions+and+attendances&sort=Relevance&size=10&page=1#top.
50. Britton M. The burden of COPD in the U.K.: results from the Confronting COPD survey. Respiratory medicine. 2003;97 Suppl C:S71-9.

51. Wouters EF. Economic analysis of the Confronting COPD survey: an overview of results. Respiratory medicine. 2003;97 Suppl C:S3-14.
52. Fletcher MJ, Upton J, Taylor-Fishwick J, Buist SA, Jenkins C, Hutton J, et al. COPD uncovered: an international survey on the impact of chronic obstructive pulmonary disease [COPD] on a working age population. BMC public health. 2011;11:612.
53. Janson C, Marks G, Buist S, Gnatiuc L, Gislason T, McBurnie MA, et al. The impact of COPD on health status: findings from the BOLD study. Eur Respir J. 2013;42(6):1472-83.
54. Miravitlles M, Soriano JB, Garcia-Rio F, Munoz L, Duran-Tauleria E, Sanchez G, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. Thorax. 2009;64(10):863-8.
55. Gore JM, Brophy CJ, Greenstone MA. How well do we care for patients with end stage chronic obstructive pulmonary disease (COPD)? A comparison of palliative care and quality of life in COPD and lung cancer. Thorax. 2000;55(12):1000-6.
56. Menezes AM, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, Valdivia G, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet. 2005;366(9500):1875-81.
57. de Marco R, Accordini S, Cerveri I, Corsico A, Anto JM, Kunzli N, et al. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. American journal of respiratory and critical care medicine. 2007;175(1):32-9.
58. Quality and Outcomes Framework- 2011-12, England level: Clinical domain, chronic obstructive pulmonary disease data tables: Health and Social Care Information Centre; 2013 [cited 2013 29/10/2013]. Available from: http://www.hscic.gov.uk/searchcatalogue?productid=9548&q=qof&topics=0%2fPrimary+care+services&sort=Relevance&size=10&page=1#top.
59. 2011 Census, population estimates by single year of age and sex for local authorities in the United Kingdom: Office for National Statistics; 2013 [cited 2013 12/12/2013]. Available from: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-294277.
60. Jordan RE, Lam KB, Cheng KK, Miller MR, Marsh JL, Ayres JG, et al. Case finding for chronic obstructive pulmonary disease: a model for optimising a targeted approach. Thorax. 2010;65(6):492-8.
61. Shahab L, Jarvis M, Britton J, West R. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. Thorax. 2006;61(12):1043 - 7.
62. Soriano JB, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. Lancet. 2009;374(9691):721-32.
63. Talamo C, de Oca MM, Halbert R, Perez-Padilla R, Jardim JR, Muino A, et al. Diagnostic labeling of COPD in five Latin American cities. Chest. 2007;131(1):60-7.
64. Fromer L. Diagnosing and treating COPD: understanding the challenges and finding solutions. International journal of general medicine. 2011;4:729-39.
65. Kesten S, Ulrich J, Rich D. PUblic awareness of chronic obstructive pulmonary disease. CHEST Journal. 2003;124(4_MeetingAbstracts):167S-S.
66. Hernandez P, Balter M, Bourbeau J, Hodder R. Living with chronic obstructive pulmonary disease: a survey of patients' knowledge and attitudes. Respiratory medicine. 2009;103(7):1004-12.
67. Jones RC, Price D, Ryan D, Sims EJ, von Ziegenweidt J, Mascarenhas L, et al. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. The lancet Respiratory medicine. 2014;2(4):267-76.
68. Yawn BP, Wollan PC. Knowledge and attitudes of family physicians coming to COPD continuing medical education. International journal of chronic obstructive pulmonary disease. 2008;3(2):311-7.
69. Rutschmann OT, Janssens JP, Vermeulen B, Sarasin FP. Knowledge of guidelines for the management of COPD: a survey of primary care physicians. Respiratory medicine. 2004;98(10):932-7.
70. Eaton T, Withy S, Garrett JE, Mercer J, Whitlock RM, Rea HH. Spirometry in primary care practice: the importance of quality assurance and the impact of spirometry workshops. Chest. 1999;116(2):416-23.
71. Levy ML, Quanjer PH, Booker R, Cooper BG, Holmes S, Small I, et al. Diagnostic spirometry in primary care: Proposed standards for general practice compliant with American Thoracic Society and European Respiratory Society recommendations: a General Practice Airways Group (GPIAG)1 document, in association with the Association for Respiratory Technology & Physiology (ARTP)2 and Education for Health3 1 www.gpiag.org 2 www.artp.org 3 www.educationforhealth.org.uk. Prim Care Respir J. 2009;18(3):130-47.

72. Tinkelman DG, Price DB, Nordyke RJ, Halbert RJ. Misdiagnosis of COPD and asthma in primary care patients 40 years of age and over. The Journal of asthma : official journal of the Association for the Care of Asthma. 2006;43(1):75-80.
73. The Lancet Respiratory M. Primary care at the heart of respiratory medicine in the UK. The Lancet Respiratory Medicine. 2014;2(2):83.
74. van der Palen J, Monninkhof E, van der Valk P, Visser A. Managing COPD: no more nihilism! Patient education and counseling. 2004;52(3):221-3.
75. Celli BR. Chronic obstructive pulmonary disease: from unjustified nihilism to evidence-based optimism. Proceedings of the American Thoracic Society. 2006;3(1):58-65.
76. Fletcher C, Peto R. The natural history of chronic airflow obstruction. British medical journal. 1977;1(6077):1645-8.
77. Godtfredsen NS, Vestbo J, Osler M, Prescott E. Risk of hospital admission for COPD following smoking cessation and reduction: a Danish population study. Thorax. 2002;57(11):967-72.
78. Godtfredsen NS, Lam TH, Hansel TT, Leon ME, Gray N, Dresler C, et al. COPD-related morbidity and mortality after smoking cessation: status of the evidence. European Respiratory Journal. 2008;32(4):844-53.
79. Carter B, Hood K. Balance algorithm for cluster randomised trials. BMC Med Res Methodol. 2008;8:65.
80. Bauld L, Bell K, McCullough L, Richardson L, Greaves L. The effectiveness of NHS smoking cessation services: a systematic review. Journal of public health. 2010;32(1):71-82.
81. Tashkin DP, Kanner R, Bailey W, Buist S, Anderson P, Nides MA, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. The Lancet. 2001;357(9268):1571-5.
82. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of fev1: The lung health study. JAMA. 1994;272(19):1497-505.
83. Hoogendoorn M, Rutten-van Molken MP, Hoogenveen RT, Al MJ, Feenstra TL. Developing and applying a stochastic dynamic population model for chronic obstructive pulmonary disease. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011;14(8):1039-47.
84. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2006(4):CD003793.
85. Puhan MA, Scharplatz M, Troosters T, Steurer J. Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality – a systematic review. Respiratory Research. 2005;6(1):54-.
86. Griffiths TL, Phillips CJ, Davies S, Burr ML, Campbell IA. Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. Thorax. 2001;56(10):779-84.
87. Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2006(1):CD002733.
88. Calderon-Larranaga A, Carney L, Soljak M, Bottle A, Partridge M, Bell D, et al. Association of population and primary healthcare factors with hospital admission rates for chronic obstructive pulmonary disease in England: national cross-sectional study. Thorax. 2011;66(3):191-6.
89. Sethi S. INfectious etiology of acute exacerbations of chronic bronchitis*. Chest. 2000;117(5_suppl_2):380S-5S.
90. Walters JA, Smith S, Poole P, Granger RH, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2010(11):Cd001390.
91. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2003;361(9356):449-56.
92. Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. American journal of respiratory and critical care medicine. 2008;178(4):332-8.
93. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. The New England journal of medicine. 2008;359(15):1543-54.
94. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax. 2013;68(11):1029-36.
95. McCrory DC, Brown C, Gray RN, Goslin RE, Kolimaga JT, MacIntyre NR, et al. Management of acute exacerbations of chronic obstructive pulmonary disease. Evidence report/technology assessment. 2000(19):1-4.

96. Wood-Baker R, Walters EH, Gibson P. Oral corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2001(2):CD001288.
97. Singh JM, Palda VA, Stanbrook MB, Chapman KR. Corticosteroid therapy for patients with acute exacerbations of chronic obstructive pulmonary disease: a systematic review. Arch Intern Med. 2002;162(22):2527-36.
98. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2006(2):CD004403.
99. Crockett AJ, Cranston JM, Moss JR, Alpers JH. A review of long-term oxygen therapy for chronic obstructive pulmonary disease. Respiratory medicine. 2001;95(6):437-43.
100. Mapel DW, Dalal AA, Blanchette CM, Petersen H, Ferguson GT. Severity of COPD at initial spirometry-confirmed diagnosis: data from medical charts and administrative claims. Int J Chronic Obstr. 2011;6:573-81.
101. Coultas DB, Mapel D, Gagnon R, Lydick E. The health impact of undiagnosed airflow obstruction in a national sample of United States adults. American journal of respiratory and critical care medicine. 2001;164(3):372-7.
102. Bastin AJ, Starling L, Ahmed R, Dinham A, Hill N, Stern M, et al. High prevalence of undiagnosed and severe chronic obstructive pulmonary disease at first hospital admission with acute exacerbation. Chronic respiratory disease. 2010;7(2):91-7.
103. Myint PK, Lowe D, Stone RA, Buckingham RJ, Roberts CM. U.K. National COPD Resources and Outcomes Project 2008: patients with chronic obstructive pulmonary disease exacerbations who present with radiological pneumonia have worse outcome compared to those with non-pneumonic chronic obstructive pulmonary disease exacerbations. Respiration. 2011;82(4):320-7.
104. Kinnula VL, Vasankari T, Kontula E, Sovijarvi A, Saynajakangas O, Pietinalho A. The 10-year COPD Programme in Finland: effects on quality of diagnosis, smoking, prevalence, hospital admissions and mortality. Prim Care Respir J. 2011;20(2):178-83.
105. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. American journal of respiratory and critical care medicine. 2000;161(2 Pt 1):381-90.
106. Pelkonen M, Tukiainen H, Tervahauta M, Notkola IL, Kivela SL, Salorinne Y, et al. Pulmonary function, smoking cessation and 30 year mortality in middle aged Finnish men. Thorax. 2000;55(9):746-50.
107. Kanner RE, Connett JE, Williams DE, Buist AS. Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: the Lung Health Study. The American journal of medicine. 1999;106(4):410-6.
108. Gorecka D, Bednarek M, Nowinski A, Puscinska E, Goljan-Geremek A, Zielinski J. Diagnosis of airflow limitation combined with smoking cessation advice increases stop-smoking rate. Chest. 2003;123(6):1916-23.
109. Bednarek M, Gorecka D, Wielgomas J, Czajkowska-Malinowska M, Regula J, Mieszko-Filipczyk G, et al. Smokers with airway obstruction are more likely to quit smoking. Thorax. 2006;61(10):869-73.
110. Stratelis G, Molstad S, Jakobsson P, Zetterstrom O. The impact of repeated spirometry and smoking cessation advice on smokers with mild COPD. Scandinavian journal of primary health care. 2006;24(3):133-9.
111. Parkes G, Greenhalgh T, Griffin M, Dent R. Effect on smoking quit rate of telling patients their lung age: the Step2quit randomised controlled trial. BMJ. 2008;336(7644):598-600.
112. Ulrik CS, Lokke A, Dahl R, Dollerup J, Hansen G, Cording PH, et al. Early detection of COPD in general practice. International journal of chronic obstructive pulmonary disease. 2011;6:123-7.
113. Buffels J, Degryse J, Decramer M, Heyrman J. Spirometry and smoking cessation advice in general practice: a randomised clinical trial. Respiratory medicine. 2006;100(11):2012-7.
114. UK Screening Portal London: Public Health England; 2014 [cited 2014 06.12.2014]. Available from: http://www.screening.nhs.uk/screening.
115. Differences between screening, diagnostic tests, and case finding Buckinghamshire: Public Health Action Support Team; 2014 [cited 2014 06.12.2014]. Available from: http://www.healthknowledge.org.uk/public-health-textbook/disease-causation-diagnostic/2c-diagnosis-screening/screening-diagnostic-case-finding.
116. Lin K, Watkins B, Johnson T, Rodriguez JA, Barton MB, Force USPST. Screening for chronic obstructive pulmonary disease using spirometry: summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;148(7):535-43.
117. Jordan R, Lam K-B, Cheng K, Miller M, Marsh J, Ayres J, et al. Case finding for chronic obstructive pulmonary disease: a model for optimizing a targeted approach. Thorax. 2010;65:492 - 8.

118. Invisible lives: chronic obstructive pulmonary disease (COPD) — finding the missing millions. London: British Lung Foundation, 2007.
119. Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, managment, and prevention of chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease, 2013.
120. An outcomes strategy for people with chronic obstructive pulmonary disease (COPD) and asthma in England London: Department of Health; 2011 [cited 2013 29/10/2013]. Available from: https://www.gov.uk/government/publications/an-outcomes-strategy-for-people-with-chronic-obstructive-pulmonary-disease-copd-and-asthma-in-england.
121. van Schayck CP, Halbert RJ, Nordyke RJ, Isonaka S, Maroni J, Nonikov D. Comparison of existing symptom-based questionnaires for identifying COPD in the general practice setting. Respirology. 2005;10(3):323-33.
122. Price DB, Tinkelman DG, Halbert RJ, Nordyke RJ, Isonaka S, Nonikov D, et al. Symptom-based questionnaire for identifying COPD in smokers. Respiration. 2006;73(3):285-95.
123. Jordan R, Adab P, Jowett S, Marsh J, Riley R, Enocson A, et al. TargetCOPD: a pragmatic randomised controlled trial of targeted case finding for COPD versus routine practice in primary care: protocol. BMC Pulmonary Medicine. 2014;14(1):157.
124. Hanania NA, Mannino DM, Yawn BP, Mapel DW, Martinez FJ, Donohue JF, et al. Predicting risk of airflow obstruction in primary care: Validation of the lung function questionnaire (LFQ). Respiratory medicine. 2010;104(8):1160-70.
125. Thorn J, Tilling B, Lisspers K, Jorgensen L, Stenling A, Stratelis G. Improved prediction of COPD in at-risk patients using lung function pre-screening in primary care: a real-life study and cost-effectiveness analysis. Prim Care Respir J. 2012;21(2):159-66.
126. Perez-Padilla R, Vollmer WM, Vázquez-García JC, Enright PL, Menezes AMB, Buist AS. Can a normal peak expiratory flow exclude severe chronic obstructive pulmonary disease? The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2009;13(3):387-93.
127. Chuaychoo B, Maranetra N, Lertakyamanee J, Naruman C, Dejsomritrutai W, Tongdee T, et al. The cost-effectiveness of chest radiography as a screening test for chronic obstructive pulmonary disease among the Bangkok elderly. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2003;86(11):1042-50.
128. Mapel D, Frost F, Hurly J, Petersen H, Roberts M, Marton J, et al. An algorithm for the identification of undiagnsoed COPD cases using administrative claims data. J Manag Care Pharm. 2006;12(6):458 - 65.
129. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008;336(7659):1475-82.
130. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX™ and the assessment of fracture probability in men and women from the UK. Osteoporosis International. 2008;19(4):385-97.
131. Collins GS, Altman DG. Identifying patients with undetected colorectal cancer: an independent validation of QCancer (Colorectal). British Journal of Cancer. 2012;107(2):260-5.
132. Abbasi A, Peelen LM, Corpeleijn E, van der Schouw YT, Stolk RP, Spijkerman AMW, et al. Prediction models for risk of developing type 2 diabetes: systematic literature search and independent external validation study2012 2012-09-18 10:49:34.
133. Cartwright S. An evaluation of screening for COPD against the National Screening Committee criteria. 2012.
134. Rennard S, Decramer M, Calverley PM, Pride NB, Soriano JB, Vermeire PA, et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. Eur Respir J. 2002;20(4):799-805.
135. Vize R. Reality of the NHS budget squeeze. BMJ. 2011;343.

CHAPTER 2: DIAGNOSTIC ACCURACY OF SCREENING TESTS FOR COPD: A SYSTEMATIC REVIEW AND META-ANALYSIS

This chapter is based on a published systematic review protocol: Haroon S, Adab PA, Jordan RE. Case finding for COPD in primary care: a systematic review (protocol). Primary Care Respiratory Journal. 2012: 21(3):354-7.

2.1 Abstract

Background

COPD is widely under-diagnosed. A number of studies have evaluated the accuracy of screening tests for COPD but their findings have not been formally summarised. This review aims to determine and compare the diagnostic accuracy of screening tests for COPD in primary care.

Methods

Systematic review and meta-analysis of the diagnostic accuracy of screening tests for COPD confirmed by spirometry in primary care. Medline, Embase, and other bibliographic databases were searched from 1997 to 2013 for diagnostic accuracy studies that evaluated one or more index tests in primary care among individuals aged ≥35 years with no prior diagnosis of COPD. Bivariate meta-analysis of sensitivity and specificity was performed where appropriate. Methodological quality was assessed independently by two reviewers using the QUADAS-2 tool.

Results

Ten studies were included. Eight assessed screening questionnaires (the COPD Diagnostic Questionnaire [CDQ] was the most evaluated, n=4), four assessed handheld flow meters (e.g. COPD-6®), and one assessed their combination. Post-bronchodilator spirometry was used as the reference standard in all studies included in the meta-analyses. Among ever smokers the CDQ (score threshold ≥19.5; n=4) had a pooled sensitivity of 64.5% (95% CI 59.9% to 68.8%) and specificity 65.2% (52.9 to 75.8%), and handheld flow meters (n=3) had a sensitivity of 79.9% (95% CI 74.2% to 84.7%) and specificity 84.4% (68.9 to 93.0%). Inadequate blinding between index tests and spirometry was the main risk of bias.

Conclusions

Handheld flow meters demonstrated higher test accuracy than the CDQ for COPD screening in primary care. However there is a need for high quality studies directly comparing screening tests for COPD, that use a clinical rather than just a physiological definition of COPD.

2.2 Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death,(1) ranks ninth for lost disability adjusted life years,(2) and is an important cause of healthcare expenditure.(3) Despite this, as much as 50-90% of the disease burden remains undiagnosed.(4) Patients often under-recognise the significance of respiratory symptoms,(5) and clinicians frequently miss opportunities to diagnose COPD at primary care consultations.(6) Early detection may offer opportunities to reduce disease progression and improve quality of life, for example through smoking cessation interventions (7) and pulmonary rehabilitation.(8)

There is now a policy drive to identify undiagnosed COPD.(8-11) However, a systematic review of spirometric screening concluded that this should not be recommended, partly because it estimated that hundreds of smokers would need to be screened to prevent a single COPD exacerbation.(12) Furthermore this approach could potentially identify asymptomatic individuals with airflow obstruction, who would not meet the clinical criteria for COPD according to current guidelines.(11) A number of studies have evaluated the diagnostic accuracy of a variety of other screening tests and approaches, which are likely to be more efficient than performing spirometry on all high risk individuals.(13, 14) However the findings of these studies have not been systematically reviewed and quantitatively synthesised. Although one narrative review (15) compared existing symptom-based questionnaires, it did not include other screening tests and needs updating.

This is a systematic review and meta-analysis of published studies that summarises and compares the accuracy of screening tests for COPD in primary care.

2.3 Methods

2.3.1 Protocol and registration

The protocol for this review was previously published (16) and registered.(17)

2.3.2 Eligibility criteria

Diagnostic accuracy studies were sought, of any design that evaluated one or more index tests, were conducted in primary care (including general practices and community pharmacies), and recruited individuals aged ≥35 years with no prior diagnosis of COPD. Index tests included screening questionnaires, handheld flow meters (e.g. Piko-6® or COPD-6®), peak flow meters, chest radiography, and risk prediction models or decision aids, either alone or in combination. Studies were only included if they used pre- or post-bronchodilator spirometry as the reference test and specified the target condition as COPD, defined by the presence of airflow obstruction using diagnostic criteria from internationally/nationally accepted standards (although studies were ideally sought that used a clinical definition of COPD, requiring both relevant symptoms [e.g. dyspnoea, cough, sputum production, wheeze] and airflow obstruction).

2.3.3 Outcomes

The primary outcome was identification of COPD, defined by the presence of pre- or post-bronchodilator airflow obstruction. The main measures of test accuracy examined were sensitivity and specificity.

2.3.4 Search strategy

The following databases were searched from March/April 2012 for the previous 15 years: Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials,

Table 2.1 Search terms

Disease	AND	Index test
Chronic obstructive pulmonary disease		Case finding
OR		**OR**
Chronic obstructive airways disease		Screening
OR		**OR**
Chronic obstructive lung disease		Early detection
OR		**OR**
COPD		Secondary prevention
OR		**OR**
COAD		Spirometry
OR		**OR**
Emphysema		Questionnaire
OR		**OR**
Chronic bronchitis		Peak flow
OR		**OR**
Airflow obstruction		Chest X-ray
OR		**OR**
Airflow limitation		Decision aid
		OR
		Algorithm
		OR
		Sensitivity
		OR
		Specificity

and the Health Technology Database. An updated search was performed on Medline and Embase up to December 2013. Searches limited to the first 100 articles were also performed on Google Scholar, Turning Research into Practice, HTAi VORTAL and DogPile, and selected conference abstracts for the previous two years. Search terms (Table 2.1) included Medical Subject Heading terms and free text synonyms for COPD, screening tests and measures of test accuracy, with no language restrictions.

2.3.5 Study selection and data extraction

Titles and abstracts were screened independently by two reviewers. Relevant full text articles were independently assessed for eligibility by two reviewers and disagreements resolved through discussion. Pre-specified data were extracted from full text articles by one reviewer and verified by a second. The number of true positives, false positives, true negatives and false negatives were extracted for

construction of two-by-two contingency tables. Where these data were not provided, reported measures of test accuracy were used to derive these values.

2.3.6 Risk of bias assessment

Included studies were assessed independently by two reviewers for risk of methodological bias and applicability concerns against criteria from the QUADAS-2 tool.(18) Disagreements were resolved through discussion.

2.3.7 Statistical analysis

Forest plots of sensitivity and specificity were constructed using Review Manager (RevMan) version 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). These plots were used to visually explore between-study variation in the diagnostic accuracy of each test. Differences in population screened, screening test, diagnostic criteria, and study design were also explored.

Where there was sufficient clinical and methodological homogeneity, the *xtmelogit* command was used in Stata version 13.1 (Stata-Corp, College Station, Texas, USA) to fit the bivariate model (19, 20) to derive summary estimates of sensitivity and specificity and their 95% confidence intervals. If there were fewer than four studies, the bivariate model was simplified to two univariate random effects logistic regression models for sensitivity and specificity by assuming no correlation between both measures. Two approaches were used to compare the diagnostic accuracy of the screening tests. First, all relevant studies were used that evaluated one or more tests, and second, the analysis was restricted to studies that made direct (head-to-head) comparisons. Where meta-analysis was possible, tests were compared by

adding a covariate for test type to the bivariate model to assess whether average sensitivity and/or specificity differed between the tests.

Positive and negative predictive values (PPV and NPV) were estimated from the sensitivity and specificity of each test, assuming a prevalence of undiagnosed COPD of 5.5% (21) in a hypothetical population of 1000 patients aged ≥40 years. The number-needed-to-screen (NNS) to identify one individual with COPD was estimated as the total number screened divided by the number of true positives, and the number of diagnostic assessments needed (NND) as the reciprocal of the PPV.

2.4 Results

2.4.1 Study selection

The stages of study selection are shown in Figure 2.1. After excluding duplicates the search yielded 2605 records. From these, full text articles were retrieved for 266 studies. Ten studies met the inclusion criteria, and five were suitable for meta-analysis (since these were sufficiently similar with respect to the included population, screening tests, and definition of COPD). Figure 2.1 lists the reasons for excluding articles, the most common of which was the inclusion of patients with previously known COPD.

2.4.2 Study characteristics

Characteristics of included studies are summarised in Tables 2.2 and 2.3 (see Tables S2.1-2.3 for details of each study). All were cross-sectional test accuracy studies, of which two used a paired design to compare two screening tests (screening questionnaires and handheld flow meters).(14, 22) Nine studies were multicentre and all were based in general practices.

2.4.3 Recruitment and population selection

Four studies opportunistically recruited patients routinely attending primary care, three actively recruited participants through postal invitations or local advertisements, two used a combination of both strategies, and one study did not report the method of recruitment.(23) All studies specified age in the inclusion criteria with most requiring subjects to be over 40 years. Seven studies also required a positive smoking history but only one required participants to report respiratory symptoms as

part of the entry criteria.(24) The main exclusion criterion was an established history of lung disease.

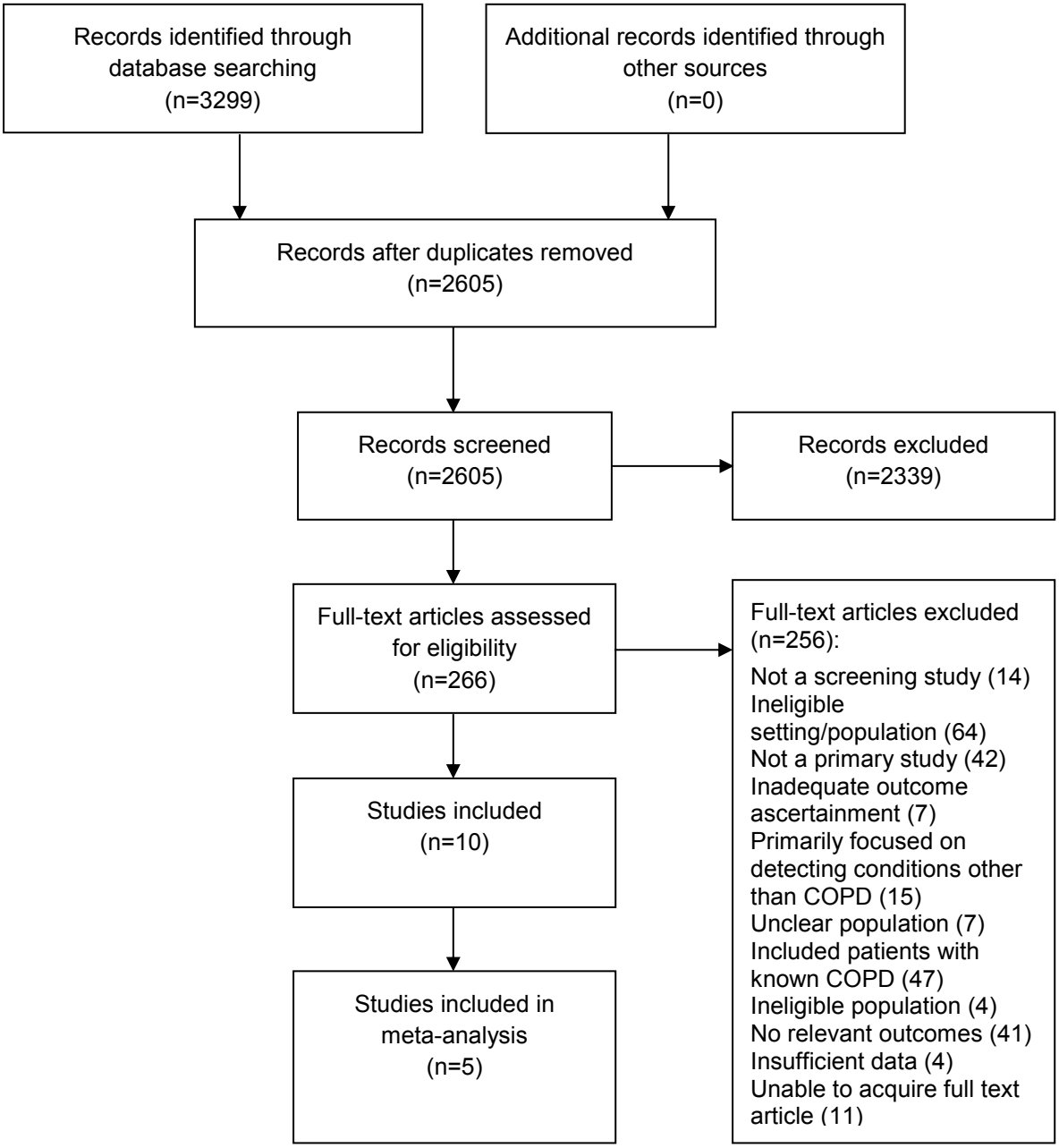

Figure 2.1 Study selection

Table 2.2 Characteristics of studies evaluating screening questionnaires (8 studies) (13, 14, 22-27)

Characteristic		Range/no. of studies
Study designs	Cross-sectional test accuracy	8
Participants		237-3158
Mean age (years)		52.3-65.3
Male (%)		38.1-69.0
Required smoking status:	Only current/ex-smokers	5
	Included never smokers	3
Required respiratory symptoms		1
Setting	General practice(s)	8
Number of centres		1-36
	Multicentre	7
	Single centre	1
Recruitment strategy	Active	2
	Opportunistic	3
	Active & opportunistic	2
	Not reported	1
Questionnaires	COPD Diagnostic Questionnaire*	4
	Lung Function Questionnaire	2
	Not named	2
Common items		
	Age	7
	Smoking status	7
	Respiratory symptoms	8
	Allergies	5
Reference test- spirometry		
Post-bronchodilator		6
Definition of AO	Post-BD FEV_1/FVC<0.7	7
	Other**	1
Included symptoms in definition of COPD		1
Spirometry quality control	Yes	8
Range of results		
Sensitivity		57-93%
Specificity		24-80%
Severity of new COPD cases	≥80%	11-39%
(FEV_1 % predicted)* **	50-80%	43-61%
	<50%	10-37%

AO=airflow obstruction, BD=bronchodilator, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity

*Also referred to as the Respiratory Health Screening Questionnaire and the International Primary Airways Group (IPAG) questionnaire

**Pre-BD FEV_1/FVC<88.5% predicted for men & FEV_1/FVC<89.3% for women

***Based on 5 studies

Table 2.3 Characteristics of studies evaluating handheld flow meters (4 studies) (14, 22, 28, 29)

Characteristic		Range/no. of studies
Study designs	Cross-sectional test accuracy study	4
Participants		305-2464
Mean age (years)		52.0-65.3
Male (%)		43.3-99.7
Required smoking status	Only current/ex-smokers	3
	Included never smokers	1
Required respiratory symptoms		0
Setting	General practice(s)	4
Number of centres		4-25
	Multicentre	4
Recruitment strategy	Active	1
	Opportunistic	2
	Active & opportunistic	1
Handheld flow meter		
Device	Piko-6®	3
	COPD-6®	1
Operator	Nurse	2
	GP	1
	Not reported	1
Use of bronchodilator	Pre-bronchodilator	3
	Post-bronchodilator	1
Test threshold	$FEV_1/FEV_6<$	0.70-0.75
Reference test- spirometry		
Post-bronchodilator		4
Definition of AO	Post-BD $FEV_1/FVC<0.7$	4
Included symptoms in definition of COPD		0
Spirometry quality control	Yes	2
	No	1
	Unclear	1
Range of results		
Sensitivity		79-86%
Specificity		71-99%
Severity of new COPD cases	≥80%	35-48%
(FEV_1 % predicted)	50-80%	48-65%
	<50%	0-16%

AO= airflow obstruction, BD=bronchodilator, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, RCT=randomised controlled trial

2.4.4 Index and reference tests

All studies first applied one or more index tests to the eligible population and then performed the reference test (spirometry) on either all (n=8 studies) or a random sample (25, 28) (n=2) of subjects. Index tests included screening questions or questionnaires (n=8) and handheld flow meters (n=4). One study also assessed the combined accuracy of using a screening questionnaire sequentially with a handheld flow meter.(14) No studies evaluating other screening tests met the inclusion criteria.

2.4.5 Reference standard

Pre- and post-bronchodilator spirometry was the reference standard in two (25, 27) and eight studies, respectively. Most studies sufficiently described spirometry and quality control procedures. Spirometry was performed by trained technicians (n=4), GPs (n=1), pulmonary physicians (n=1) and nurses (n=2), while quality control was usually performed by a respiratory specialist or physiologist who reviewed spirometry results.

2.4.6 Methodological quality

Most studies gave a clear description of participants, index and reference tests, and diagnostic criteria (Figure 2.2 and Table S2.4). However there was often underreporting of withdrawals (n=4), participant flow diagrams (n=5), and uninterpretable spirometry tests (n=5). The main risk of bias arose from inadequate blinding between index and reference tests (n=7; Figures 2.3 and 2.4). There was also potential for bias in the flow and timing domain (n=5), where the number of participants undergoing index and reference tests was unclear, and where significant numbers of participants were excluded from the analysis.

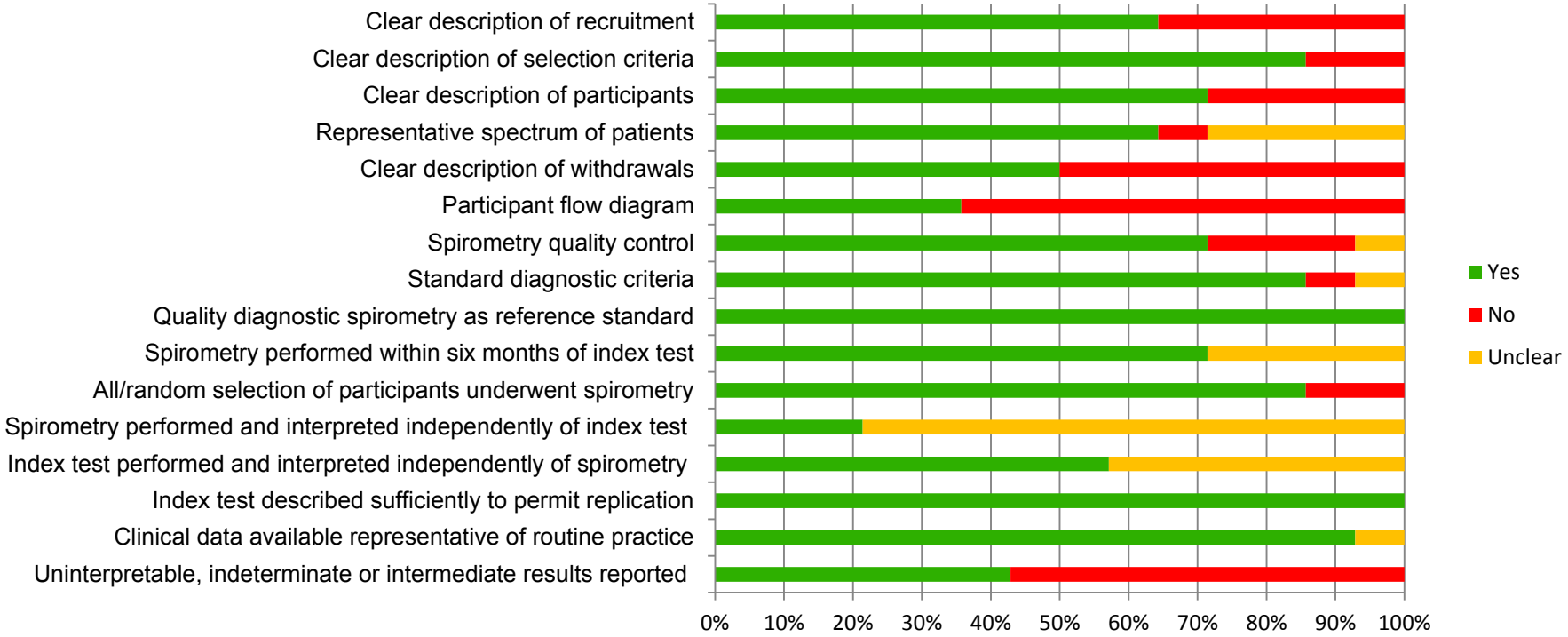

Figure 2.2 Quality of reporting

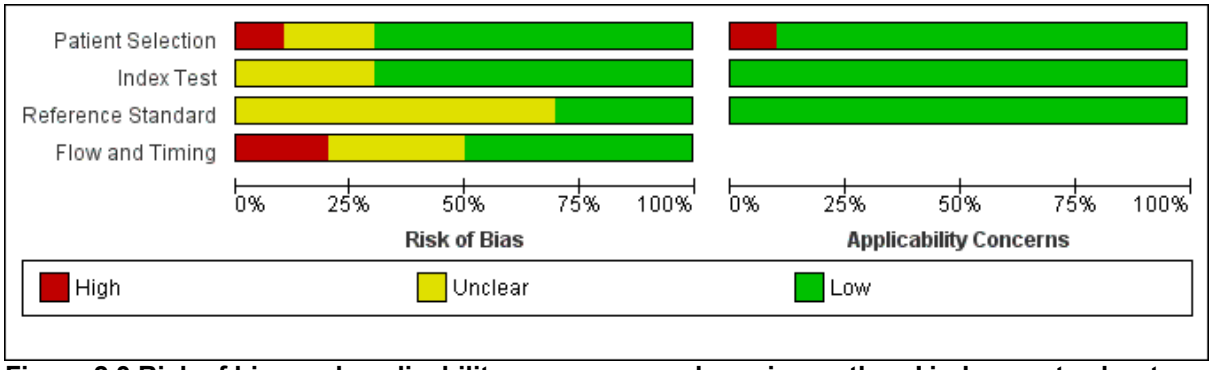

Figure 2.3 Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies

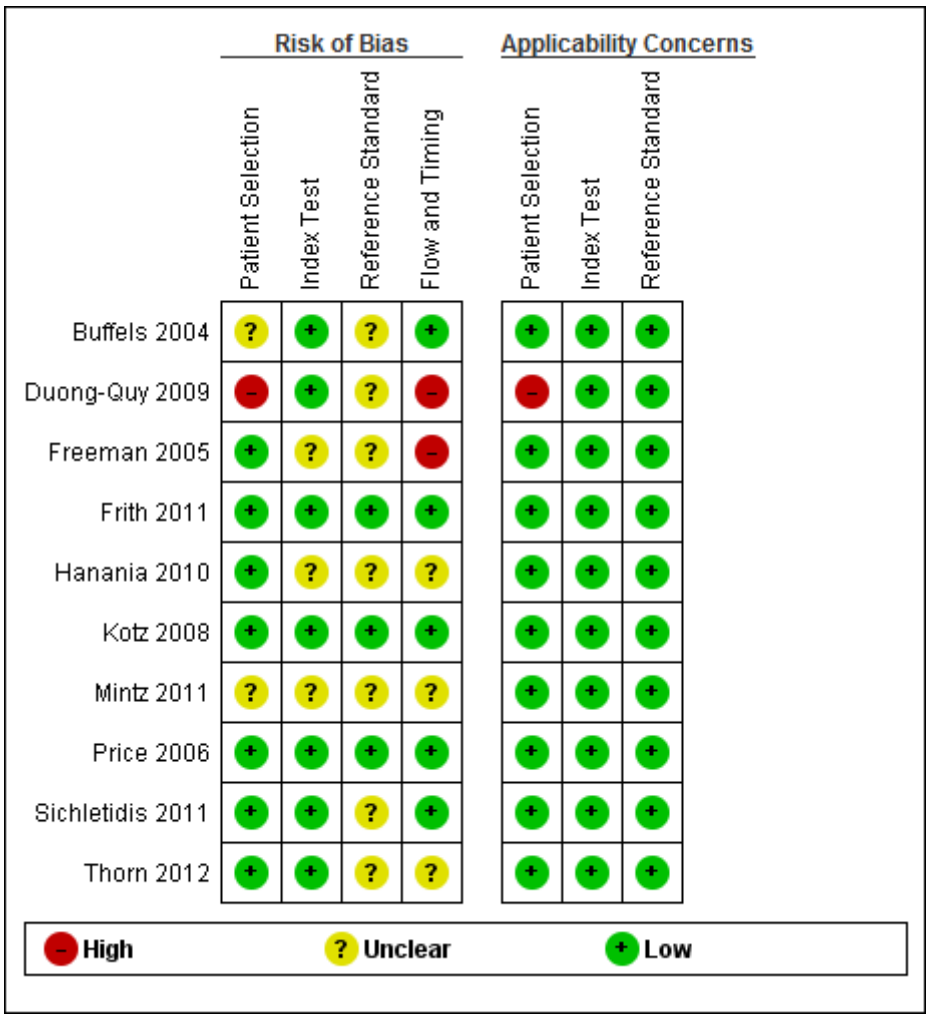

Figure 2.4 Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study

2.4.7 Screening questionnaires

Altogether four screening questionnaires were evaluated on a total of 9472 participants in eight studies (Table 2.2), of which the COPD Diagnostic Questionnaire (CDQ),(13) also referred to as the International Primary Airways Group (IPAG) Questionnaire,(14) was the most widely validated (n=4). All instruments included questions related to the presence of respiratory symptoms (usually cough, dyspnoea and wheeze). Other items included in some, but not all questionnaires related to smoking history, allergies, age, body mass index (BMI) and physical functioning. Overall, participants were similar in age (range 52.3 to 65.3 years) but varied by sex (range 38 to 69% male).

2.4.7.1 COPD Diagnostic Questionnaire

Four studies (13, 14, 22, 24) that evaluated the CDQ in ever smokers were included in a meta-analysis. Using a score threshold of ≥19.5 the pooled sensitivity was 64.5% (95% CI 59.9% to 68.8%) and specificity 65.2% (95% CI 52.9% to 75.8%; Table 2.4). With a prevalence of undiagnosed COPD of 5.5%, this gave a PPV of 9.7% (95% CI 6.9% to 14.2%), NPV of 96.9% (95% CI 95.8% to 97.7%), and would require 29 individuals (95% CI 27 to 31) to complete the CDQ and 11 (95% CI 7 to 15) to undergo a diagnostic assessment to identify one individual with COPD. At a lower score threshold of ≥16.5, the pooled sensitivity was higher but the specificity lower, requiring 21 individuals (95% CI 20 to 22) to complete the questionnaire and 13 (95% CI 11 to 16) to undergo a diagnostic assessment for each new diagnosis.

2.4.7.2 All other questionnaires

There was considerable between-study heterogeneity in the design of other screening questionnaires, which precluded their meta-analysis. In these four studies, sensitivities ranged from 57% to 88% and specificities from 25% to 80% (Figure 2.5).

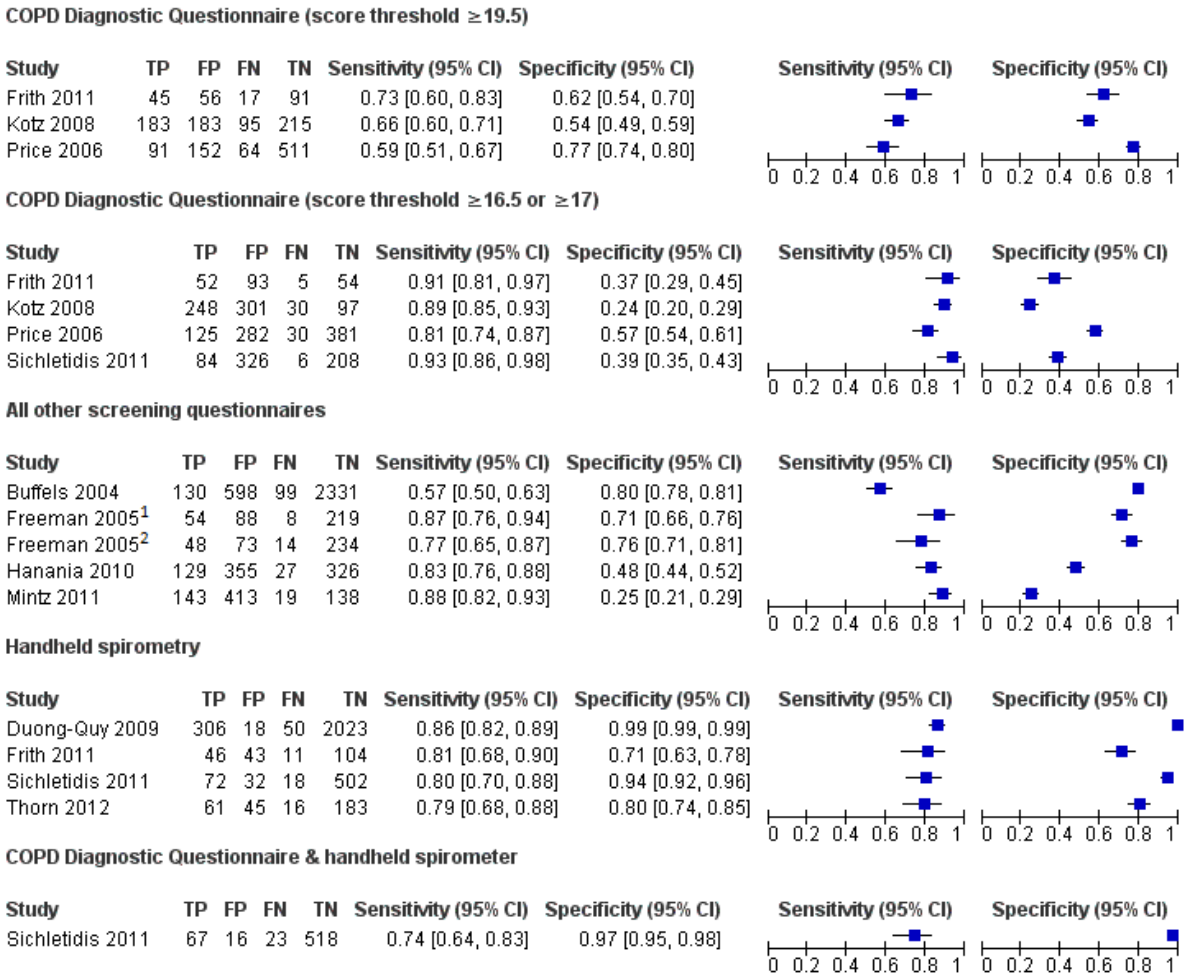

Figure 2.5 Forest plot of sensitivity and specificity of each screening test
TP= true positive, FP= false positive, FN= false negative, TN= true negative
1. Binary response questionnaire, 2. Multiple response questionnaire

Table 2.4 Summary estimates of the accuracy of each test for diagnosis of COPD in ever smokers

Index test	Studies	Cases/ Participants	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	NNS (95% CI)	NND (95% CI)
CDQ (score ≥19.5)	3	495/1703	64.5 (59.9-68.8)	65.2 (52.9 -75.8)	9.7 (6.9-14.2)	96.9 (95.8-97.7)	29 (26-31)	11 (7-15)
CDQ (score ≥16.5)	4	580/2322	87.5 (83.1-90.9)	38.8 (27.7-51.3)	7.7 (6.3-9.8)	98.2 (96.6-99.0)	21 (20-22)	13 (11-16)
Handheld flow meters	3	224/1133	79.9 (74.2-84.7)	84.4 (68.9-93.0)	23.0 (12.2-41.3)	98.6 (97.9-99.1)	23 (22-24)	5 (3-9)
CDQ & handheld flow meter	1	90/624	74.4 (64.2-83.1)	97.0 (95.2-98.3)	59.1 (43.8-74.0)	98.5 (97.9-99.0)	25 (22-29)	2 (2-3)

CDQ=COPD Diagnostic questionnaire, PPV=positive predictive value, NPV=negative predictive value, NNS=number-needed-to-screen to identify one with COPD, NND=number of diagnostic assessments needed to identify one individual with COPD

The PPV, NPV, NNS and number of subjects requiring a diagnostic assessment to identify one individual with COPD have been calculated assuming a prevalence of undiagnosed COPD of 5.5% in a theoretical population of 1000 people.

2.4.8 Handheld flow meters

The test accuracy of handheld flow meters was evaluated in 1400 participants across four studies (Table 2.3).(14, 22, 28, 29) Subjects were similar in age (range 52 to 65.3 years) but varied by sex (range 43 to 99.7% male). Only one study included never smokers and stratified the results by smoking status.(14)

Handheld flow meters differ from diagnostic spirometers in that they are limited to measuring the forced expiratory volume in one and six seconds (FEV_1 and FEV_6, respectively), are usually performed with three blows and are cheaper and quicker to administer. They were used without a bronchodilator in three studies (22, 28, 29) and were supervised by either trained nurses or GPs. A narrow range of thresholds were used to denote a positive test ranging from FEV_1/FEV_6<0.7-0.75.

Their sensitivity ranged from 79% to 86% and specificity from 71% to 99% (Table 2.3). Three studies (14, 22, 29) that enrolled ever smokers were similar enough to be included in a meta-analysis. The pooled sensitivity was 79.9% (95% CI 74.2% to 84.7%) and specificity was 84.4% (95% CI 68.9% to 93.0%). Using the same assumptions, this would require 23 individuals (95% CI 22 to 24) to be screened and 5 (95% CI 3 to 9) to undergo a diagnostic assessment to identify one individual with COPD (Table 2.4).

3.4.9 Combination of tests

In the single study that reported the combined accuracy of a screening questionnaire (CDQ) with a handheld flow meter, the sensitivity was 74% (95% CI 64 to 83%) and specificity 97% (95% CI 95 to 98%).(14) This would reduce the need for diagnostic

assessment to two individuals (95% CI 2 to 3) to identify one with COPD (Table 2.4 and Figure 2.6).

2.4.10 Comparison of test accuracy

Based on an indirect comparison in ever smokers, there was evidence that the CDQ at a score threshold of ≥19.5 had a lower sensitivity (p=0.003) but no difference in specificity (p=0.09) compared to handheld flow meters. At the lower score threshold of ≥16.5 (or 17), there was evidence to suggest a higher sensitivity (p=0.03) but a much lower specificity (p=0.01) than handheld flow meters. Two studies directly compared handheld flow meters and the CDQ (14, 22) and their findings were consistent with the results of the indirect comparison. Furthermore, Frith and colleagues (22) also reported both higher sensitivity and specificity of handheld flow meters compared to the CDQ at the score threshold of ≥19.5.

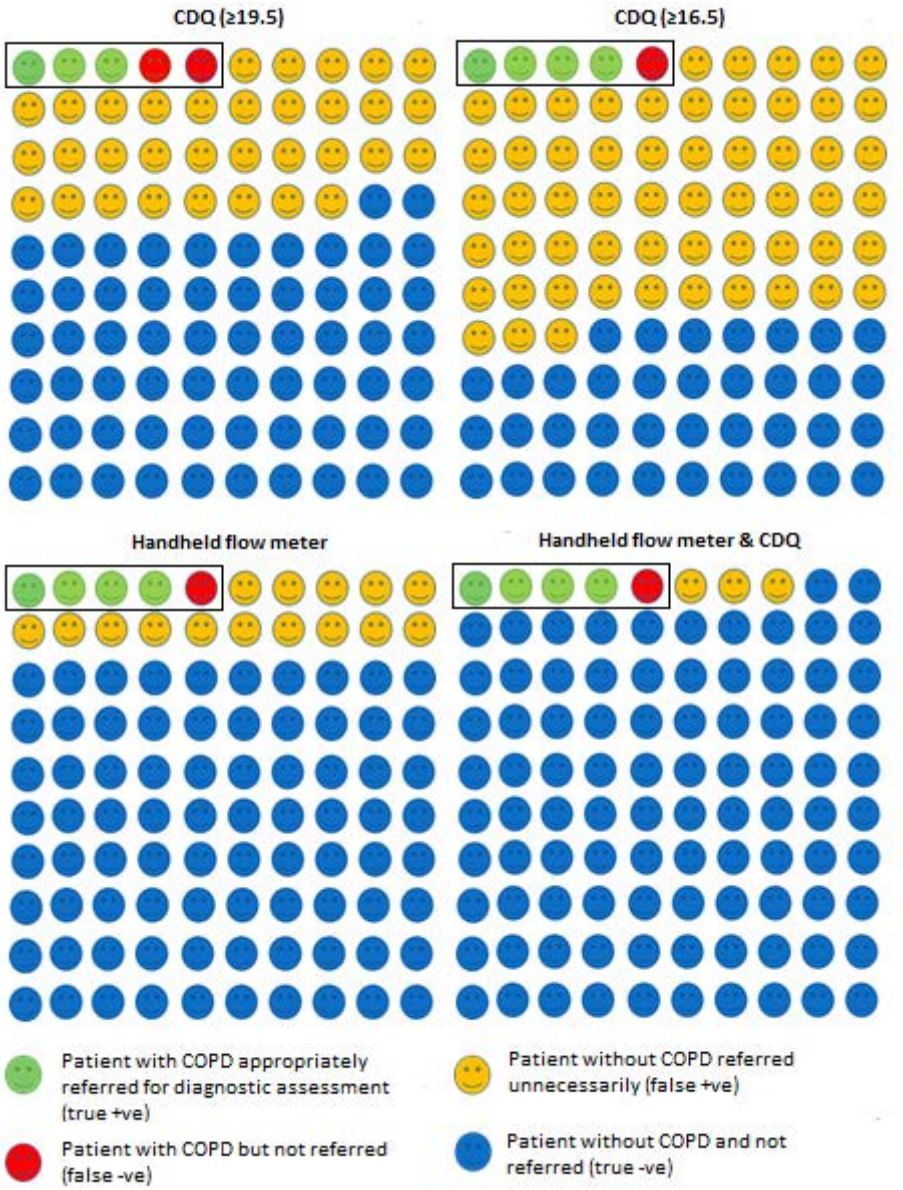

Figure 2.6 Test accuracy of each screening test in a hypothetical population of 100 individuals, five of whom have undiagnosed COPD
CDQ=COPD Diagnostic Questionnaire (score threshold)

2.5 Discussion

2.5.1 Summary of evidence

This review incorporated evidence on the test accuracy of questionnaires and handheld flow meters for COPD screening in primary care. The CDQ developed by Price and colleagues (13) was the most widely validated of the four screening questionnaires included. However use of handheld flow meters under the supervision of trained health professionals was significantly more accurate than the CDQ for discriminating between ever smokers with and without COPD and a combination of both instruments may improve the accuracy still further, potentially reducing the number of diagnostic assessments required.(14) Studies evaluating the CDQ and handheld flow meters had generally few methodological biases, the main being insufficient clarity on blinding between index and reference tests.

Unfortunately only one study by Kotz and colleagues (24) considered the accuracy of a screening test (handheld flow meter) for identifying airflow obstruction in symptomatic patients (reporting cough, sputum, or dyspnoea), which is closer to identifying clinical COPD. The remainder evaluated the accuracy for identifying airflow obstruction without explicitly requiring the presence of symptoms. Nevertheless the results are still likely to apply since the findings from Kotz et al (24) were very similar to studies that did not exclusively select patients with respiratory symptoms.

2.5.2 Relationship to other studies

The US Preventive Services Task Force (USPSTF) and the UK National Screening Committee recommended against routine screening for COPD partly due to concerns

about efficiency and costs.(12, 30) However the USPTF evidence review did not consider the use of screening tests such as questionnaires and handheld flow meters that may help triage high risk patients for diagnostic assessment as suggested by our findings. Screening was recommended against on the basis that it would lead largely to the diagnosis of mild disease, for which there is limited evidence on effective interventions.(12, 31) However, a significant proportion of new diagnoses of COPD in our included studies had moderate-to-severe airflow obstruction (48.9% (24) to 88.5% (27) with an FEV_1 <80% predicted)- these patients are likely to benefit from established therapies for COPD.(8)

In 2005 van Schayck and colleagues (15) compared symptom-based questions for identifying COPD (pre-bronchodilator FEV_1/FVC<lower limit of normal) and validated their accuracy using data from NHANES III. Age, BMI, smoking status, smoking intensity, self-reported asthma, chronic bronchitis or emphysema, and chronic cough or phlegm represented the optimal combination of variables for identifying individuals with airflow obstruction, having a sensitivity of 71% and specificity of 67%. Many of these risk factors have been incorporated in screening questionnaires evaluated in our review and their combined accuracy appears to be lower than handheld flow meters. Furthermore a meta-analysis of studies evaluating the accuracy of FEV_1/FEV_6 measured by standard diagnostic spirometry for detecting airflow obstruction showed it has a sensitivity of 89% (95% CI 83 to 93%) and specificity of 98% (95 to 99%).(32) While the accuracy of handheld flow meters (which measure FEV_1/FEV_6) appears to be lower than this, the findings from the current review suggest that they are still sufficiently accurate to screen for airflow limitation.

Finally, two recent relevant studies were identified that fell outside the time window of the literature search. The first invited ever smokers aged 40-85 years from 36 general practices to complete the CDQ and perform pre- and post-bronchodilator spirometry.(33) The CDQ showed a sensitivity and specificity of 63.0% and 70.1%, respectively when using a score threshold of ≥19.5 and 79.7% and 46.8% using a cut-point of ≥16.5. The second study evaluated the NPV of handheld flow meters among a small sample (n=54) of ex-smokers aged ≥50 years who had been referred for diagnostic post-bronchodilator spirometry by their GP.(34) The NPV was estimated at 94.4% (95% CI 86.4 to 98.5%) when using the fixed ratio of $FEV_1/FVC<0.7$ to define airflow obstruction. Both findings are in keeping with the meta-analyses in the current review.

2.5.3 Strengths and weaknesses of the review

Strengths of this review include the methods used to identify and appraise the available literature. Other than the limitation of the case definition discussed above, the weaknesses result mainly from the methodological limitations of included studies, particularly with respect to inadequate reporting of withdrawals and indeterminate results and blinding of operators performing and interpreting index and reference tests. This may have resulted in overestimation of test accuracy since positive index tests could plausibly influence performance and interpretation of reference spirometry. There was also a lack of head-to-head comparisons with only two studies evaluating more than one screening test.(14, 22) Indirect comparisons are potentially biased because of differences in population and study characteristics.

The criteria for airflow obstruction used in the included studies is also a point of contention given that that using a fixed cut-off of $FEV_1/FVC<0.7$ may lead to

overdiagnosis of the elderly.(35) Future studies should therefore consider using a definition that accounts for age, sex and ethnicity biases, ideally using an FEV_1/FVC ratio below the lower limit of normal (36) and using the fixed ratio for sensitivity analyses. Interpretation and comparison of studies included in this review was made difficult due to differences in the definition of COPD, including differences in the use of pre- and post-bronchodilator spirometry to demonstrate and define airflow obstruction. Future studies should use standard definitions of COPD to ensure the reference standards are consistent across studies.

Finally, the included studies did not report acceptability and uptake of screening tests, which are all important for evaluating their overall effectiveness. This review can therefore only be used to comment on test accuracy and not on comparative clinical and cost-effectiveness in routine practice, which ideally should be evaluated through head-to-head trials.

2.5.4 Implications for research and practice

The findings suggest that handheld flow meters are likely to be more accurate than questionnaires for COPD screening in primary care. This finding is perhaps predictable, given that in the majority of included studies COPD was defined solely by the presence of airflow obstruction demonstrated by spirometry. Handheld flow meters measure two parameters (FEV_1 and FEV_6) captured by standard spirometry (the reference standard), and therefore are likely to be superior to questionnaires. However several key limitations of previous studies are also highlighted. Future studies should provide clear descriptions of withdrawals, including participant flow diagrams, ensure that spirometry is performed without prior knowledge of index tests, and that indeterminate results particularly with respect to spirometry, are reported.

Future studies should also aim to recruit subjects with no prior diagnosis of COPD (thus reducing the risk of spectrum bias (37)) and use a case definition that includes presence of respiratory symptoms to increase generalizability to real-life practice. More studies are needed to evaluate the accuracy and effectiveness of combining screening tests and to assess their cost-effectiveness. Finally, it remains unclear whether early detection of COPD significantly improves clinical outcomes and quality of life. This should first be demonstrated in prospective studies before firm recommendations are made.

2.5.5 Conclusions

Handheld flow meters used under the supervision of a trained health professional are more accurate than the CDQ for detecting spirometry-confirmed COPD in primary care. Limited evidence suggests that combining both tests may potentially improve test accuracy. Future studies should employ a case definition of COPD that aligns with current recommendations and include head-to-head comparisons.

2.6 Supplementary Tables

Table S2.1 Characteristics of included studies

Study	Country	Setting	Recruitment method	Eligibility criteria	Index/reference tests	Definition of COPD
Buffels 2004 (25)	Belgium	20 general practitioners	Invited patients routinely attending general practice over a 12 week period in 1999.	Inclusion criteria: Age 35-70 years Exclusion criteria: Receiving bronchodilators and/or inhaled corticosteroids	Index test: Screening questionnaire Reference test: Pre-BD spirometry in all subjects with respiratory symptoms and 10% sample of asymptomatic subjects	Pre-BD $FEV_1/FVC<88.5\%$ predicted for men & $FEV_1/FVC<89.3\%$ for women
Duong-Quy 2009 (28)	Vietnam	12 primary care medical centres in one city	Broadcast an advertisement on the local television daily for one week. A recruitment company was used to help with participant recruitment (details not reported). Eligible subjects expressing an interest in participating were advised to attend one of the 12 primary care centres from January 2007 to February 2008.	Inclusion criteria: Active and former smokers with >10 pack-years and aged >40 years Exclusion criteria: Previously diagnosed respiratory disease (asthma, COPD and tuberculosis)	Index test: Pre-BD handheld flow meter (Piko-6®) Reference test: Full medical assessment including clinical examination, pulmonary radiology, ECG, and post-BD spirometry for those who had an index $FEV_1/FEV_6<0.7$ and a sample of those with $FEV_1/FEV_6\geq0.7$	Post-BD $FEV_1/FVC<0.7$ with <200mL or 12% reversibility

Study	Country	Setting	Recruitment method	Eligibility criteria	Index/reference tests	Definition of COPD
Freeman 2005 (26)	UK	One general practice	Postal invitation from October 1997 to April 2002.	Inclusion criteria: Age ≥40 years & current/ex-smoker & had either received respiratory medications in the preceding 2 years or had a history of asthma Exclusion criteria: None	Index test: Screening questions Reference test: Pre-/ post-BD spirometry on all subjects	Post-BD $FEV_1/FVC<0.7$ and lack of reversibility (reversibility defined as increase in FEV_1 of 200mL and 15% from pre-BD FEV1 (not clear if all were post-BD)
Frith 2011 (22)	Australia	4 primary care practices	Recruited during routine practice visits, invitation to study days, and local newspaper advertisement between August and December 2006.	Inclusion criteria: Age ≥50 years & current/ex- smoker & no prior diagnosis of obstructive lung disease (COPD, emphysema, chronic bronchitis, asthma) & no treatment for obstructive lung disease in past 12months Exclusion criteria: Refusal or inability to give consent, pre-existing non-obstructive lung disease, symptoms suggestive of unstable heart disease, and spirometry contraindications	Index test: Pre-BD handheld flow meter (Piko-6®) & screening questionnaire (COPD Diagnostic Questionnaire) Reference test: Pre-/ post-BD spirometry on all patients	Post-BD $FEV_1/FVC<0.7$

Study	Country	Setting	Recruitment method	Eligibility criteria	Index/reference tests	Definition of COPD
Hanania 2010 (27)	US	Two family physician group offices	Invited patients aged ≥40 years visiting the practices from March-May 2008	Inclusion criteria: Age ≥40 years Exclusion criteria: None	Index test: Screening questionnaire (Lung Function Questionnaire) Reference test: Pre-BD spirometry	Pre-BD $FEV_1/FVC<0.7$
Kotz 2008 (24)	Netherlands	General population and primary care practices	Advertisements in a local newspaper, flyers, posters and mailings to households and invitation during primary care consultations from Jan 2005-Dec 2006.	Inclusion criteria: Age 40-70 years & current smoker with ≥10 pack years & motivated to stop smoking & able to read and speak Dutch & reporting a respiratory symptom (cough, phlegm or dyspnoea) Exclusion criteria: Prior respiratory diagnosis, spirometry in previous 12 months or contraindications to smoking cessation therapy	Index test: Questionnaire (COPD Diagnostic Questionnaire) Reference test: Pre-/post-BD spirometry in all participants	Post-BD $FEV_1/FVC<0.7$
Mintz 2011 (23)	US	36 primary care centres	NR	Inclusion criteria: Age ≥30 years old & current/ex- smoker with ≥10 pack years Exclusion criteria: Regular use of respiratory medications within 4 weeks of the study, known diagnosis of substantial lung conditions with regular use of respiratory medications.	Index test: Screening questionnaire (Lung Function Questionnaire) Reference test: Pre-/ post-BD spirometry	LFQ≤18 & post-BD $FEV_1/FVC<0.7$

Study	Country	Setting	Recruitment method	Eligibility criteria	Index/reference tests	Definition of COPD
Price 2006 (13)	UK & US	2 primary care practices	Postal invitation	Inclusion criteria: Age ≥40 years & current/ex-smoker Exclusion criteria: Refusal to consent, history of non-obstructive lung disease, use of respiratory medications in past year, acute symptoms of unstable heart disease	Index test: Screening questionnaire (COPD Diagnostic Questionnaire) Reference test: Pre-/post-BD spirometry	Post-BD $FEV_1/FVC<0.7$
Sichletidis 2011 (14)	Greece	25 general practices	Invited first 50 patients meeting the inclusion criteria who visited each participating GP from 1st March-31st May 2009.	Inclusion criteria: Age >40 years Exclusion criteria: Confirmed diagnosis of lung disease, thoracic surgery in previous 6 months, acute respiratory infection, uncontrolled cardiac disease, or could not perform acceptable spirometry	Index tests: 1. Screening questionnaire (International Primary Airways Group Questionnaire, also known as the COPD Diagnostic Questionnaire) 2. Post-BD handheld flow meter (Piko-6®) (Bronchodilator=400µg salbutamol) Reference test: Pre-/post-BD spirometry	Post-BD $FEV_1/FVC<0.7$
Thorn 2012 (29)	Sweden	21 primary healthcare centres	Invited patients attending participating primary healthcare centres over a 5 month period.	Inclusion criteria: Age 45-85 years & current/ex-smoker with ≥15 pack years Exclusion criteria: None	Index test: Pre-BD handheld flow meter (COPD-6) Reference test: Pre-/post-BD spirometry	Post-BD $FEV_1/FVC<0.7$

BD=bronchodilator, FEV_1=forced expiratory volume in one second, FEV_6=forced expiratory volume in 6 seconds, FVC=forced vital capacity, NR=not reported

Table S2.2 Results: studies evaluating screening questionnaires

Study	Population	Questionnaire	Spirometry (reference test)	Number screened	New COPD cases
Buffels 2004 (25)	Eligible: 3158 Invited: 3158 Attended: 3158 Data on subjects who underwent spirometry Mean age: NR Male: 45% <u>Smoking status</u> Current: 30.7% Former: 18.1% Never: 50.1%	<u>Items</u> • Cough >2 weeks • Dyspnoea during mild exercise/at night • Nasal allergy/hay fever • Visit to doctor for wheeze or chronic cough <u>Threshold</u> ≥1 symptom	Device: Spirobank spirometer with Winspiro software Bronchodilator: None Operator: GPs who had received 12 hours of training Standard: NR Quality control: Technical support was provided to GPs throughout the study. Accuracy of GP-performed spirometry was compared to that from a lab technician.	<u>Index test</u> Total: 3158 Positive: 728 <u>Reference test (spirometry)</u> Total: 703 with positive index test and 222 with negative index test. Acceptable quality: NR	Subjects with positive index test: 126/703 (17.9%) Subjects with negative index test: 9/222 (4.1%) <u>FEV_1 % predicted</u> >80%: 53 (39%) 50-80%: 69 (51%) 30-50%: 12 (9%) ≤30%: 1 (<1%)
Freeman 2005 (26)	Eligible: 1195 Invited: 1195 Attended: 624 Data on subjects who performed spirometry Mean age: 61.7 Male: 52% <u>Smoking status</u> Current: 54.1% Former: 45.9%	<u>Items</u> • Age • Smoking status • Pack-years • Cough • Dyspnoea • Wheeze <u>Threshold</u> NR (included only “best” reported)	Device: Micro-Med handheld spirometer with Spida software Bronchodilator: 5mg salbutamol for those with prior respiratory medication or history of asthma or FEV_1<80% predicted Operator: Trained respiratory nurse Standard: ATS standards. Minimum of 3 tests or until reproducibility within 5%. Quality control: All spirometry results were reviewed by a physician to ensure compliance with ATS standards.	<u>Index test</u> Total: 369 Positive: 121* (multiple response questionnaire), 142* (binary response questionnaire) <u>Reference test (spirometry)</u> Total: 369 Acceptable quality: NR	62/369 (16.8%) <u>FEV_1 % predicted</u> NR

Study	Population	Questionnaire	Spirometry (reference test)	Number screened	New COPD cases
Frith 2011 (22)	Eligible: 233 Invited: 237 Attended:237 Data on subjects with acceptable spirometry Mean age: 61 Male: 69% <u>Smoking status</u> Current: 45% Former: 55% Never: <1%	COPD diagnostic questionnaire (CDQ) <u>Items</u> See Price 2006 (below) <u>Thresholds:</u> Score ≥19.5, ≥16.5	Device: EasyOne spirometer (ndd Medical) Bronchodilator: 360mcg salbutamol Operator: trained operators using ATS/ERS guidelines Standard: ATS/ERS standards. At least 3 adequate baseline and post-BD FVC manoeuvres performed. Quality control: spirometry quality monitored by a respiratory physiologist blinded to the questionnaire and Piko-6® results.	<u>Index test</u> Total: 233 Positive: 110* (threshold ≥19.5), 165* (threshold ≥16.5) <u>Reference test (spirometry)</u> Total: NR Acceptable quality: 204	57/204 (27.9%) <u>FEV_1 % predicted</u> >80%: 19 (33.3%) 50-80%: 35 (61.4%) 30-50%: 3 (5.3%) <30%: 0
Hanania 2010 (27)	Eligible: NR Invited: NR Attended: 937 Data on subjects with acceptable spirometry and adequate data Mean age: NR Male: 38.1% <u>Smoking status</u> NR	Lung Function Questionnaire (LFQ) <u>Items:</u> • Age • Cough • Wheeze • Dyspnoea • Smoking <u>Threshold:</u> Score ≤18	Device: EasyOne spirometer (ndd Medical) Bronchodilator: None Operator: NR Standard: NR Quality control: Investigators rated spirometry quality based on reliability and reproducibility. Only included traces considered reliable.	<u>Index test</u> Total: 937 Positive: 484* <u>Reference test</u> Total: 937 Acceptable quality: NR Analysed: 837	156/837 (18.6%) <u>FEV1 % predicted</u> ≥80%: 17 (11.5%) 50-80%: 76 (51.4%) 30-50%: 44 (29.7%) <30%: 11 (7.4%) (NB. Reported numbers do not add up to 156)

Study	Population	Questionnaire	Spirometry (reference test)	Number screened	New COPD cases
Kotz 2008 (24)	Eligible: 1052 Invited: 1052 Attended: 826 Data on subjects with spirometry Mean age:52.3 Male:58.7% <u>Smoking status</u> Current: 100%	COPD Diagnostic Questionnaire (CDQ) <u>Items:</u> See Price 2006 (below) <u>Thresholds:</u> Score ≥19.5, ≥16.5	Device: Vitalograph 2120 Bronchodilator: 500 µg terbutaline Operator: Two qualified research assistants under the supervision of a pulmonologist Standard: ATS/ERS standards Quality control: spirometry performed according to ATS/ERS standards. All spirometry test results were validated by a pulmonologist and specialised lung function laboratory assistant not involved in the trial- both were blinded to the questionnaire scores.	<u>Index test</u> Total: 1052 Analysed: 676 Positive: 549* (threshold ≥16.5) 366* (threshold ≥19.5) <u>Reference test</u> Total: 826 Acceptable quality: 716	278/676 (41.1%) <u>FEV1 % predicted</u> ≥80%: 142 (51.1%) 50-80%: 119 (42.8%) <50%: 17 (6.1%)
Mintz 2011 (23)	Eligible: 1724 Invited: 4956 Attended: 2284 Data on subjects who completed index test Mean age: 53.9* Male: 51.2% <u>Smoking status</u> Current: 57.6% Former: 42.4%	Lung Function Questionnaire (LFQ) <u>Items</u> • Age • Cough • Wheeze • Dyspnoea • Smoking • Activity limitation <u>Threshold</u> Score ≤18	Device: Biomedical Systems, St Louis, MO Bronchodilator: 360µg albuterol Operator: Trained site staff Standard: ATS standards Quality control: Only data collected from acceptable spirometric manoeuvres were included. Patients producing unacceptable spirometry were allowed to repeat this within 7 days of the study visit.	<u>Index test</u> Total: 1575 Positive: 1216 <u>Reference test (spirometry)</u> Total: 1225 Acceptable quality: 849 (713 in subjects ≥40 years)	162/713 (22.7%) (NB. restricted to subjects ≥40 years) <u>FEV_1 % predicted</u> NR

Study	Population	Questionnaire	Spirometry (reference test)	Number screened	New COPD cases
Price 2006 (13)	Eligible: NR Invited: 17,361 Attended: 898 Data on subjects with acceptable spirometry Mean age: 58.2 Male: 49.3% <u>Smoking status</u> Current: 44.5% Former: 55.5%	COPD Diagnostic Questionnaire <u>Items</u> • Age • Pack-years • Weather-affected cough • Productive phlegm in absence of a cold • Early morning cough • Wheeze • Allergies <u>Thresholds</u> Score ≥19.5, ≥16.5	Device: EasyOne spirometer (ndd Medical) Bronchodilator: 2.5mg salbutamol/albuterol Operator: NR Standard: ATS standards Quality control: Principal investigators conducted blinded review of all spirometry loops. A pulmonologist not associated with the study reviewed all loops on which there was disagreement	<u>Index test</u> Total: 898 Positive: 267* (threshold ≥16.5) 446* (threshold ≥19.5) <u>Reference test (spirometry)</u> Total: 898 Acceptable quality: 818 572 (70%) used for questionnaire development, 246 (30%) used for validation	155/818 (18.9%) <u>FEV_1 % predicted</u> NR
Sichletidis 2011 (14)	Eligible: 1250 Invited: 1250 Attended: 1250 Data on subjects with acceptable spirometry Mean age: 65.3 Male: 57.1% <u>Smoking status</u> Ever: 48.8% Never: 51.2%	COPD Diagnostic Questionnaire (also referred to as International Primary Airways Group questionnaire) <u>Items:</u> See Price 2006 (above) <u>Threshold</u> Score ≥17	Device: Vitalograph Bronchodilator:400µg salbutamol Operator: Pulmonary specialists Standard: ATS/ERS standards Quality control: Spirometry performed and interpreted by pulmonary specialists according to ATS/ERS standards	<u>Index test</u> Total: 1250 Positive: 409* (smokers) 594* (smokers & non-smokers) <u>Reference test (spirometry)</u> Total: NR Acceptable quality: 1078	Ever smokers: 90/624 (14.4%) Ever smokers & non-smokers: 111/1078 (10.3%) <u>FEV_1 % predicted</u> ≥80%:40 (36.0%) 50-80%:53 (47.7%) 30-50%:16 (14.4%) <30%:2 (1.8%)

*Derived values (may differ from reported test performance)

BD= bronchodilator, NR= not reported, FEV_1= forced expiratory volume in 1 second, FVC= forced vital capacity, FEV_6= forced expiratory volume in 6 seconds

Table S2.3 Results: studies evaluating handheld flow meters

Study	Recruited population	Handheld flow meter	Spirometry (reference test)	Number screened	New COPD cases
Duong-Quy 2009 (28)	Eligible: 2464 Invited: NR Attended: 2464 Data on subjects who undertook index test Mean age: 52 Male:99.7% Smoking status Current: 88.9% Former: 11.1%	Pre-BD Piko-6® Operator: NR 3 manoeuvres were taken and the best of 3 selected. All measures where FEV_1/FEV_6>1 were excluded. Threshold FEV_1/FEV_6<0.7	Device: SpiroLab II Bronchodilator: short-acting β2 agonist (unspecified) Operator: NR Standard: Required at least 3 measures and at least 2 within 150mL to ATS/ERS standards. Quality control: NR	Index test Total: 2464 Positive: 324 Reference test (spirometry) Total: 144 subjects with positive index test and 123 with negative index test. Acceptable quality: NR	Subjects with positive index test: 136/144 (94.4%) Subjects with negative index test: 3/123 (2.4%) FEV_1 % predicted (in subjects with positive index test) <80%: 65 (47.8%) 50-79%: 63 (46.3%) 30-49%: 8 (5.9%) <30%: 0
Frith 2011 (22)	Eligible: 233 Invited: 237 Attended:237 Data on subjects with acceptable spirometry Mean age: 61 Male: 69% Smoking status Current: 45% Former: 55% Never: <1%	Pre-BD Piko-6® Operator: Study nurse or GP Threshold FEV_1/FEV_6<0.75 (optimal cut-point)	Device: EasyOne spirometer (ndd Medical) Bronchodilator: 360mcg salbutamol Operator: trained operators using ATS/ERS guidelines Standard: ATS/ERS standards. At least 3 adequate baseline and post-BD FVC manoeuvres performed. Quality control: spirometry quality monitored by a respiratory physiologist blinded to the questionnaire and Piko-6® results.	Index test Total: 233 Positive: 101* Reference test (spirometry) Total: NR Acceptable quality: 204	57/204 (27.9%) FEV_1 % predicted >80%: 19 (33.3%) 50-80%: 35 (61.4%) 30-50%: 3 (5.3%) <30%: 0

Study	Recruited population	Handheld flow meter	Spirometry (reference test)	Number screened	New COPD cases
Sichletidis 2011 (14)	Eligible: 1250 Invited: 1250 Attended: 1250 Data on subjects with acceptable spirometry Mean age: 65.3 Male: 57.1% Smoking status Ever: 48.8% Never: 51.2%	Post-BD Piko-6® Bronchodilator: 400µg salbutamol Operator: GPs with 2 hours training Threshold Post-BD FEV_1/FEV_6<0.7	Device: Vitalograph Bronchodilator: 400µg salbutamol Operator: Pulmonary specialists Standard: ATS/ERS standards Quality control: Spirometry performed and interpreted by pulmonary specialists according to ATS/ERS standards	Index test Total: 1250 Positive ‡: 104* (ever smokers) 137* (ever smokers & non-smokers) Reference test (spirometry) Total: NR Acceptable quality: 1078	Ever smokers: 90/624 (14.4%) Ever smokers & non-smokers: 111/1078 (10.3%) FEV_1 % predicted ≥80%:40 (36.0%) 50-80%:53 (47.7%) 30-50%:16 (14.4%) <30%:2 (1.8%)
Thorn 2012 (29)	Eligible: NR Invited: NR Attended: 305 Data on subjects who performed the index and reference tests Mean age: 61.2 Male: 43.3% Smoking status Ever: 100%	Pre-BD COPD 6® Operator: Nurses Threshold FEV_1/FVC<0.73	Device: NR Bronchodilator: 0.5mg terbutaline Operator: Nurses Standard: ATS standards Quality control: Spirometry performed according to ATS standards. No other quality control measures reported.	Index test Total: 305 Positive: 106* Reference test (spirometry) Total:305 Acceptable quality: NR	77/305 (25.2%) FEV_1 % predicted ≥80%:35 (45.5%) 50-80%:41 (53.2%) 30-50%:1 (1.3%) <30%:0

*Derived values (may differ from reported test performance)

‡ 83* (smokers) and 109* (smokers & non-smokers) positive index tests when using a combination of the CDQ and handheld flow meter

BD= bronchodilator, NR= not reported, FEV_1= forced expiratory volume in 1 second, FVC= forced vital capacity, FEV_6= forced expiratory volume in 6 seconds

Table S2.4 Quality of reporting

	Buffels 2004	Duong-Quy 2009	Freeman 2005	Frith 2011	Hanania 2010	Kotz 2008	Mintz 2011	Price 2006	Sichletidis 2011	Thorn 2012
Clear description of recruitment	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Clear description of participants	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Clear description of withdrawals	Y	Y	N	N	U	Y	Y	Y	Y	N
Participant flow diagram	Y	N	N	Y	N	Y	Y	Y	N	N
Spirometry quality control	Y	N	Y	Y	Y	Y	Y	Y	Y	U
Standard diagnostic criteria	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Representative spectrum of patients	U	N	Y	Y	U	Y	Y	Y	Y	Y
Clear description of selection criteria	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Spirometry as reference standard	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Spirometry performed within six months of index test	Y	U	Y	Y	Y	U	Y	Y	U	Y
All or random selection of participants underwent spirometry	Y	N	Y	Y	Y	Y	N	Y	Y	Y
Spirometry performed and interpreted independently of screening test result	U	U	U	Y	U	Y	U	Y	U	U
Screening test performed and interpreted independently of spirometry	Y	Y	U	Y	U	Y	U	Y	Y	Y
Intervention described in sufficient detail to permit its replication	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Clinical data available representative of routine practice	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Uninterpretable, indeterminate or intermediate results reported	N	N	N	Y	N	Y	Y	Y	Y	N

Y=yes, N=no, U=unclear

2.7 References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
2. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-223.
3. Britton M. The burden of COPD in the U.K.: results from the Confronting COPD survey. Respiratory medicine. 2003;97 Suppl C:S71-9.
4. Soriano J, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. Lancet. 2009;374(9691):721 - 32.
5. Fromer L. Diagnosing and treating COPD: understanding the challenges and finding solutions. International journal of general medicine. 2011;4:729-39.
6. Jones RCM, Price D, Ryan D, Sims EJ, von Ziegenweidt J, Mascarenhas L, et al. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. The Lancet Respiratory Medicine. 2014.
7. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. American journal of respiratory and critical care medicine. 2000;161(2 Pt 1):381-90.
8. Chronic obstructive pulmonary disease : management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Institute for Health and Clinical Excellence; 2010.
9. Invisible lives: chronic obstructive pulmonary disease (COPD) — finding the missing millions. London: British Lung Foundation, 2007.
10. Bakke PS, Ronmark E, Eagan T, Pistelli F, Annesi-Maesano I, Maly M, et al. Recommendations for epidemiological studies on COPD. European Respiratory Journal. 2011;38(6):1261-77.
11. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease, 2013.
12. Lin K, Watkins B, Johnson T, Rodriguez JA, Barton MB, Force USPST. Screening for chronic obstructive pulmonary disease using spirometry: summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;148(7):535-43.
13. Price DB, Tinkelman DG, Nordyke RJ, Isonaka S, Halbert RJ, Group CQS. Scoring system and clinical application of COPD diagnostic questionnaires. Chest. 2006;129(6):1531-9.
14. Sichletidis L, Spyratos D, Papaioannou M, Chloros D, Tsiotsios A, Tsagaraki V, et al. A combination of the IPAG questionnaire and PiKo-6(R) flow meter is a valuable screening tool for COPD in the primary care setting. Prim Care Respir J. 2011;20(2):184-9, 1 p following 9.
15. van Schayck CP, Halbert RJ, Nordyke RJ, Isonaka S, Maroni J, Nonikov D. Comparison of existing symptom-based questionnaires for identifying COPD in the general practice setting. Respirology. 2005;10(3):323-33.
16. Haroon SM, Adab PA, Jordan RE. Case finding for COPD in primary care: a systematic review. Prim Care Respir J. 2012;21(3):354-7.
17. PROSPERO: International prospective register of systematic reviews York: Centre for Reviews and Dissemination, University of York; 2014 [cited 2014]. Available from: http://www.crd.york.ac.uk/PROSPERO/.
18. Whiting P, Rutjes AW, Dinnes J, Reitsma J, Bossuyt PM, Kleijnen J. Development and validation of methods for assessing the quality of diagnostic accuracy studies. Health technology assessment. 2004;8(25):iii, 1-234.
19. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol. 2005;58(10):982-90.
20. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach. J Clin Epidemiol. 2006;59(12):1331-2; author reply 2-3.
21. Jordan RE, Lam KB, Cheng KK, Miller MR, Marsh JL, Ayres JG, et al. Case finding for chronic obstructive pulmonary disease: a model for optimising a targeted approach. Thorax. 2010;65(6):492-8.

22. Frith P, Crockett A, Beilby J, Marshall D, Attewell R, Ratnanesan A, et al. Simplified COPD screening: validation of the PiKo-6(R) in primary care. Prim Care Respir J. 2011;20(2):190-8, 2 p following 8.
23. Mintz ML, Yawn BP, Mannino DM, Donohue JF, Hanania NA, Grellet CA, et al. Prevalence of airway obstruction assessed by lung function questionnaire. Mayo Clinic proceedings. 2011;86(5):375-81.
24. Kotz D, Nelemans P, van Schayck CP, Wesseling GJ. External validation of a COPD diagnostic questionnaire. Eur Respir J. 2008;31(2):298-303.
25. Buffels J, Degryse J, Heyrman J, Decramer M, Study D. Office spirometry significantly improves early detection of COPD in general practice: the DIDASCO Study. Chest. 2004;125(4):1394-9.
26. Freeman D, Nordyke RJ, Isonaka S, Nonikov DV, Maroni JM, Price D, et al. Questions for COPD diagnostic screening in a primary care setting. Respiratory medicine. 2005;99(10):1311-8.
27. Hanania NA, Mannino DM, Yawn BP, Mapel DW, Martinez FJ, Donohue JF, et al. Predicting risk of airflow obstruction in primary care: Validation of the lung function questionnaire (LFQ). Respiratory medicine. 2010;104(8):1160-70.
28. Duong-Quy S, Hua-Huy T, Mai-Huu-Thanh B, Doan-Thi-Quynh N, Le-Quang K, Nguyen-Van H, et al. [Early detection of smoking related chronic obstructive pulmonary disease in Vietnam]. Revue des maladies respiratoires. 2009;26(3):267-74.
29. Thorn J, Tilling B, Lisspers K, Jorgensen L, Stenling A, Stratelis G. Improved prediction of COPD in at-risk patients using lung function pre-screening in primary care: a real-life study and cost-effectiveness analysis. Prim Care Respir J. 2012;21(2):159-66.
30. Cartwright S. An evaluation of screening for COPD against the National Screening Committee criteria. 2012.
31. The UK NSC policy on Chronic Obstructive Pulmonary Disease: Public Health England; 2013 [cited 2014 19/08/2014]. Available from: http://www.screening.nhs.uk/copd.
32. Jing J-y, Huang T-c, Cui W, Xu F, Shen H-h. Should fev1/fev6 replace fev1/fvc ratio to detect airway obstruction?: A metaanalysis. Chest. 2009;135(4):991-8.
33. Stanley AJ, Hasan I, Crockett AJ, van Schayck OCP, Zwar NA. Validation of the COPD Diagnostic Questionnaire in an Australian general practice cohort: a cross-sectional study. Prim Care Resp J. 2014;23(1):92-7.
34. van den Bemt L, Wouters BCW, Grootens J, Denis J, Poels PJ, Schermer TR. Diagnostic accuracy of pre-bronchodilator FEV1/FEV6 from microspirometry to detect airflow obstruction in primary care: a randomised cross-sectional study. Npj Primary Care Respiratory Medicine. 2014;24.
35. Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Mørkve O. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. European Respiratory Journal. 2002;20(5):1117-22.
36. Quanjer P, Stanojevic S, Cole T, Baur X, Hall G, Culver B, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40:1324 - 43.
37. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. The New England journal of medicine. 1978;299(17):926-30.

CHAPTER 3: EFFECTIVENESS OF COPD CASE FINDING IN PRIMARY CARE: A SYSTEMATIC REVIEW AND META-ANALYSIS

This chapter is based on a published systematic review protocol: Haroon S, Adab PA, Jordan RE. Case finding for COPD in primary care: a systematic review (protocol). Primary Care Respiratory Journal. 2012: 21(3):354-7.

3.1 Abstract

Objective

There is a large underdiagnosis of COPD worldwide but the most effective approach for identifying these patients is unknown. We report a systematic review to summarise relevant published literature.

Methods

Systematic review and meta-analysis of primary studies of any design evaluating case finding strategies for COPD in primary care among individuals aged ≥35 years with no prior diagnosis. Medline, Embase and other bibliographic databases were searched from 1997 to 2013 and methodological quality of included studies assessed using criteria adapted from the QUADAS-1, QUADAS-2 and Cochrane Risk of Bias tools. Results were tabulated and described and meta-analysis of the uptake of screening and diagnostic tests and the yield from different approaches was performed where there was sufficient homogeneity.

Results

3 RCTs, 1 controlled trial and 35 uncontrolled studies were identified assessing the yield from case finding. A range of approaches were evaluated including use of screening questionnaires (n=13) or handheld flow meters (n=5) prior to diagnostic spirometry, or direct invitation to diagnostic spirometry (n=30). Studies were heterogeneous and were limited by a lack of comparison groups, inadequate reporting, and diversity in the definition of COPD. The comparative studies suggest that nurse-led case finding may be more effective than routine care, and that opportunistic invitation of patients clinically suspected to have COPD for spirometry is more effective than more widespread, public invitation for screening. Indirect comparisons suggest that uptake of screening is likely to be higher with opportunistic than postal invitation, and that targeting ever smokers with a history of respiratory symptoms may improve the yield. Screening with either questionnaires or handheld flow meters prior to diagnostic spirometry may uncover a similar proportion of patients with undiagnosed COPD compared to direct invitation for diagnostic spirometry but may reduce the number of diagnostic assessments needed.

Conclusions

There is extensive heterogeneity in studies evaluating case finding strategies for COPD, with few RCTs. There is a need for well conducted RCTs comparing case finding approaches to help identify the most effective target population, recruitment strategy and use of screening and diagnostic tests, that use a clinical definition of COPD, and address the limitations highlighted in this review.

3.2 Introduction

COPD is the third leading cause of mortality,(1) is an important cause of disability,(2) and is a source of significant healthcare expenditure.(3) However, much of the disease burden remains undiagnosed with estimates as high as 70-90%.(4) People with undiagnosed COPD often under-recognise the significance of their symptoms,(5) and there is poor awareness of the condition among the general public.(6, 7) Clinicians in primary care also frequently miss opportunities to diagnose COPD.(8) Although undiagnosed patients are more likely to have mild-to-moderate airflow obstruction, there are likely to be a significant number with more severe disease and symptom burden who would benefit from symptomatic or disease modifying therapies.(9) Furthermore, a higher prevalence of undiagnosed COPD has been associated with higher rates of COPD-related hospitalisations (10) and patients with undiagnosed COPD often receive their diagnosis during an acute hospital admission following an exacerbation.(11) There is now a policy drive to identify undiagnosed COPD earlier in the course of the disease in order to initiate secondary prevention,(12, 13) particularly smoking cessation support,(14) and to offer symptomatic relief through pulmonary rehabilitation,(15) and pharmacological therapies.(16) However, the optimal strategy for achieving this remains unknown.(17)

A systematic review published in 2008 evaluated the effectiveness of population-based screening for COPD using spirometry but concluded that this would identify many asymptomatic individuals with mild-to-moderate airflow obstruction, for whom there are limited therapeutic options.(18) However since then there have been a large number of studies conducted in primary care evaluating the effectiveness of a variety of potentially more efficient approaches for identifying undiagnosed COPD,

including the use of screening questionnaires (19) and handheld flow meters (e.g. Piko-6® or COPD-6®).(20) The accuracy of screening tests for COPD was reviewed in the previous chapter but this did not consider the full screening process which depends also on the target population, method of recruitment, response rates, and uptake (Figure 3.1).

This chapter reports a systematic review and meta-analysis to identify and compare the effectiveness (yield) of alternative case-finding approaches for COPD in primary care.

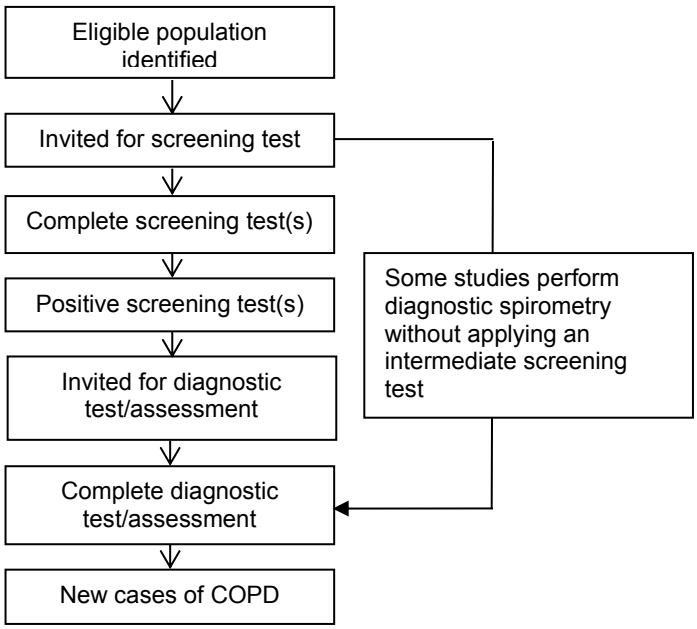

Figure 3.1 Case finding pathway

3.3 Methods

3.3.1 Protocol and registration

The protocol for this review was previously published (21) and registered on the PROSPERO register of systematic reviews (CRD42012002074).(22)

3.3.2 Eligibility criteria

Since RCTs were known to be rare, primary studies of any design were sought that were conducted in primary care (including general practices and community pharmacies), and recruited individuals aged ≥35 years with no prior diagnosis of COPD, and aimed to detect undiagnosed COPD confirmed by pre- or post-bronchodilator spirometry. Eligible screening tests included questionnaires, clinical examination, handheld flow meters, peak flow meters, decision aids/risk prediction models, and chest radiography, either alone or in combination.

3.3.3 Search strategy

The same search strategy was used to identify articles for both systematic reviews in this thesis. See section 2.3.4 and Table 2.1.

3.3.4 Study selection and data extraction

Titles and abstracts were screened independently by two reviewers. Full text papers were obtained for all potentially relevant studies and the eligibility criteria applied independently with disagreements resolved through discussion. Data were extracted on the characteristics of the selected population, approaches to recruitment, method of screening, number of participants newly diagnosed with COPD, and numbers who were eligible, participated in screening, and underwent diagnostic spirometry. Where

these data were not provided, where possible we used information provided in the paper to derive them.

3.3.5 Methodological quality assessment

Included studies were assessed independently by two reviewers against criteria adapted from the QUADAS-1 (23) and QUADAS-2 (24) checklists, and the Cochrane risk of bias assessment tool for RCTs.(25) Disagreements were resolved through discussion.

3.3.6 Statistical analysis

Results from comparative studies were described but not suitable for synthesis. We therefore used data from individual study arms of the trials together with the non-comparative studies to summarise uptake of tests and yields. The yield was calculated as the proportion of all eligible subjects who were newly diagnosed with COPD. Where there was sufficient methodological homogeneity these were combined using random effects meta-analyses to estimate the uptake of screening and diagnostic tests and the proportion diagnosed with COPD for each case finding approach. Forest plots were constructed to visually explore between-study heterogeneity in the yield, including differences in population characteristics, screening tests, diagnostic criteria, and study design. All analyses were performed using Stata version 13.1 (Stata-Corp, College Station, Texas, USA) and StatsDirect version 2.7.9.

3.4 Results

3.4.1 Study selection

After removing duplicates, 2605 citations were identified and 266 full-text articles assessed for eligibility (Figure 3.2). 39 studies were finally selected from which 18 were included in meta-analyses. Studies that did not exclude patients with previously known COPD, or did not provide sufficient data to separate out new from existing diagnoses of COPD, were excluded.

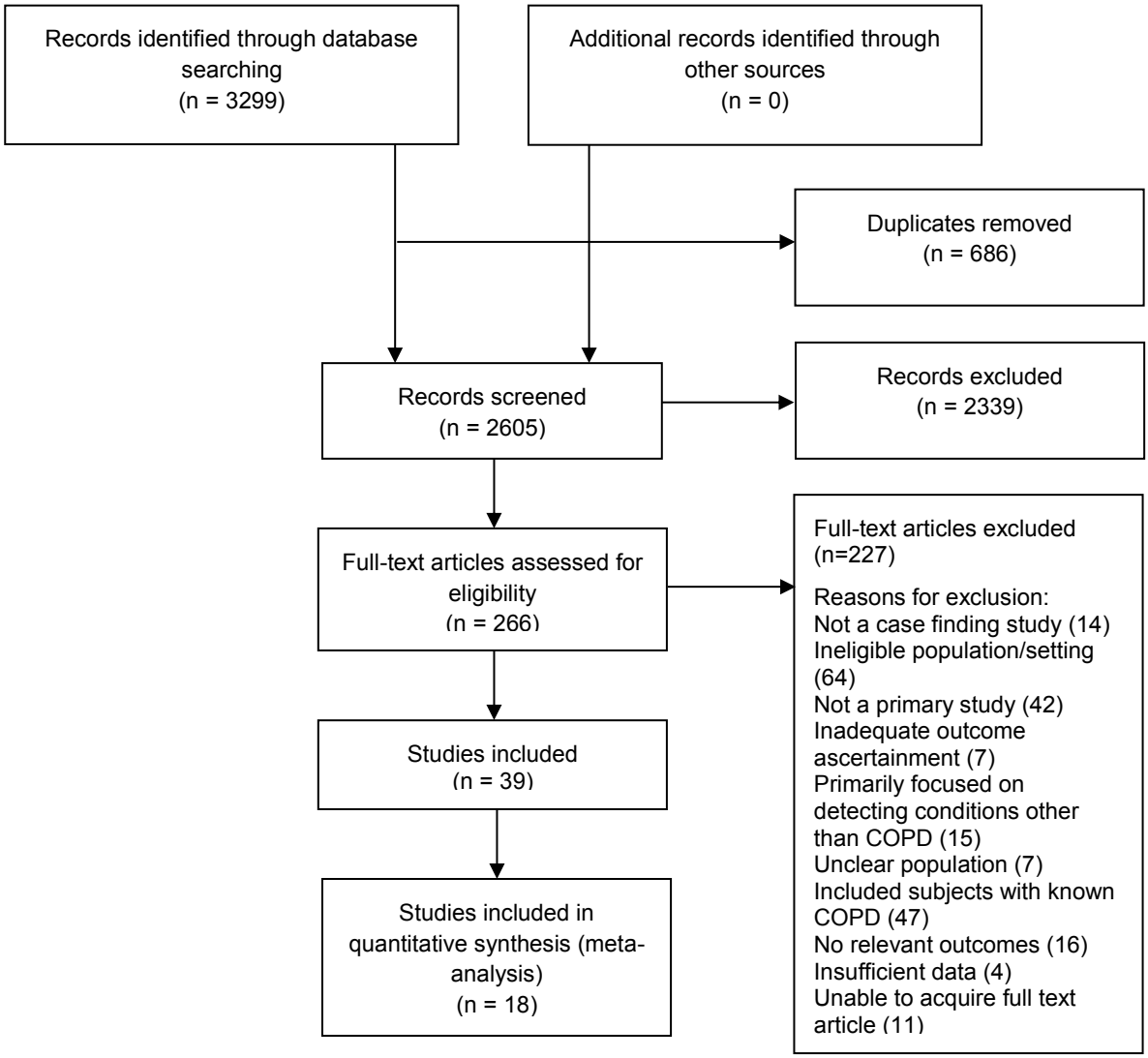

Figure 3.2 Article selection

3.4.2 Overall study characteristics

Of the 39 included studies, there were two individually randomised controlled trials (RCTs), one cluster RCT, one non-randomised controlled trial, 25 single arm before-after studies and ten cross-sectional test accuracy studies (Table S3.1). Most were conducted in general practices (n=34) and two were conducted in community pharmacies. They evaluated the use of screening questionnaires (n=13), handheld flow meters (n=5), and diagnostic spirometry (n=30). No studies evaluating other screening tests met the inclusion criteria.

3.4.3 Comparative studies

The comparative studies were highly heterogeneous with major differences in trial design (individually randomised controlled trials, cluster RCT, and non-randomised controlled trial) and comparators (usual care, invitation of high risk patients for spirometry, and screening with questionnaires; Table 3.1). An RCT of nurse-led case finding using written invitations to attend post-bronchodilator spirometry among eligible patients in four general practices in Australia showed this to have a 2.3% (95%CI 0.7 to 3.9%) higher yield of new cases than usual care.(26) A cluster RCT in the Netherlands found that a practice-managed approach to scoring a respiratory screening questionnaire and arranging follow-up was more effective than leaving patients to score their own questionnaires and request a spirometry assessment (difference in yield 0.9% [0.5 to 1.3%]).(27) Our own pilot trial of postal versus opportunistic invitation for screening using a respiratory questionnaire prior to pre-bronchodilator diagnostic spirometry indicated that a postal questionnaire might lead to higher yield though the study lacked sufficient power to detect a significant difference.(28) Finally, a non-randomised trial comparing public invitation for

spirometry for people with chronic respiratory symptoms (cough, sputum production, wheeze, or dyspnoea) to offering pre-/post-bronchodilator spirometry to patients attending primary care suspected by their GP to have COPD, found that the latter approach resulted in a significantly higher yield (difference in yield 18.6% (95% CI 12.6 to 24.6%]).(29) These comparative studies suffered from methodological problems but the main risks of bias arose from problems of randomisation, inadequate blinding of assessors to intervention arms and insufficient clarity about whether the populations in trial arms were comparable (Table 3.2). There was too much heterogeneity in their design and outcomes to combine their results.

Table 3.1 Comparative studies

Study	Study design & setting	Eligibility criteria	Intervention	Comparator	COPD definition	COPD[1]/eligible[2]	Limitations
Bunker 2009 (26)	RCT: nurse-led case finding using spirometry versus usual care in four practices (recruitment dates not reported)	Inclusion criteria Ever smokers aged 40-80 years Exclusion criteria Known diagnosis of COPD, cognitive impairment, non-English speaking, and <2 visits to practice in preceding year	**Case finding arm** Spirometry (unclear whether pre- or post-BD) performed by practice nurses	**Routine care**	$FEV_1/FVC<70\%$ (unclear whether pre- or post-BD)	Case finding 10/400 (2.5%) Routine care 1/408 (0.2%) Difference in yield=2.3% (95% CI 0.7 to 3.9%)	Method of randomisation not described. Inadequate outcome ascertainment. Outcome assessors not blinded. Unclear whether intervention groups comparable.
Dirven 2013 (30)	Cluster RCT: patient versus practice-managed scoring of a screening questionnaire in 16 general practices from May to September 2012	Inclusion criteria Age 40-70 years Exclusion criteria Previous diagnosis of asthma, COPD or significant lung disease. Also excluded patients using oxygen supplementation and with impaired mobility.	**Patient-managed arm** Stage 1 Patients mailed Respiratory Health Screening Questionnaire, self-calculated risk of COPD and advised to consult GP if score >19.5 Stage 2: Post-BD spirometry for subjects scoring >19.5	**Practice-managed arm** Stage 1 Patients were mailed the questionnaire but scoring performed by healthcare staff Stage 2: Post-BD spirometry on subjects scoring >19.5	Post-BD $FEV_1/FVC<0.7$ & physician's clinical evaluation	Patient-managed 25/6393 (0.4%) Practice-managed 48/3715 (1.3%) Difference in yield=0.9% (95% CI 0.5 to 1.3%)	Unclear whether intervention groups comparable (although practices were stratified by socioeconomic status). Unclear whether outcome assessors were blinded.

Study	Study design & setting	Eligibility criteria	Intervention	Comparator	COPD definition	COPD[1]/eligible[2]	Limitations
Haroon 2013 (28)	RCT: active versus opportunistic case finding in two general practices from May 2010 to January 2011	Inclusion criteria Ever smokers aged 35-79 years. Exclusion criteria Prior diagnosis of COPD or asthma.	**Active arm** Stage 1 Postal screening questionnaire Stage 2 Pre-BD spirometry in subjects with symptoms	**Opportunistic arm** Stage 1 Opportunistic screening questionnaire provided at routine primary care visits Stage 2 Pre-BD spirometry in subjects with symptoms	Pre-BD $FEV_1/FVC<0.7$ with $FEV_1<80\%$ predicted, lack of reversibility (reversibility defined as increase in FEV_1 of 200mL and 15% from pre-BD FEV1) and presence of respiratory symptoms.	Active 10/815 (1.2%) Opportunistic 6/819 (0.7%) Difference in yield=0.5% (95% CI -0.5 to 1.5%)	Unclear whether outcome assessors were blinded. Poor spirometry attendance.
Konstantikaki 2011 (29)	Non-randomised controlled trial: open spirometry programme versus case finding strategy in 24 semirural general practices from November 2008 to October 2009	Inclusion criteria >30 years Exclusion criteria History of respiratory tract infection in previous four weeks and inability to perform spirometry	**Open spirometry arm** Public invitation through local advertisements offering free spirometry to people with chronic respiratory symptoms	**Case finding strategy** Primary care physicians identified patients with a probable diagnosis of COPD in their daily practice and spirometry performed by research team.	History of exposure to noxious particles or gases, particularly smoking, compatible symptoms, and post-BD $FEV_1/FVC<0.7$	Open spirometry 76/1084 (7.0%) Case-finding 56/219 (25.6%) Difference in yield=18.6% (95% CI 12.6 to 24.6%)	No randomisation. Poor description of recruitment, selection criteria and spirometry.

1. Subjects newly diagnosed with COPD, 2. Eligible subjects
BD=bronchodilator, NR=not reported, FEV1=forced expiratory volume in 1 second, FVC=forced vital capacity, RCT=randomised controlled trial

Table 3.2 Quality assessment of randomised controlled trials

	Bunker 2009 (26)	Haroon 2013 (28)	Dirven 2013a (27)
Adequate description of method of randomisation	No	Yes	Yes
Adequate description of method of allocation concealment	No	No	No
Comparison groups similar except for intervention received	Unclear	Yes	Unclear
Participants blinded to intervention arm	Yes	Yes	Yes
Outcome assessors blinded to intervention arm	No	No	Unclear
Outcome data completeness described for each outcome, including attrition and exclusions from the analysis	No	Yes	Yes
Evidence of selective outcome reporting	No	No	No
Other sources of bias	Inadequate outcome ascertainment in control group	Poor spirometry attendance in both arms	Did not report number of spirometry procedures that were of acceptable quality

3.4.4 Estimating the effect of different case-finding approaches using all data from uncontrolled studies and single arms of trials

3.4.4.1 Methodological quality

The majority of included studies were uncontrolled single-arm studies and were highly heterogeneous. They generally provided a clear description of recruitment, selection criteria, characteristics of screened and clinically assessed participants, and how spirometry was performed. Most used standard diagnostic criteria for COPD or airflow obstruction as the outcome. However there were deficiencies in the reporting of eligible populations (the complete targeted population), withdrawals, uninterpretable and indeterminate test results, participant flow, and spirometry quality control procedures (Figure 3.3, and Tables S3.2a/b).

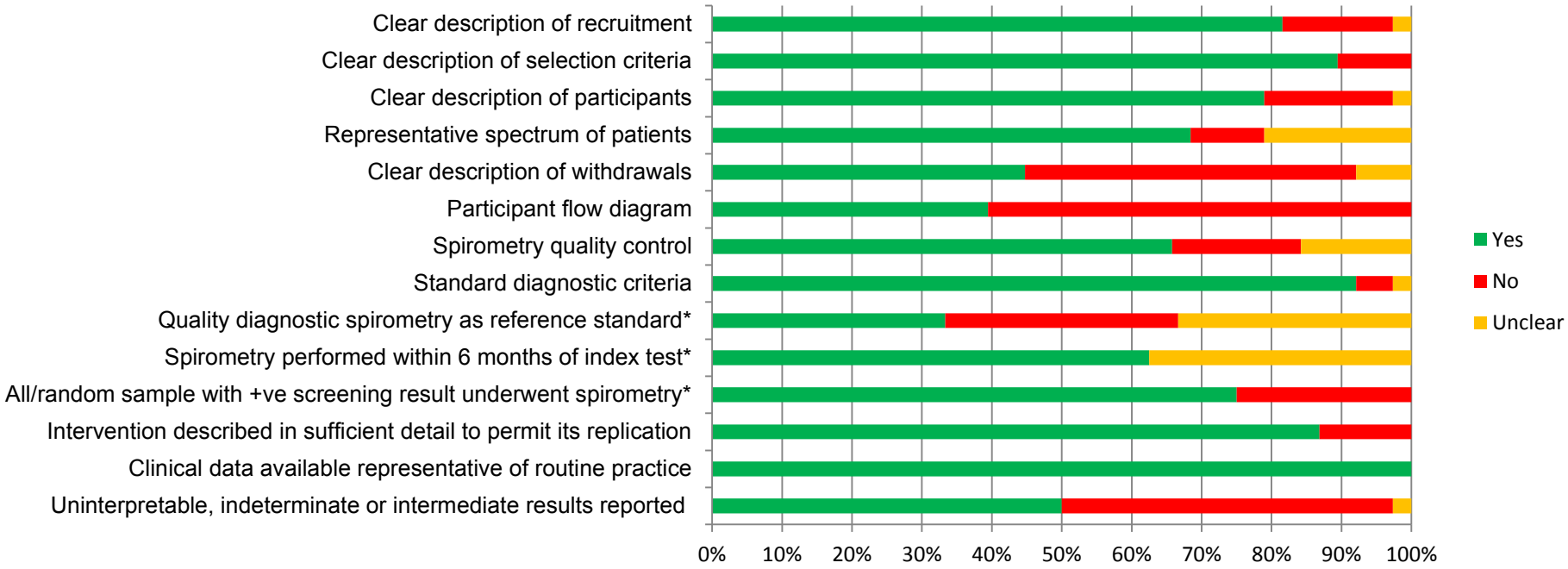

Figure 3.3 Quality assessment
*Only studies evaluating screening questionnaires and/or handheld flow meters

3.4.4.2 Recruitment and population selection

Participants were actively recruited through postal invitations, telephone calls, and advertisements (n=17 studies), opportunistically invited at primary care consultations (n=17), or recruited through a combination of both approaches (n=2; Table S3.1). Age (usually ≥40 years) and a positive smoking history were the main eligibility criteria although more than half of studies included never-smokers. A small number of studies specified additional eligibility criteria including presence of respiratory symptoms,(31-34) or recent acute respiratory infections.(35)

3.4.4.3 Screening tests and diagnosis of COPD

Strategies for targeting those at high risk included using basic patient characteristics only (e.g. age and smoking status (n=30)), use of respiratory screening questionnaires (n=13), and administration of handheld flow meters (n=5) prior to diagnostic spirometry. Only nine studies included a clinical component to the case definition of COPD, requiring reporting of relevant symptoms and exposures, or clinical judgment. All other studies used a purely physiological definition of COPD based on airflow limitation, most commonly a forced expiratory volume in one second to forced vital capacity ratio of less than 70% ($FEV_1/FVC<0.7$; n=30). In addition, 13 used pre-bronchodilator spirometry only for diagnosis.

3.4.4.4 Yield of new COPD cases with different approaches

Table 3.3 summarises the characteristics and yield of all of the included studies for each case finding approach. With direct invitation for diagnostic spirometry, the overall proportion of all eligible subjects newly diagnosed with COPD (as defined by each study), ranged from 1.7 to 30.5% (18 studies; Tables 3.4 and S3.3). Most had

mild-to-moderate disease although in some studies, a significant proportion (up to 37.2%) had severe disease (FEV_1<50% predicted). Studies with the highest yields were mainly test accuracy studies and those that limited recruitment to symptomatic patients.

Among 13 studies that used screening questionnaires prior to diagnostic spirometry (Tables 3.3, 3.5 and S3.4), the COPD Diagnostic Questionnaire (19) (CDQ- also referred to as the International Primary Airways Group Questionnaire, and the Respiratory Health Screening Questionnaire) was the most widely evaluated (n=5 studies). Overall, new cases of COPD ranged from 0.4% to 22.3% of those eligible, again with the highest yields found in test accuracy studies.

Five (mostly test accuracy) studies evaluated screening with handheld flow meters prior to diagnostic spirometry (Tables 3.3, 3.5, and S3.5). Overall, the yield (new cases of COPD) ranged from 6-20% of those eligible and all but one recruited patients only opportunistically.

From this overview, because of the huge heterogeneity of methodology and participants it was not possible to determine which of the approaches had greater yield. However with an initial screening test (either a screening questionnaire or handheld flow meter) the yield from the final diagnostic assessment (i.e. the proportion of those diagnosed with COPD out of all those who underwent spirometry) seemed higher (19-94% when using handheld flow meters, 14.3-42.1% when using screening questionnaires, and 4.1-40.2% when directly inviting patients for diagnostic spirometry).

Table 3.3 Studies evaluating spirometry, screening questionnaires and handheld flow meters

		Diagnostic spirometry (n=30)	Screening questionnaires (n=13)	Handheld flow meters (n=5)
Study design	RCT	1	1	0
	Cluster RCT	0	1	0
	Non-randomised trial	1	0	0
	Test accuracy study	7	8	4
	Single arm study	21	3	1
Participants*	Screened	-	18,932	4759
	Performed spirometry	63,087	8845	568
	Diagnosed with COPD	10,428	1996	346
Mean age (years)		47.9-65.3	52.3-65.3	52-65
Male (%)		19.6-100	38.1-69	37.7-99.7
Required smoking status	Current/ex-smokers	11	7	2
	Inc. never smokers	19	6	3
Required respiratory symptoms		5	0	0
Setting	General practice(s)	24	12	5
	Pharmacies	1	1	0
	Other	3	0	0
	Not reported	2	0	0
Number of centres		1-821	1-36	3-25
	Multicentre	24	12	5
	Single centre	2	1	0
	Not reported	4	0	0
Recruitment strategy	Active	13	6	1
	Opportunistic	14	4	3
	Active & opportunistic	1	2	1
	Not reported	2	1	0
Questionnaires	CDQ[1]	-	6	-
	LFQ	-	2	-
	Not named	-	5	-
Common items	Age	-	11	-
	Smoking status	-	12	-
	Respiratory symptoms	-	13	-
	Allergies	-	7	-

		Diagnostic spirometry (n=30)	Screening questionnaires (n=13)	Handheld flow meters (n=5)
Handheld spirometers				
Device	Piko-6®	-	-	4
	COPD-6®	-	-	1
Operator	Nurse	-	-	3
	GP	-	-	1
	Not reported	-	-	1
Use of bronchodilator	Pre-bronchodilator	-	-	3
	Post-bronchodilator	-	-	2
Test threshold	$FEV_1/FEV_6<0.7$	-	-	3
	$FEV_1/FEV_6<0.75$	-	-	1
	$FEV_1/FEV_6<0.8$	-	-	1
Spirometry	Post-bronchodilator	15	10	5
	Pre-bronchodilator	13	3	0
	Not reported	2	0	0
Definition of airflow obstruction	Post-BD $FEV_1/FVC<0.7$	12	9	3
	Pre-BD $FEV_1/FVC<0.7$	9	2	
	Post-BD $FEV_1/FVC<LLN$	1		
	Pre-BD $FEV_1/FVC<LLN$	1		
	Other	7	2	2
Symptoms in definition of COPD		4	3	0
Spirometry quality control	Yes	22	11	2
	No	4	2	1
	Unclear	4	0	2
Range of results				
New COPD cases/eligible subjects*		1.7-30.5% (19)	0.4-22.3% (8)	6-20% (3)
New COPD cases/no. screened		-	1.5-30.0% (12)	3-20% (5)
New COPD cases /no. assessed with spirometry		4.1-40.2% (30)	14.3-42.1% (13)	19-94% (5)
Severity of new cases (FEV_1 % predicted)**	≥80%	11.5-86.7%	11.5-51.1%	33.3-64.3%
	50-80%	12.9-68.2%	42.8-87.5%	35.7-61.4%
	<50%	0-37.2%	5.3-37.2%	0-16.2%

BD=bronchodilator, CDQ=COPD Diagnostic Questionnaire (also referred to as the Respiratory Health Screening Questionnaire and the International Primary Airways Group Questionnaire), FEV1=forced expiratory volume in 1 second, FVC=forced vital capacity, LFQ=Lung Function Questionnaire, LLN=lower limit of normal, RCT=randomised controlled trial.

*A number of studies did not report the total eligible population **Restricted to studies that reported severity staging according to the GOLD strategy.(16)

Table 3.4 Yield from case finding with spirometry (30 studies)

Study	Recruitment strategy	Mean age (years)	Male (%)	Smoking status	Population		Diagnosed with COPD	New diagnoses of COPD as a percentage of those:	
					Eligible	Spirometry**		Eligible	Spirometry**
Al Ghobain 2011	Opportunistic	47.9	89.6	Smokers	1380	1380	71	5.1	5.1
Bednarek 2008	Active	56.7	39.0	Any	2250	1986	149	6.6	7.5
Broekhuizen*	Opportunistic	63	45	Any	NR	353	102	NR	28.9
Bunker 2009	Active	62.4	57	Smokers	400	79	10	2.5	12.7
Clotet 2004	NR	54	80	Smokers	177	155	36	20.3	23.2
DeJong 2004	Active	55	49	Smokers	NR	243	43	NR	17.7
Freeman 2005	Active	61.7	52	Smokers	1195	369	62	5.2	16.8
Frith 2011	Active & opportunistic	61	69	Smokers	233	233	57	24.5	24.5
Fuller 2012	Active	55	40	Any	NR	185	16	NR	8.6
Geijer 2005	Active	50	100	Smokers	918	805	210	22.9	26.1
Hanania 2010	Opportunistic	NR	38.1	Any	NR	937	156	NR	16.6
Kimura 2011a	Active	63.3	33.7	Any	839	814	59	7.0	7.2
Kimura 2011b	Active	NR	NR	Any	1300	363	22	1.7	6.1
Kögler 2010*	Opportunistic	NR	62.2	Smokers	NR	1282	516	NR	40.2
Konstantikaki 2011[1]	Active	62.5	64	Any	1084	1084	76	7.0	7.0
Konstantikaki 2011[2]	Active	63.5	19.6	Any	NR	219	56	NR	25.6
Kotz 2008	Active	52.3	58.7	Smokers	1052	826	278	26.4	33.7
Leuppi 2010	Opportunistic	51.6	58.6	Smokers	26400	24995	4231	16.0	16.9
Lokke 2012*	Opportunistic	57.5	51	Smokers	4000	4049	878	22.0	21.7
Price 2006	Active	58.2	49.3	Smokers	NR	898	155	NR	17.3
Queiroz 2012	Opportunistic	65	NR	Smokers	NR	214	45	NR	21.0
Sandelowsky 2011*	Active	55	44.2	Smokers	250	150	38	15.2	25.3
Sichletidis 2011	Opportunistic	65.3	57.1	Any	1250	1250	111	8.9	8.9
Stratelis 2004	Active	48	43	Smokers	5332	512	141	2.6	27.5
Takahashi 2003	NR	63.1	76.3	Any	NR	1168	281	NR	24.1
Takemura 2005	Opportunistic	49.8	69.3	Any	NR	10256	425	NR	4.1
Thorn 2012	Opportunistic	61.2	43.3	Smokers	NR	305	77	NR	25.2
Ulrik 2011*	Opportunistic	58	49	Smokers	10050	3095	1079	10.7	34.9
Vandevoorde 2007	Opportunistic	52.3	42.5	Smokers	141	129	43	30.5	33.3
Vrijhoef 2003	Opportunistic	53.5	48.5	Smokers	NR	231	17	NR	7.4
Van Schayck	Opportunistic	NR	NR	Smokers	229	201	30	13.1	14.9

1. Open spirometry programme, 2. Case-finding programme, NR=not reported

*Only recruited subjects complaining of respiratory symptoms or an acute respiratory infection

**Received a spirometry assessment

Table 3.5 Yield from case finding with screening questionnaires and/or handheld flow meters

Study	Recruitment strategy	Mean age (years)	Male (%)	Smoking status	Population			COPD	Subjects diagnosed with COPD as a percentage of those:		
					Eligible	Screened	Received spirometry		Eligible	Screened	Received spirometry
Screening questionnaires											
CDQ (≥19.5)											
Dirven 2013a[1]	Active	53.5	51	Any	6393	1715	140	25	0.4	1.5	17.9
Dirven 2013a[2]	Active	53.7	49.7	Any	3715	1855	135	48	1.3	2.6	35.6
Dirven 2013b	Active	NR	NR	Any	849	293	39	9	1.1	3.1	23.1
Frith 2011	Combined	61	69	Smokers	233	233	107	40	17.2	17.2	37.4
Kotz 2008	Active	52.3	58.7	Smokers	1052	1052	554	233	22.1	22.1	42.1
Price 2006	Active	58.2	49.3	Smokers	NR	898	243	91	NR	10.1	37.4
CDQ (≥16.5)											
Frith 2011	Combined	61	69	Smokers	233	233	163	52	22.3	22.3	31.9
Kotz 2008	Active	52.3	58.7	Smokers	1052	1052	844	316	30.0	30.0	37.4
Price 2006	Active	58.2	49.3	Smokers	NR	898	406	125	NR	13.9	30.8
Sichletidis 2011	Opportunistic	65.3	57.1	Any	1250	1250	693	103	8.2	8.2	14.9
All other questionnaires											
Buffels 2004	Opportunistic	NR	45	Any	3158	3158	703	126	4.0	4.0	17.9
Castillo 2009	Opportunistic	55	42	Any	NR	161	96	21	NR	13.0	21.9
Freeman 2005[3]	Active	61.7	52	Smokers	1195	369	121	47	3.9	12.7	38.8
Freeman 2005[4]	Active	61.7	52	Smokers	1195	369	142	54	4.5	14.6	38.0
Hanania 2010	Opportunistic	NR	38.1	Any	NR	937	537	129	NR	13.8	24.0
Haroon 2013	Opportunistic	55.3	67.6	Smokers	819	111	28	6	0.7	5.4	21.4
Haroon 2013	Active	53.0	60.8	Smokers	815	212	70	10	1.2	4.7	14.3
Laniado-Laborin 2011	Active	57.6	39.8	Any	NR	NR	2617	472	NR	NR	18.0
Mintz 2011	NR	53.9	51.2	Smokers	NR	1575	1225	315	NR	20.0	25.7
Handheld flow meter											
Duong-Quy 2009	Active	52	99.7	Smokers	2464	2464	144	136	5.5	5.5	94.4
Frith 2011	Combined	61	69	Smokers	233	233	97	46	19.7	19.7	47.4
Kaufmann 2009	Opportunistic	54.8	37.7	Any	NR	507	74	14	NR	2.8	18.9
Sichletidis 2011	Opportunistic	65.3	57.1	Any	1250	1250	147	89	7.1	7.1	60.5
Thorn 2012	Opportunistic	61.2	43.3	Smokers	NR	305	106	61	NR	20.0	57.5
CDQ & handheld flow meter											
Sichletidis 2011	Opportunistic	65.3	57.1	Any	1250	1250	111	82	6.6	6.6	73.9

1. Patient-managed arm, 2. Practice-managed arm, 3. Multiple response questions, 4. Binary response questions
CDQ=COPD Diagnostic Questionnaire (score threshold), Combined=active and opportunistic, NR=not reported

3.4.4.5 Exploring the effect of different target populations and recruitment strategies

It was only possible to combine the results using meta-analyses in a selection of studies that had apparent homogeneity as described below. Studies among ever smokers were chosen, and a further subset among those already reporting respiratory symptoms.

3.4.4.6 Uptake of screening/diagnostic tests

A meta-analysis of studies among ever smokers invited for diagnostic spirometry showed that opportunistic invitation at routine primary care attendances was associated with a significantly higher uptake of spirometry (97% [95% CI 90 to 100%]; n=5 studies (33, 36-39)) than when actively inviting patients by post (47% [16 to 80%]; n=6 studies (26, 35, 40-43)), although confidence intervals for the latter were wide. Meta-analysis of the proportion responding to postal questionnaires (n=4 studies (27, 28, 40, 44)) showed an average response of 30% (95% CI 20 to 41%). There were insufficient data to estimate the response when questionnaires were distributed opportunistically at primary care attendances.

3.4.4.7 Target populations

From four similar studies, where ever smokers aged ≥40 years were opportunistically invited directly for diagnostic spirometry, 20% (95% CI 7 to 37%; n=4 studies (36, 38, 45, 46)) were diagnosed with airflow obstruction (Figure 3.4) although the confidence intervals were wide and not all of these subjects would necessarily have clinical symptoms. Restricting recruitment to ever smokers reporting a history of respiratory symptoms/infections provided a higher yield of 32% (95% 21 to 44%; n=3 studies (32, 33, 47)) and these would constitute new clinical diagnoses of COPD, although

again these confidence intervals were wide and overlap with the yield from inviting ever smokers. Note that these studies were limited to those where patients attended primary care and were opportunistically invited to participate and did not include active written invitation to patients.

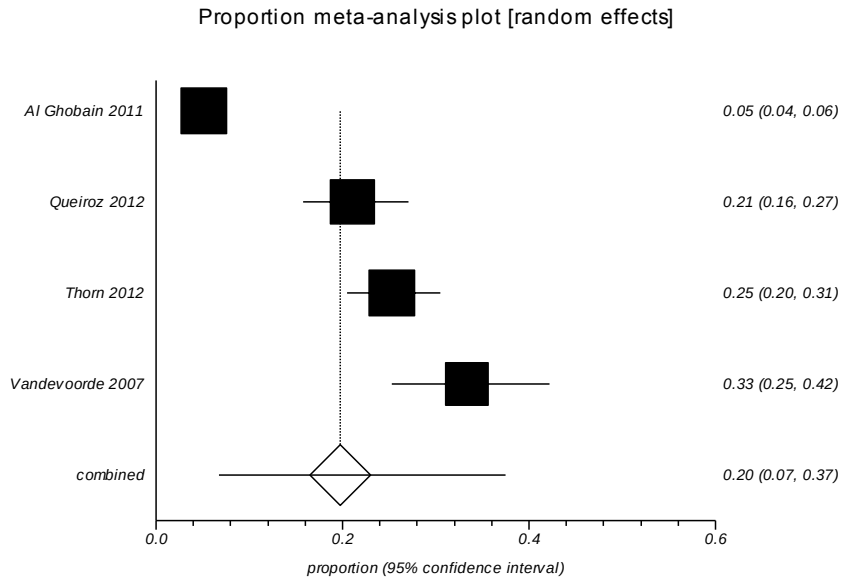

Figure 3.4 Random effects meta-analysis of the proportion of eligible ever smokers diagnosed with COPD when opportunistically invited for spirometry (restricted to studies that defined airflow obstruction as FEV1/FVC<0.7)

3.5 Discussion

3.5.1 Main findings

This review incorporated evidence from 39 primary studies and summarised the effectiveness of case finding using a number of approaches. The few comparative studies had a number of methodological limitations and were highly heterogeneous. Their findings suggest that active case finding in primary care is likely to identify a greater number of patients with undiagnosed COPD compared to usual care, that arrangement of follow-up should be performed by practices rather than by patients, and that assessment of patients clinically suspected to have COPD is likely to be more effective than widespread invitation of the general public for screening. The majority of studies found were non-comparative and also highly heterogeneous, with significant limitations in study design and the reporting of eligible populations, withdrawals, indeterminate results and spirometry quality control procedures. The lack of direct comparisons and the heterogeneity in populations, study design, definition of COPD and methods for estimating the yield limited the ability to combine results and to draw conclusions about the most effective case finding approach.

Indirect comparisons suggest that uptake for spirometry is higher when patients are invited opportunistically at routine primary care visits than with active written invitation by post and response to mailed screening questionnaires is likely to be around 30%. Studies that opportunistically invited patients with a history of respiratory symptoms to undertake spirometry seemed to have a higher yield than those that invited ever smokers without first eliciting a history of relevant symptoms, although the difference in the yields for both groups was not statistically significant. The yields from the different approaches (direct invitation for spirometry, and screening with a postal

questionnaire or handheld flow meter) were highly heterogeneous and no approach was clearly associated with a higher overall yield. However studies that first screened patients using either a questionnaire or handheld flow meter seemed to achieve a higher yield at the diagnostic assessment, suggesting that fewer diagnostic assessments may be needed per case detected. However, this would be at the expense of applying screening tests to the target population prior to referral for diagnostic assessment. Again these estimates were highly heterogeneous and comparisons were indirect, so these findings could be biased by differences in study design and population characteristics. Finally, case finding is likely to uncover a significant burden of disease, and although the majority of this will be of mild-to-moderate severity, a significant proportion will have severe airflow obstruction.

3.5.2 Relationship to existing reviews

The UK National Screening Committee recently recommended against screening for COPD due to a lack of relevant RCTs, and insufficient evidence on the optimal approach and the benefits of early treatment.(17) They also concluded that case-finding among symptomatic individuals with more developed COPD is likely to be cost-effective and should continue. A systematic review on the use of diagnostic spirometry for population screening similarly concluded that it could not be recommended on the basis that it would require a large number of assessments to prevent a single COPD exacerbation and would largely unveil patients with asymptomatic airflow obstruction for whom there are limited therapeutic options.(18) Our findings agree that there are currently few RCTs but also highlight several important methodological limitations that should be addressed in future trials evaluating case finding strategies. Our review also agrees that targeting symptomatic

individuals may increase the efficiency of case finding but also shows that while the majority of patients found have mild disease (which is arguably when secondary prevention may be most effective), a significant proportion of those diagnosed are likely to have moderate-to-severe disease that would most likely benefit from recommended therapies for COPD.(9)

Jithoo and colleagues recently compared alternative case finding strategies using data from the Burden of Obstructive Lung Disease Study and concluded that peak flow meters were a cost-effective screening test for COPD.(48) However the peak expiratory flow rate was derived from quality-controlled spirometry measurements and may not necessarily reflect the accuracy of actual peak flow meters used in everyday clinical practice. Our search strategy did not identify any studies directly evaluating peak flow meters for case finding. RCTs comparing the effectiveness of screening with peak flow meters against other screening tests such as questionnaires and handheld flow meters should therefore be considered.

3.5.3 Strengths and limitations

We performed an extensive review of the literature and incorporated detailed evidence on 39 primary studies. However there was extensive heterogeneity, which limited the quantitative synthesis. There were also very few RCTs and those that were identified were highly heterogeneous, preventing direct comparison. We therefore mainly relied on indirect comparisons, which may potentially be biased because of differences in study design and population characteristics. The size of eligible populations was often not reported which limited estimates of the uptake of screening tests and could potentially bias estimates obtained from the meta-

analyses. Furthermore many of the combined results had wide confidence intervals and should be interpreted with caution.

Another important limitation was that most studies used a purely physiological definition of COPD without clearly specifying the requirement for relevant symptoms, associated risk factors or compatible clinical history. Use of a physiological definition of COPD is likely to overestimate the effectiveness of case finding- an analysis of the Health Survey for England (49) I conducted found that only about half of individuals with undiagnosed airflow obstruction have chronic respiratory symptoms in keeping with a clinical diagnosis of COPD. Identification of individuals with asymptomatic airflow obstruction is problematic in the absence of evidence-based recommendations to guide their management.(18)

3.5.4 Implications for practice, research and policy

Case finding through any approach is likely to uncover a substantial number of patients with undiagnosed COPD. Primary care services wishing to identify patients with undiagnosed COPD are likely to achieve a higher uptake for spirometry by offering this opportunistically to high risk patients at routine primary care visits than by using postal invitations. However it is unclear which approach results in a higher overall yield. Targeting patients with a history of respiratory symptoms or infections may improve the case finding yield and screening using either a respiratory questionnaire such as the CDQ or handheld flow meter followed by diagnostic assessment in those with a positive screening test may reduce the number of diagnostic assessments needed compared to directly inviting all high risk patients for diagnostic spirometry. However it is unclear whether screening with a handheld flow meter would actually reduce the overall number of clinical contacts or improve the

use of healthcare resources. While the majority of patients identified through case finding will have mild-to-moderate disease, around one in five is likely to have severe disease requiring more extensive management.

There is extensive heterogeneity in the literature on evaluations of case finding strategies for COPD with few RCTs, making comparative assessments on the effectiveness of different approaches, in terms of yield, highly problematic. Future studies should directly compare alternative approaches, particularly addressing the most effective patient population to target (e.g. smokers with a history of respiratory symptoms or those identified as at high risk by prediction models), the recruitment strategy (opportunistic invitation at primary care attendance versus a more active approach using written [mailed/emailed/texted] invitations) and use of screening tests (e.g. screening questionnaires, handheld flow meters, peak flow meters, risk prediction models, alone and in combination).

A high yield at the diagnostic assessment (i.e. a high proportion of subjects attending a spirometry assessment receiving a diagnosis of COPD) does not necessarily imply a high yield for the case finding process as a whole. This is particularly the case if a large proportion of eligible subjects did not attend a screening or diagnostic assessment. Studies evaluating case finding strategies should thus consider the whole targeted population when considering the overall yield of that strategy in terms of the proportion of that population who are subsequently identified with COPD.

Future studies should also use a clinical definition of COPD that aligns with current recommendations, requiring the presence of both relevant symptoms and clinical features in addition to airflow limitation (50) using a standardised definition so that

findings across studies can be compared. They should also report withdrawals and indeterminate results and present this in a participant flow chart, including a description of the size and characteristics of the eligible population as well as those who received a screening and diagnostic assessment. They should also employ strict quality control procedures for spirometry to avoid misdiagnosis. The findings of these studies will be important to enable economic evaluations of alternative case finding strategies in order to aid policy makers to make appropriate decisions on the most cost-effective approach.

3.5.5 Conclusion

There is extensive heterogeneity and few RCTs among studies evaluating case finding strategies for COPD in primary care. Uptake for spirometry assessments may be higher when opportunistically inviting patients at routine primary care visits than active written invitations, though it is unclear which approach has the higher overall yield. Targeting ever smokers with a history of respiratory symptoms may improve the yield and using screening tests such as questionnaires may reduce the number of diagnostic assessments needed to identify a patient with COPD. High quality RCTs are needed to make direct comparisons of alternative case finding strategies, including the target population, recruitment strategy and screening tests, using a standardised clinical definition of COPD, and taking into consideration the methodological limitations of previous studies highlighted in this review.

3.6 Supplementary Tables

Table S3.1 Study characteristics

Study	Country	Study design	Setting	Recruitment method	Eligibility criteria	Screening & diagnostic test(s)
Al Ghobain 2011 (36)	Saudi Arabia	Single arm before-after study	60 primary healthcare clinics	Invited patients routinely attending private primary healthcare clinics. Dates of recruitment not reported.	Inclusion criteria Age ≥40 years & current/ex-smoker of >5 years duration Exclusion criteria Known lung disease, upper respiratory tract infection or spirometry contraindications	Pre-/post-BD spirometry
Bednarek 2008 (51)	Poland	Single arm before-after study	Single primary care practice	Personalised letter from primary care physician. Dates of recruitment not reported.	Inclusion criteria Age ≥40 years Exclusion criteria None	Pre-/post-BD spirometry
Broekhuizen 2010 (31)	Netherlands	Single arm before-after study	73 general practitioners	Invited patients visiting their GP for persistent cough lasting ≥14 days during the winter period from January 2006-April 2009	Inclusion criteria Age >50 years & persistent cough lasting ≥14 days Exclusion criteria Known COPD or asthma, suspected pneumonia, severe psychiatric symptoms, or terminal illness	Extensive diagnostic work-up 90 days after presentation, including pre- /post-BD spirometry
Buffels 2004 (52)	Belgium	Cross-sectional test accuracy study	20 general practitioners	Invited patients routinely attending general practice over a 12 week period in 1999	Inclusion criteria Age 35-70 years Exclusion criteria Receiving bronchodilators and/or inhaled corticosteroids	Stage 1 Screening questionnaire Stage 2 Pre-BD spirometry in all subjects with respiratory symptoms and 10% sample of asymptomatic subjects

Study	Country	Study design	Setting	Recruitment method	Eligibility criteria	Screening & diagnostic test(s)
Bunker 2009 (26)	Australia	RCT (case finding vs. usual care)	4 general practices	Postal invitation with two reminder letters. Dates of recruitment not reported.	Inclusion criteria Current/ex-smokers aged 40-80 years Exclusion criteria Known diagnosis of COPD, cognitive impairment, non-English speaking, <2 visits to practice in preceding year	Spirometry (unclear whether pre- or post-BD)
Castillo 2009 (53)	Spain	Single arm before-after study	13 community pharmacies	Invited subjects visiting participating pharmacies in April/May 2007	Inclusion criteria Age >40 years Exclusion criteria History of lung disease or use of inhalers	Stage 1 Screening questionnaire Stage 2 Pre-BD spirometry for those with ≥3 positive answers
Clotet 2004 (54)	Spain	Single arm before-after study	NR	NR	Inclusion criteria Age 40-76 years & active smoker for ≥10 years with no or only mild respiratory symptoms Exclusion criteria Previous diagnosis of COPD, asthma, bronchiectasis, cystic fibrosis, tuberculosis, chronic bronchitis, restrictive pulmonary disease or receiving bronchodilators	Pre-BD spirometry
DeJong 2004 (55)	US	Single arm before-after study	Range of settings – unclear	Direct mailing to 1500 individuals who were coded as being a current/ex- smoker within a large primary care clinic system. Advertised via article in the local newspaper and posters placed in 6 physician offices and 1 hospital. (Dates not reported)	Inclusion criteria Age 40-60 years (although no subjects were turned away) Exclusion criteria None	Pre-BD spirometry

Study	Country	Study design	Setting	Recruitment method	Eligibility criteria	Screening & diagnostic test(s)
Dirven 2013a (30)	Netherlands	Cluster RCT (patient vs. practice-managed screening approach)	16 general practices in four cities	The COPD Diagnostic Questionnaire (referred to as the "Respiratory Health Screening Questionnaire") was posted to all eligible patients registered at participating practices from May to September 2012	Inclusion criteria Age 40-70 years Exclusion criteria Previous diagnosis of asthma, COPD or significant lung disease such as lung cancer, pneumoconiosis, tuberculosis, bronchiectasis and pneumonectomy. Also excluded patients using oxygen supplementation and with impaired mobility.	Stage 1 In the "patient-managed" arm subjects were asked to calculate their risk of COPD using a screening questionnaire (COPD Diagnostic Questionnaire) and advised to consult their GP if their score was >19.5. In the "practice-managed" arm the scoring was performed by the practice and subjects with a score >19.5 were invited for spirometry. Stage 2: Post-BD spirometry for subjects with a score >19.5
Dirven 2013b (44)	Netherlands	Single arm before-after study	10 general practices in two cities (five low socioeconomic status (SES) practices and five moderate-to-high SES)	The COPD Diagnostic Questionnaire (referred to as the "Respiratory Health Screening Questionnaire") was posted to all eligible patients registered at participating practices from May-July 2012.	Inclusion criteria Age 40-70 years Exclusion criteria As above (Dirven 2013a)	Stage 1: Screening questionnaire (COPD Diagnostic Questionnaire; score completed by practice assistant) Stage 2: Post-BD spirometry for subjects with a score ≥19.5
Duong-Quy 2009 (56)	Vietnam	Cross-sectional test accuracy study	12 primary care medical centres in one city	Broadcast an advertisement on the local television daily for one week. A recruitment company was used to help with recruiting participants (details not reported). Eligible subjects expressing an interest in participating were advised to attend one of the twelve primary care centres from January 2007- February 2008.	Inclusion criteria Current/ex-smokers aged >40 years with >10 pack-years Exclusion criteria Previously diagnosed respiratory disease (asthma, COPD and tuberculosis)	Stage 1 Pre-BD handheld flow meter (Piko-6®) Stage 2 Full medical assessment including clinical examination, pulmonary radiology, ECG, and post-BD spirometry for subjects with $FEV_1/FEV_6<0.7$ and a sample of subjects with $FEV_1/FEV_6 \geq 0.7$
Freeman 2005 (40)	UK	Cross-sectional test accuracy study	One general practice	Postal invitation from October 1997-April 2002	Inclusion criteria Current/ex-smokers aged ≥40 years & had either received respiratory medications in the preceding two years or history of asthma	Stage 1 Screening questions Stage 2 Pre-/ post-BD spirometry on all subjects

Study	Country	Study design	Setting	Recruitment method	Eligibility criteria	Screening & diagnostic test(s)
Frith 2011 (20)	Australia	Cross-sectional test accuracy study	Four primary care practices	Recruited during routine practice visits, invitation to study days, and via local newspaper advertisement between August-December 2006	Inclusion criteria Current/ex-smokers aged ≥50 years with no prior diagnosis of obstructive lung disease (COPD, emphysema, chronic bronchitis, asthma) & no treatment for obstructive lung disease in past 12 months Exclusion criteria Refusal or inability to give consent, pre-existing non-obstructive lung disease, symptoms suggestive of unstable heart disease, and spirometry contraindications	Stage 1: Pre-BD Piko-6® & screening questionnaire (COPD Diagnostic Questionnaire) Stage 2: Pre-/ post-BD spirometry on all subjects
Fuller 2012 (57)	US	Single arm before-after study	Four community pharmacies and offsite screening events. Each pharmacy was an established patient care centre which had a clinical pharmacist and provided services such as immunisation, medication therapy management and smoking cessation counselling	Screening was offered to any interested subjects fulfilling the eligibility criteria. Participation was encouraged by in-store advertising, brochures, prescription bag ties and fliers. Recruitment took place from March-June 2010	Inclusion criteria Age ≥35 years Exclusion criteria History of lung cancer, pregnancy at time of screening, previous diagnosis of COPD, lung surgery or resection, recent abdominal or thoracic surgery, respiratory infection within the previous 3 weeks, uncontrolled hypertension (>160/90 mm Hg),and inability to produce three acceptable tracings during spirometry	Pre-BD spirometry
Geijer 2005 (41)	Netherlands	Single arm before-after study	Primary care (otherwise unspecified)	Mailed invitation ascertaining smoking status, only inviting current smokers in 1998 with follow-up measurements in 2003	Inclusion criteria Males aged 40-65 years who had smoked ≥1 cigarette per day during previous 12 months Exclusion criteria Prior history of lung disease, ex-/non-/pipe/cigar smokers	Pre-/post-BD spirometry (post-BD spirometry only performed if pre-BD FEV_1 % predicted<85%)
Hanania 2010 (58)	US	Cross-sectional test accuracy study	Two family physician group offices	Invited patients visiting the practices from March-May 2008	Inclusion criteria Age ≥40 years Exclusion criteria: None	Stage 1 Screening questionnaire (Lung Function Questionnaire) Stage 2 Pre-BD spirometry in all subjects

Study	Country	Study design	Setting	Recruitment method	Eligibility criteria	Screening & diagnostic test(s)
Haroon 2013 (28)	UK	RCT (targeted vs. opportunistic case finding)	Two general practices	Postal invitation ("targeted") vs. invitation to patients routinely attending primary care ("opportunistic") from May 2010-January 2011	Inclusion criteria Current/ex-smokers aged 35-79 years Exclusion criteria Prior diagnosis of COPD or asthma	Stage 1 Screening questionnaire Stage 2 Pre-BD spirometry in subjects with symptoms
Kaufmann 2009 (59)	Austria	Single arm before-after study	Three general practices	Invited patients who attended participating practices from May-June 2005	Inclusion criteria NR Exclusion criteria Known lung or psychiatric disease	Stage 1 Pre-BD handheld flow meter (Piko-6®) Stage 2 Post-BD spirometry
Kimura 2011 (60)	Japan	Repeated single arm before-after studies (reported two separate studies)	Community health centre	Personalised postal invitation from the local government to the general population from 2004-2007. COPD was described in a newsletter and a lecture was delivered by one of the authors before the study, emphasizing the prevention of severe life-threatening disease	Inclusion criteria Age >40 years (study 1). Inclusion criteria not specified for study 2 Exclusion criteria Illiteracy	Pre-BD spirometry
Kögler 2010 (32)	Germany	Single arm before-after study	684 urban and rural primary care practices and 137 respiratory physicians	Invited consecutive patients routinely attending primary care (dates not reported)	Inclusion criteria Age ≥40 years with no prior diagnosis of lung disease. Subjects were then selected either if they had ever smoked or regularly suffered from cough and/or breathlessness.	Assessment by a pulmonologist, including spirometry (unclear whether pre- or post-BD)
Konstantikaki 2011 (29)	Greece	Non-randomised controlled trial	24 semirural primary care practices	Public invitation with local advertisement offering free spirometry to individuals with chronic respiratory symptoms (open spirometry programme) from November 2008-October 2009. Primary care physicians identified patients with a probable diagnosis of COPD in their daily practice (case finding strategy).	Inclusion criteria >30 years Exclusion criteria History of respiratory tract infection in previous four weeks and inability to perform spirometry	Post-BD spirometry

Study	Country	Study design	Setting	Recruitment method	Eligibility criteria	Screening & diagnostic test(s)
Kotz 2008 (42)	Netherlands	Cross-sectional test accuracy study	General population and primary care practices	Advertisements in a local newspaper, flyers, posters, mailings to households and invitation during primary care consultations from January 2005-December 2006	Inclusion criteria Current smokers aged 40-70 years with ≥10 pack years & motivated to stop smoking, able to read and speak Dutch & reporting a respiratory symptom (cough, phlegm or dyspnoea) Exclusion criteria: Prior respiratory diagnosis, spirometry in previous 12 months or contraindications to smoking cessation therapy	Stage 1 Questionnaire (COPD Diagnostic Questionnaire) Stage 2 Pre-/post-BD spirometry in all participants
Laniado-Laborin 2011 (61)	Mexico	Single arm before-after study	Primary care practices in 27 cities from March-October 2008	Received phone call from family physician to schedule an assessment from March-October 2008	Inclusion criteria Age ≥40 years Exclusion criteria None	Stage 1 Screening questionnaire Stage 2 Subjects with risk factors or symptoms proceeded to post-BD spirometry
Leuppi 2010 (37)	Switzerland	Single arm before-after study	Primary care practices with 440 GPs	Invited patients attending primary care (dates not reported)	Inclusion criteria Current smokers aged ≥40 years Exclusion criteria None	Pre-BD spirometry
Løkke 2012 (33)	Denmark	Single arm before-after study	Primary care practices with 241 GPs	Invited consecutive patients attending practices during March-August 2010	Inclusion criteria Age ≥35 years & current/ex-smoker or relevant occupational exposure & ≥1 respiratory symptom (dyspnoea, cough, wheeze, sputum and/or recurrent chest infections) Exclusion criteria Unable to perform spirometry or previous diagnosis of chronic respiratory disease	Pre-BD spirometry with bronchodilator reversibility for patients with airway obstruction and corticosteroid reversibility test for subjects with an increase in FEV_1 between 200-500mL

Study	Country	Study design	Setting	Recruitment method	Eligibility criteria	Screening & diagnostic test(s)
Mintz 2011 (62)	US	Cross-sectional test accuracy study	36 primary care centres	NR. Study took place from 18th February to 29th May 2009.	Inclusion criteria Current/ex-smokers aged ≥30 years old with ≥10 pack years Exclusion criteria Regular use of respiratory medication within 4 weeks of study, known diagnosis of substantial lung conditions with regular use of respiratory medication.	Stage 1 Screening questionnaire (Lung Function Questionnaire) Stage 2 Pre-/post-BD spirometry on subjects with LFQ ≤18 & first two subjects with LFQ ≥18 at each site
Price 2006 (19)	UK & US	Cross-sectional test accuracy study	Two primary care practices	Postal invitation (dates not reported)	Inclusion criteria Current/ex-smokers aged ≥40 years Exclusion criteria Refusal to consent, history of non-obstructive lung disease, use of respiratory medications in previous year, and acute symptoms of unstable heart disease	Stage 1 Screening questionnaire (COPD Diagnostic Questionnaire) Stage 2 Pre-/post-BD spirometry on all subjects
de Queiroz 2012 (45)	Brazil	Single arm before-after study	Three primary healthcare clinics	Invited individuals routinely attending primary healthcare clinics between May-September 2011	Inclusion criteria Age ≥40 years & ≥20 pack-years smoking or ≥80 hour-year history of exposure to biomass smoke Exclusion criteria Acute respiratory symptoms, previous history of bronchial asthma, allergic rhinitis, chronic lung diseases other than COPD, extra-pulmonary disease potentially affecting lung function and not meeting the criteria for spirometry	Pre-/post-BD spirometry

Study	Country	Study design	Setting	Recruitment method	Eligibility criteria	Screening & diagnostic test(s)
Sandelowsky 2011 (35)	Sweden	Single arm before-after study	Primary healthcare centre and urgent primary care unit	Patients meeting the inclusion criteria were telephoned from January-March 2005. Telephone conversations were followed by formal written invitations.	Inclusion criteria Current/ex-smokers aged 40-75 years & visited a primary healthcare centre or urgent primary care unit & diagnosed with acute respiratory infection (confirmed with a review of the medical records). Exclusion criteria Poor knowledge of Swedish, severe cardiac, psychiatric or multi-organ disease, prior history of lung disease (except asthma), or on beta-blockers	Pre-/post-BD spirometry
Sichletidis 2011 (63)	Greece	Cross-sectional test accuracy study	25 general practices	Invited first 50 patients meeting the inclusion criteria who attended each participating GP from March-May 2009	Inclusion criteria Age >40 years Exclusion criteria Confirmed diagnosis of lung disease, thoracic surgery in previous six months, acute respiratory infection, uncontrolled cardiac disease, or could not perform acceptable spirometry	Stage 1 Screening questionnaire (International Primary Airways Group [IPAG] questionnaire, also known as COPD Diagnostic Questionnaire) Stage 2 Post-BD Piko-6® (using 400µg salbutamol) Stage 3 Pre-/post-BD spirometry
Stratelis 2004 (43)	Sweden	Single arm before-after study	Primary care centres (number of centres not reported)	Placards advertising the study displayed in each healthcare centre and advertisement in local newspaper (dates not reported)	Inclusion criteria Current smokers aged 40-55 years (or had stopped smoking within 3 months of the study) Exclusion criteria None	Pre-BD spirometry
Takahashi 2003 (64)	Japan	Single arm before-after study	56 primary care facilities (23 hospitals and 33 general practices)	Not reported	Inclusion criteria Considered to be high risk for COPD (not otherwise defined) Exclusion criteria Established diagnosis of COPD, asthma or other chronic respiratory disease	Pre-BD spirometry

Study	Country	Study design	Setting	Recruitment method	Eligibility criteria	Screening & diagnostic test(s)
Takemura 2005 (65)	Japan	Single arm before-after study	Health screening clinic	Invited patients attending a medical check-up from 1997-2001	Inclusion criteria Age >30 years Exclusion criteria Established diagnosis of chronic respiratory disease, abnormalities on chest X-ray and unknown smoking status	Pre-BD spirometry
Thorn 2012 (46)	Sweden	Cross-sectional test accuracy study	21 primary healthcare centres	Invited patients attending participating primary healthcare centres over a five month period (dates not reported)	Inclusion criteria Current/ex-smokers aged 45-85 years with ≥15 pack years Exclusion criteria None	Stage 1 Pre-BD handheld spirometer (COPD-6®) Stage 2 Pre-/post-BD spirometry
Ulrik 2011 (34)	Denmark	Single arm before-after study	Primary care practices involving 335 GPs	Invited consecutive patients routinely attending primary care (dates not reported)	Inclusion criteria Age ≥35 years old & current/ex- smoker or relevant occupational exposure & ≥1 respiratory symptom (dyspnoea, cough, wheeze, sputum or recurrent chest infections) Exclusion criteria Unable to perform spirometry or previous diagnosis of chronic respiratory disease	Pre-BD spirometry
van Schayck 2002 (66)	Netherlands	Single arm before-after study	Two semirural primary care practices	Randomly invited patients routinely attending primary care (dates not reported)	Inclusion criteria Current smokers aged 35-70 years Exclusion criteria Use of respiratory medication	Pre-BD spirometry
Vandevoorde 2007 (38)	Belgium	Single arm before-after study	Six primary care practices, involving eight GPs	Invited patients routinely attending primary care over a two month period (dates not reported)	Inclusion criteria Current smokers aged 40-70 years with ≥15 pack-years Exclusion criteria History of asthma or COPD	Pre-BD spirometry

Study	Country	Study design	Setting	Recruitment method	Eligibility criteria	Screening & diagnostic test(s)
Vrijhoef 2003 (67)	Netherlands	Single-arm before-after study	Eight primary care practices	Invited patients attending primary care for reasons unrelated to respiratory disease from September 1998-July 1999	Inclusion criteria Current/ex-smokers aged 40-70 years Exclusion criteria Receiving respiratory medication, known diagnosis of asthma, COPD or chronic bronchitis, or significant co-morbidity	Stage 1 Pre-/ post-BD spirometry performed by medical undergraduates Stage 2: Pre-/post-BD spirometry performed by specialist respiratory nurse

ATS=American Thoracic Society, BD=bronchodilator, ERS=European Respiratory Society, NR=not reported, RCT=randomised controlled trial

Table S3.2a Quality assessment of studies evaluating direct invitation for spirometry

	Al Ghobain 2011	Bednarek 2008	Broekhuizen 2010	Bunker 2009	Clotet 2004	DeJong 2004	Fuller 2012	Geijer 2005	Kimura 2011	Kögler 2010	Konstantikaki 2011	Leuppi 2010	Løkke 2012	de Queiroz 2012	Sandelowsky 2011	Stratelis 2004	Takahashi 2003	Takemura 2005	Ulrik 2011	Van Shayck 2002	Vandevoorde 2007	Vrijhoef 2003
Clear description of recruitment	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y
Clear description of selection criteria	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Clear description of participants	Y	Y	Y	N	N	Y	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	Y
Representative spectrum of patients	Y	Y	Y	U	U	Y	Y	N	U	Y	N	Y	Y	U	Y	N	Y	Y	Y	U	Y	Y
Clear description of withdrawals	N	Y	U	N	N	N	N	N	N	Y	Y	N	N	Y	Y	N	N	N	N	Y	U	Y
Participant flow diagram	N	N	N	Y	Y	N	Y	N	Y	N	Y	N	N	Y	Y	N	N	N	N	N	N	Y
Spirometry quality control	Y	Y	U	Y	N	N	Y	Y	Y	U	Y	Y	U	N	U	Y	Y	Y	N	Y	Y	Y
Standard diagnostic criteria	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Intervention described in sufficient detail to permit its replication	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Clinical data available representative of routine practice	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Uninterruptable, indeterminate or intermediate results reported	Y	Y	N	N	N	N	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	N

Y=yes, N=no, U=unclear

Table S3.2b Quality assessment of studies evaluating screening questionnaires and/or handheld flow meters

	Buffels 2004	Castillo 2009	Dirven 2013a	Dirven 2013b	Duong-Quy 2009	Freeman 2005	Frith 2011	Hanania 2010	Haroon 2013	Kaufmann 2009	Kotz 2008	Laniado-Laborin 2011	Mintz 2011	Price 2006	Sichletidis 2011	Thorn 2012
Clear description of recruitment	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	N	Y	Y	Y
Clear description of selection criteria	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Clear description of participants	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Representative spectrum of patients	U	Y	Y	U	N	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y
Clear description of withdrawals	Y	Y	N	Y	Y	N	N	U	N	Y	Y	Y	Y	Y	Y	N
Participant flow diagram	Y	Y	N	N	N	N	Y	N	Y	N	Y	N	Y	Y	N	N
Spirometry quality control	Y	Y	N	N	N	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	U
Standard diagnostic criteria	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Quality diagnostic spirometry as reference standard	Y	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Spirometry performed within 6 months of index test	Y	Y	U	U	U	Y	Y	Y	Y	U	U	Y	Y	Y	U	Y
All or random selection of participants with positive screening test result underwent spirometry	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y
Intervention described in sufficient detail to permit its replication	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Clinical data available representative of routine practice	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Uninterpretable, indeterminate or intermediate results reported	N	Y	N	N	N	N	Y	N	N	U	Y	Y	Y	Y	Y	N

Y=yes, N=no, U=unclear

Table S3.3 Results: studies evaluating spirometry

Study	Population	Spirometry	Spirometry	Definition of COPD	New cases of COPD[1]
Al Ghobain 2011 (36)	Eligible: 1380 Invited: 1380 Subjects with acceptable spirometry: Mean age: 47.9 Male: 89.6% Smoking status Current: 82.6% Former: 17.4%	Device: NR Bronchodilator: 200µg salbutamol Operator: Physicians trained in the research methods Standard: ATS standards Quality control: Two investigators independently assessed the quality of spirometry tests according to ATS criteria.	Total: 1380 Acceptable: 501	Post-BD $FEV_1/FVC<0.7$ with no history of asthma or atopy, and with a smoking history of ≥5 years	71 cases FEV_1 % predicted >70%: 0 50-70%: 40 (56.3%) <50%: 31 (43.6%)
Bednarek 2008 (51)	Eligible: 2250 Invited: NR Subjects with acceptable spirometry Mean age: 56.7 Male: 39.0% Smoking status Current: 29.6% Former: 24.9% Never: 45.5%	Device: EasyOne Diagnostic (ndd Medical) Bronchodilator: 200µg salbutamol Operator: Primary care nurses who had attended two four hour training sessions in a reference lung function laboratory Standard: ATS standards Quality control: Spirometry tests were sent to one of the authors for quality assessment, reviewed according to ATS criteria	Total: 1986 Acceptable: 1960	Post-BD $FEV_1/FVC<5^{th}$ percentile of normal (using ECCS predicted values) & compatible clinical presentation (excluding asthma based on case notes review)	149 cases FEV_1 % predicted >70%: 56 (30.6%) 50-69%: 94 (51.4%) 35-49%: 28 (15.3%) <35%: 5 (2.7%)
Broekhuizen 2010 (31)	Eligible: NR Invited: NR Subjects analysed: Mean age: 63 Male: 45% Smoking status Current/ex: 74% Never: 26%	Device: NR Bronchodilator: 400µg salbutamol Operator: Lung function technicians Standard: NR Quality control: Tests performed in a secondary care lung function laboratory	Total: 353 Acceptable: NR	Consensus panel diagnosis with two physicians. Diagnosis based on recurrent respiratory symptoms & post-BD $FEV_1/FVC<0.7$ & clinical judgement	102 cases FEV_1 % predicted >80%: 71 (69.7%) 50-80%: 29 (28.4%) 30-50%: 2 (2.0%) <30%: 0

Study	Population	Spirometry	Spirometry	Definition of COPD	New cases of COPD[1]
Bunker 2009 (26)	Eligible: 400 Invited: NR Subjects who performed spirometry: Mean age: 62.4* Male: 57.0% <u>Smoking status</u> Current: 32.9% Former: 67.1%	Device: NR Bronchodilator: NR Operator: practice nurses who had attended a two hour training session on performance and interpretation of spirometry Standard: GOLD strategy Quality control: 25% of spirometry results were reviewed by a member of the study team.	Total: 79 Acceptable: NR	FEV_1/FVC<70% (unclear whether pre- or post-BD)	10 cases <u>FEV_1 % predicted</u> >80%: 5 (31.3%) 50-80%: 9 (56.3%) 30-50%: 2 (12.5%) <30%: 0 NB. FEV1 % predicted includes cases that were later deemed not to have COPD.
Clotet 2004 (54)	Eligible: 177 Invited: 177 Subjects with spirometry: Mean age: 54 Male: 80% <u>Smoking status</u> Current: 100%	Device: DATOSPIR 100 spirometer Bronchodilator: None Operator: NR Standard: Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) Quality control: NR	Total: 155 Acceptable: NR	Pre-BD FEV_1<80% predicted & FEV/FVC<70%	36 cases <u>FEV_1 % predicted</u> NR
DeJong 2004 (55)	Eligible: NR Invited: NR Subjects who performed spirometry: Mean age: 55 Male: 49% <u>Smoking status</u> Current: 49% Former: 37% Never: 14%	Spirometer: Jones handheld spirometer Bronchodilator: NR Operator: Trained respiratory therapist Standard: NR Quality control: NR	Total: 243 Acceptable: NR	Pre-BD FEV1/FVC<0.7	43 cases <u>FEV1 % predicted:</u> >80%: 15 (34.9%) 50-80%: 28 (65.1%) 30-50%: 0 <30%: 0

Study	Population	Spirometry	Spirometry	Definition of COPD	New cases of COPD[1]
Freeman 2005 (40)	Eligible: 1195 Invited: 1195 Consented: 624 Subjects who performed spirometry Mean age: 61.7 Male: 52% Smoking status Current: 54.1% Former: 45.9%	Spirometer: Micro-Med handheld spirometer with Spida software Bronchodilator: 5mg salbutamol for those with prior respiratory medication/history of asthma/FEV_1<80% predicted Operator: Trained respiratory nurse Standard: ATS standards. Minimum of 3 tests or until results within 5%. Quality control: All spirometry results were reviewed by a physician to ensure compliance with ATS standards	Total: 369 Acceptable: NR	Post-BD FEV_1/FVC<0.7 and lack of reversibility (reversibility defined as increase in FEV_1 ≥200mL and 15% from pre-BD FEV_1 (not clear if all were post-BD)	62 cases FEV1 % predicted NR
Frith 2011 (20)	Eligible: 233 Invited: 237 Subjects with acceptable spirometry: Mean age: 61 Male: 69% Smoking status Current: 45% Former: 55% Never: <1%	Device: EasyOne spirometer (ndd Medical) Bronchodilator: 360mcg salbutamol Operator: trained operators using ATS/ERS guidelines Standard: ATS/ERS standards. At least 3 adequate baseline and post-BD FVC manoeuvres performed. Quality control: spirometry quality monitored by a respiratory physiologist blinded to the questionnaire and Piko-6® results	Total: 233 Acceptable: 204	Post-BD FEV_1/FVC<0.7	57 cases FEV_1 % predicted >80%: 19 (33.3%) 50-80%: 35 (61.4%) 30-50%: 3 (5.3%) <30%: 0
Fuller 2012 (57)	Eligible: NR Invited: NR Subjects with acceptable spirometry: Mean age: 55 Male: 40% Smoking status Current: 12% Former: 34% Never: 54%	Device: EasyOne spirometer (ndd Medical) Bronchodilator: None Operator: 3 pharmacy residents and 5 clinical pharmacists who had participated in 16 hours of training from a pulmonary physician experienced in lung function testing. Standard: ATS standards Quality control: All spirometry results were reviewed independently by two study pulmonologists.	Total: 185 Acceptable: 174	Pre-BD FEV_1/FVC<LLN (using NHANES III) reference equations	16 cases FEV_1 % predicted NR

Study	Population	Spirometry	Spirometry	Definition of COPD	New cases of COPD[1]
Geijer 2005 (41)	Eligible: 918 Invited: NR Subjects with acceptable spirometry: Mean age: 50 Male: 100% <u>Smoking status</u> Current: 100%	Device: Vitalograph 2170 with Spirotrack software Bronchodilator: 250µg terbutaline Operator: Trained nurse practitioner Standard: Each subject had to perform at least three acceptable FVC manoeuvres according to ATS standards. Quality control: Two investigators independently assessed quality of spirometry curves according to ATS criteria. Where there was disagreement a final assessment was made by a lung physiologist.	Total: 805 Acceptable: 702	$FEV_1/FVC<0.7$ (unclear whether pre- or post-BD)	210 cases <u>FEV_1 % predicted</u> ≥80%: 182 (86.7%) 50-80%: 27 (12.9%) 30-49%: 1 (0.5%) <30%: 0
Hanania 2010 (58)	Eligible: NR Invited: NR Subjects with spirometry: Mean age: NR Male: 38.1% <u>Smoking status</u> NR	Device: EasyOne spirometers (ndd Medical Technologies) Bronchodilator: None Operator: NR Standard: NR Quality control: Investigators rated spirometry quality based on reliability and reproducibility and only included traces that were considered reliable.	Total: 937 Acceptable: NR	Pre-BD $FEV_1/FVC<0.7$	156 cases <u>FEV_1 % predicted</u> ≥80%: 17 (11.5%) 50-80%: 76 (51.4%) 30-50%: 44 (29.7%) <30%: 11 (7.4%) NB. Reported numbers do not summate to 156.
Kimura 2011 (60) (Study 1)	Eligible: 839 Invited: NR Eligible subjects: Mean age: 63.3 Male: 33.7% <u>Smoking status</u> NR	Device: Chestgraph Jr. H1-101 (Chest Co., Japan) Bronchodilator: None Operator: trained examiners Standard: ATS standards Quality control: All spirometry data were checked by two study authors. Only tests with at least two manoeuvres with FEV_1 within 0.2L were included in the analysis.	Total: 814 Acceptable: 630	Pre-BD $FEV_1/FVC<0.7$	59 cases <u>FEV_1% predicted</u> ≥80%: 29 (49.2%) 50-80%: 27 (45.8%) 30-50%: 3 (5.1%) <30%: 0
Kimura 2011 (60) (Study 2)	Eligible:1300 Invited:363 Mean age: NR Male: NR <u>Smoking status</u> NR	As above	Total: 363 Acceptable: 254	Pre-BD $FEV_1/FVC<0.7$	22 cases <u>FEV_1% predicted</u> ≥80%: 6 (27.3%) 50-80%: 15 (68.2%) 30-50%: 1 (4.5%) <30%: 0

Study	Population	Spirometry	Spirometry	Definition of COPD	New cases of COPD[1]
Kögler 2010 (32)	Eligible: NR Invited: 2276 Subjects with complete data: Mean age: NR Male: 62.2%* Smoking status Current/ex: 100%	Device: NR Bronchodilator: NR Operator: Pulmonologist Standard: NR Quality control: NR	Total: 1282 Acceptable: NR	Physician diagnosis (physicians were advised to follow the GOLD strategy)	516 cases FEV_1% predicted: ≥80%: 137 (12.6%) 50-80%: 290 (26.7%) <50%: 89 (8.2%)
Konstantikaki 2011 (29) - Open spirometry programme	Eligible: NR Invited: NR Subjects with acceptable spirometry: Mean age: 62.5 Male: 64% Smoking status Current: 36.2% Former: 27.1% Never: 36.7%	Device: dry spirometer (Koko Legend, Ferraris, UK) Bronchodilator: 400 µg salbutamol Standard: ATS standards Operator: Physicians who had undergone training by two chest physicians Quality control: three experienced chest physicians evaluated the quality of all spirometry readings	Total:1084 Acceptable: 905	History of exposure to noxious particles or gases, particularly smoking, compatible symptoms, and post-BD $FEV_1/FVC<0.7$	76 cases FEV_1% predicted: ≥80%: 34 (44.7%) 50-80%: 32 (42.1%) 30-50%: 8 (10.5%) <30%: 2 (2.6%)
Konstantikaki 2011 (29) - Case-finding programme	Eligible: NR Invited: NR Mean age: 63.5 Male: 19.6% Smoking status Current: 68.7% Former: 22.9% Never: 8.5%	As above	Total: 219 Acceptable: 201	As above	56 cases FEV_1% predicted ≥80%: 18 (32.1%) 50-80%: 32 (57.1%) 30-50%: 4 (7.1%) <30%: 2 (3.6%)
Kotz 2008 (42)	Eligible: 1052 Invited: 1052 Subject who performed spirometry: Mean age: 52.3 Male: 58.7% Smoking status Current: 100%	Device: Vitalograph 2120 Bronchodilator: 500µg terbutaline Operator: Two qualified research assistants under the supervision of a pulmonologist Standard: ATS/ERS standards Quality control: All spirometry results were validated by a pulmonologist and specialised lung function laboratory assistant not involved in the trial- both were blinded to the questionnaire scores	Total: 826 Acceptable: 716	Post-BD $FEV_1/FVC<0.7$	278 cases FEV_1 % predicted ≥80%: 142 (51.1%) 50-80%: 119 (42.8%) <50%: 17 (6.1%)

Study	Population	Spirometry	Spirometry	Definition of COPD	New cases of COPD[1]
Leuppi 2010 (37)	Eligible: 26,400 Invited: NR Subjects aged ≥40 years who performed spirometry: Mean age: 51.6 Male: 58.6% <u>Smoking status</u> Current: 100%	Device: EasyOne spirometer (ndd Medical Technologies) Bronchodilator: None Operator: GPs and practice nurses provided with 1-2 hours training Standard: ATS standards Quality control: spirometry quality assessed automatically by the spirometer. Only spirometry results in the top three quality grades were included in the analysis.	Total: 24,995 Acceptable: 15,084	Pre-BD $FEV_1/FVC<0.70$ in subjects <70 years Pre-BD $FEV_1/FVC<0.65$ in subjects aged 70-80 years Pre-BD $FEV_1/FVC<0.60$ in subjects aged >80 years	4231 cases <u>FEV_1 % predicted</u> ≥80%: 951 (22.5%) 50-80%: 2217 (52.4%) 30-50%: 818 (19.3%) <30%: 245 (5.8%)
Løkke 2012 (33)	Eligible: 4000 Invited: NR Data on 4049 subjects with complete data Mean age: 57.5%* Male: 51% <u>Smoking status</u> Current: 59% Former: 37% Never: 4%	Device: NR Bronchodilator: 0.4mg salbutamol for those with initial airflow obstruction Operator: NR Standard: Danish Respiratory Society guidelines. Aimed to achieve at least three forced expiratory manoeuvres and at least two measurements differing <5% Quality control: NR	Total: 4049 Acceptable: NR	Pre-BD $FEV_1/FVC≤0.7$ & post-BD FEV_1 showing <200mL improvement or a negative corticosteroid reversibility test (spirometry performed 6 weeks after administration of 1600ug budesonide daily or 37.5mg oral prednisolone daily for 14 days) for those with an FEV_1 improvement of 200-500mL	878 cases <u>FEV_1 % predicted</u> ≥80%: 307* (35%) 50-79%: 439* (50%) <50%: 132* (15%)
Price 2006 (19)	Eligible: NR Invited: 17,361 Subjects with acceptable spirometry: Mean age: 58.2 Male: 49.3% <u>Smoking status</u> Current: 44.5% Former: 55.5%	Device: EasyOne spirometer (ndd Medical Technologies) Bronchodilator: 2.5mg salbutamol/albuterol Operator: NR Standard: ATS standards Quality control: Principal investigators conducted blinded review of all spirometry loops. A pulmonologist not associated with the study reviewed all loops on which there was disagreement.	Total: 898 Acceptable: 818	Post-BD $FEV_1/FVC<0.7$	155 cases <u>FEV_1 % predicted</u> NR

Study	Population	Spirometry	Spirometry	Definition of COPD	New cases of COPD[1]
de Queiroz 2012 (45)	Eligible: NR Invited: 350 Subjects with acceptable spirometry: Mean age: 65 Male: NR <u>Smoking status</u> NR	Device: Spirotrac® (Vitalograph) Bronchodilator: NR Operator: NR Standard: Brazilian Thoracic Association Quality control: NR	Total: 214 Acceptable: 200	Post-BD FEV_1/FVC<0.7	45 cases <u>FEV1% predicted:</u> ≥80%: 22 (48.9%) 50-80%: 17 (37.8%) 30-50%: 6 (13.3%) <30%: 0
Sandelowsky 2011 (35)	Eligible: 250 Invited: 190 Subjects with acceptable spirometry: Mean age: 55 Male: 44.2% <u>Smoking status</u> Current: 52.9% Former: 47.1%	Device: Vitalograph Alpha® Bronchodilator: 8µg formoterol Operator: NR Standard: NR Quality control: NR	Total: 150 Acceptable: 138	Post-BD FEV_1/FVC<0.7 (Used ECCS reference equations for disease severity)	38 cases <u>FEV_1% predicted</u>: ≥80%: 17 (44.7%) 50-80%: 20 (52.6%) 30-50%: 1 (2.6%) <30%: 0
Sichletidis 2011 (63)	Eligible: 1250 Invited: 1250 Subjects with acceptable spirometry Mean age: 65.3 Male: 57.1% <u>Smoking status</u> Current/ex: 48.8% Never: 51.2%	Device: Vitalograph Bronchodilator:400µg salbutamol Operator: Pulmonary specialists Standard: ATS/ERS standards Quality control: Spirometry performed and interpreted by pulmonary specialists according to ATS/ERS standards	Total: 1250 Acceptable: 1078	Post-BD FEV_1/FVC<0.7	111 cases <u>FEV_1 % predicted</u> ≥80%:40 (36.0%) 50-80%:53 (47.7%) 30-50%:16 (14.4%) <30%:2 (1.8%)

Study	Population	Spirometry	Spirometry	Definition of COPD	New cases of COPD[1]
Stratelis 2004 (43)	Eligible: 5332 Invited: 5332 Subjects who performed spirometry: Mean age: 48 Male: 43% <u>Smoking status</u> NR	Device: Flowscreen version 3.10gb, Vitalograph Compact II, Vitalograph Alpha, Vicatest P2a Bronchodilator: None Operator: Trained COPD nurses Standard: ATS standards Quality control: Spirometry results were re-evaluated by an experienced physician. Spirometry judged not to be optimal or showing evidence of obstruction was performed again by the physician.	Total: 512 Acceptable: NR	Pre-BD FEV_1/VCmax<88% predicted for males and <89% predicted for females	141 cases <u>FEV_1% predicted:</u> ≥80%: 95 (63.3%) 50-80%: 52 (34.7%) 30-50%: 3 (2.0%) <30%: 0 (NB. Reported numbers do not summate to 141)
Takahashi 2003 (64)	Eligible: NR Invited: NR Subjects with acceptable spirometry: Mean age: 63.1 Male: 76.3% <u>Smoking status</u> Current: 41.7% Former: 29.8% Never: 28.5%	Device: Peakman-8, Chest Corp Bronchodilator: None Operator: Trained physician Standard: Subjects were asked to perform at least three forced expiratory manoeuvres. No standard reported. Quality control: Spirometry data were reviewed by pulmonary specialists	Total: 1168 Acceptable: 1040	Pre-BD FEV_1/FVC<0.7	281 cases <u>FEV_1% predicted:</u> ≥80%: 62 (22.1%) 50-80%: 60 (21.4%) 30-50%: 30 (10.7%) <30%: 6 (2.1%)
Takemura 2005 (65)	Eligible: NR Invited: NR Subjects aged ≥40 years who performed spirometry: Mean age: 49.8* Male: 69.3% <u>Smoking status</u> Current: 38.2% Former: 18.7% Never: 43.1%	Device: Autospiro AS-505 Bronchodilator: None Operator: Trained laboratory technologist Standard: ATS standards Quality control: Spirometry performed according to ATS standards. No other quality control measures reported.	Total: 10,256 Acceptable: NR NB. Only including subjects aged ≥40years (80.4% of all subjects)	Pre-BD FEV_1/VC<0.7	425 cases* <u>FEV_1% predicted</u> NR

Study	Population	Spirometry	Spirometry	Definition of COPD	New cases of COPD[1]
Thorn 2012 (46)	Eligible: NR Invited: NR Subjects who performed spirometry: Mean age: 61.2 Male: 43.3% Smoking status Current/ex: 100%	Device: NR Bronchodilator: 0.5mg terbutaline Operator: Nurses Standard: ATS standards Quality control: NR	Total: 305 Acceptable: NR	Post-BD $FEV_1/FVC<0.7$	77 cases FEV_1 % predicted ≥80%: 35 (45.5%) 50-80%: 41 (53.2%) 30-50%: 1 (1.3%) <30%: 0
Ulrik 2011 (34)	Eligible: 10,050 Invited: NR Subjects with complete data (n=3097): Mean age: 58 Male: 49% Smoking status Current: 65% Former: 32% Never:3%	Device: NR Bronchodilator: NR Operator: NR Standard: NR Quality control: NR	Total: 3095 Acceptable: NR	Pre-BD $FEV_1/FVC<0.7$	1079 cases FEV_1% predicted ≥80%: 302 (28%)* 50-80%: 550 (51%)* 30-50%: 194 (18%)* <30%: 22 (2%)*
van Schayck 2002 (66)	Eligible: 229 Invited: 201 Subjects who performed spirometry: Mean age: NR Male: NR Smoking status Current: 100%	Device: MicroMedical 3300 Bronchodilator: None Operator: Trained practice assistants with at least three years' experience (received two 4 hour sessions by a lung function laboratory assistant) Standard: ATS standards Quality control: Performance of practice assistants monitored by study author	Total: 201 Acceptable: 169	Pre-BD FEV_1% predicted<80%	30 cases FEV_1% predicted NR

Study	Population	Spirometry	Spirometry	Definition of COPD	New cases of COPD[1]
Vandevoorde 2007 (38)	Eligible: 141 Invited: 141 Subjects meeting inclusion criteria (n=146): Mean age:52.3 Male:42.5% <u>Smoking status</u> Current: 100%	Device: Spirobank S, One Flow FVC Bronchodilator: None Operator: Participating GPs received spirometry training consisting of a theoretical course followed by two practical sessions in a lung function laboratory. Standard: ERS standards Quality control: All spirometry curves were assessed by two study authors. Two other study authors reviewed spirometry curves where there was disagreement.	Total: 129 Acceptable: 121	Pre-BD $FEV_1/FVC<0.7$	43 cases <u>FEV_1% predicted</u> ≥80%:18 (41.9%) 50-80%:21 (48.8%) 30-50%:4 (9.3%) <30%:0
Vrijhoef 2003 (67)	Eligible: NR Invited: NR Subjects who performed spirometry: Mean age: 53.5 Male: 48.5% <u>Smoking status</u> Current: 62% Former: 38%	Device: Vitalograph 2120, Microlab 3300 Bronchodilator: 500µg terbutaline Operator: Initial spirometry performed by four medical undergraduates trained for a day at a lung function laboratory. Subsequent spirometry performed by a respiratory nurse practitioner. Standard: ERS standards. Quality control: NR	Total: 231 Acceptable: NR	Post-BD $FEV_1/FVC<0.65$ of predicted ratio or $FEV_1<84\%$ predicted following course of oral prednisolone	17 cases <u>FEV1% predicted</u> NR

*Value computed from available data

NR=not reported, Age in years

Table S3.4 Results: studies evaluating screening questionnaires

Study	Population	Questionnaire	Spirometry	Screened	Definition of COPD	New cases of COPD
Buffels 2004 (52)	Eligible: 3158 Invited: 3158 Data on subjects with spirometry Mean age: NR Male: 45% Smoking status Current: 30.7% Former: 18.1% Never: 50.1%	Items: Cough >2 weeks Dyspnoea during mild exercise or at night Nasal allergy or hay fever Visit to doctor for wheeze or chronic cough Threshold: ≥1 symptom	Device: Spirobank spirometer with Winspiro software Bronchodilator: None Operator: GPs who had received 12 hours of training Standard: NR Quality control: Technical support provided to GPs throughout the study. Accuracy of GP-performed spirometry for a patient was compared to result from a lab technician.	Questionnaire Total: 3158 Positive: 728 Spirometry Total: 703 Acceptable: NR	Pre-BD $FEV_1/FVC<88.5\%$ predicted for men & <89.3% for women	With symptoms and airflow obstruction: 126 cases FEV_1 % predicted (all spirometry tests) >80%: 53 (39%) 50-80%: 69 (51%) 30-50%: 12 (9%) ≤30%: 1 (<1%)
Castillo 2009 (53)	Eligible: NR Invited: 254 Data on subjects who completed questionnaire Mean age: 55 Male: 42% Smoking status Current/ex: 77% Never: 23%	Items: More breathlessness than people of same age Chronic cough Chronic sputum Age >40 years Smoking Threshold: ≥3 positive items	Device: EasyOne Spirometer (ndd Medical Technologies) Bronchodilator: None Operator: Pharmacists who had attended a four-day spirometry training course. Standard: ERS/ATS standards Quality control: All spirometry curves reviewed by a lung function expert. Subjects with $FEV_1/FVC<0.7$ referred to lung function unit for spirometry.	Questionnaire Total: 161 Positive: 100 Spirometry Total: 96 Acceptable: 86	Pre-BD $FEV_1/FVC<0.7$	21 cases Severity: Mild: 13 (61.9%) Moderate: 7 (33.3%) Severe: 1 (4.8%) (Severity grading criteria not reported)
Dirven 2013a (30) -Patient-managed arm	Eligible: 6,393 Invited: 6,393 Data on subjects who completed questionnaire Mean age: 53.5 Male: 51.0% Smoking status Current: 40% Former: 12% Never: 48%	COPD Diagnostic Question (referred to as "Respiratory Health Screening Questionnaire") Items: See Price 2006 Threshold: Score >19.5	Device: NR Bronchodilator: NR Operator: NR Standard: Dutch College of General Practitioners Quality control: NR	Questionnaire Total: 1715 Positive: 186 Spirometry Total: 140 Acceptable: NR	Post-BD $FEV_1/FVC<0.7$ & physician's clinical evaluation	25 cases FEV_1 % predicted NR

Study	Population	Questionnaire	Spirometry	Screened	Definition of COPD	New cases of COPD
Dirven 2013a (30) -Practice-managed arm	Eligible: 3,715 Invited: 3,715 Data on subjects who completed questionnaire Mean age: 53.7 Male: 49.7% <u>Smoking status</u> Current: 44% Former: 14% Never: 42%	As above	As above	<u>Questionnaire</u> Total: 1855 Positive: 251 <u>Spirometry</u> Total: 135 Acceptable quality: NR	As above	48 cases <u>FEV_1 % predicted</u> NR
Dirven 2013b (44)	Eligible: 849 Invited: 831 Mean age: NR Male: NR Smoking status: Current: NR Former: NR Never: NR	As above (Dirven 2013a)	Device: NR Bronchodilator: NR Operator: NR Standard: NR Quality control: NR	<u>Questionnaire</u> Total: 293 Positive: 50 <u>Spirometry</u> Total: 39 Acceptable: NR	Post-BD FEV_1/FVC<0.7 & physician's clinical evaluation	9 cases <u>FEV_1 % predicted</u> NR
Freeman 2005 (40)	Eligible: 1195 Invited: 1195 Data on subjects with spirometry Mean age: 61.7 Male: 52% <u>Smoking status</u> Current: 54.1% Former: 45.9%	Multiple response questionnaire <u>Items:</u> Age Smoking status Pack-years Cough Dyspnoea Wheeze <u>Threshold:</u> NR (included only "best" reported)	Spirometer: Micro-Med handheld spirometer with Spida software Bronchodilator: 5mg salbutamol for those with prior respiratory medication/history of asthma/FEV_1<80% predicted Operator: Trained respiratory nurse Standard: ATS standards. Minimum of 3 tests or until results within 5%. Quality control: All spirometry results reviewed by a physician to ensure compliance with ATS standards	<u>Questionnaire</u> Total: 369 Positive: 121* <u>Spirometry</u> Total: 369 Acceptable: NR	Post-BD FEV_1/FVC<0.7 and lack of reversibility (reversibility defined as increase in FEV_1 of ≥200mL and 15% from pre-BD FEV_1 (not clear if all were post-BD)	47 cases* <u>FEV_1 % predicted</u> NR

Study	Population	Questionnaire	Spirometry	Screened	Definition of COPD	New cases of COPD
Freeman 2005 (40)	Eligible: 1195 Invited: 1195 Data on subjects with spirometry Mean age: 61.7 Male: 52% Smoking status Current: 54.1% Former: 45.9%	Binary response questionnaire As above	As above	Questionnaire Total: 369 Positive: 142* Spirometry Total: 369 Acceptable: NR	As above	54 cases* FEV_1 % predicted NR
Frith 2011 (20)	Eligible: 233 Invited: 237 Data on subjects with acceptable spirometry: Mean age: 61 Male: 69% Smoking status Current: 45% Former: 55% Never: <1%	COPD Diagnostic Questionnaire Items: See Price 2006 Threshold: ≥19.5	Device: EasyOne spirometer (NDD) Bronchodilator: 360mcg salbutamol Operator: trained operators using ATS/ERS guidelines Standard: ATS/ERS standards. At least 3 adequate baseline and post-BD FVC manoeuvres performed. Quality control: spirometry quality monitored by a respiratory physiologist blinded to the questionnaire and Piko-6® results	Questionnaire Total: 233 Positive: 107* Spirometry Total: NR Acceptable: 204	Post-BD $FEV_1/FVC<0.7$	40 cases* FEV_1 % predicted see table S3.3
Frith 2011 (20)	As above	As above Threshold: ≥16.5	As above	Questionnaire Total: 233 Positive: 163* Spirometry As above	As above	52 cases* FEV_1 % predicted see table S3.3
Hanania 2010 (58)	Eligible: NR Invited: NR Data on 837 subjects with spirometry: Mean age: NR Male: 38.1% Smoking status NR	Lung Function Questionnaire Items: Age Cough Wheeze Dyspnoea Smoking Threshold: Score ≤18	Device: EasyOne spirometers (ndd Medical Technologies) Bronchodilator: None Operator: NR Standard: NR Quality control: Investigators rated spirometry quality based on reliability and reproducibility. Only included traces considered reliable.	Questionnaire Total: 937 Positive: 537* Spirometry Total: 937 Acceptable: NR Analysed: 837	Pre-BD $FEV_1/FVC<0.7$	129 cases* FEV_1 % predicted See table S3.3

Study	Population	Questionnaire	Spirometry	Screened	Definition of COPD	New cases of COPD
Haroon 2013 (28)	Eligible: 815 Invited: 813 Data on subjects who returned questionnaire Mean age: 53.0 Male: 60.8% Smoking status Current: 62.3% Former: 45.8%	Postal questionnaire Items Cough Wheeze Sputum Dyspnoea Smoking Occupational exposures Demographics Threshold ≥1 chronic respiratory symptom	Device: Microloop and Micro GP spirometers with Spida 5 software Bronchodilator: None Operator: Trained practice nurses Standard: ATS/ERS standards Quality control: First five spirometry results were quality checked by a respiratory scientist	Questionnaire Total: 212 Positive: 166 Spirometry Total: 70 Acceptable: NR	Pre-BD $FEV_1/FVC<0.7$ with $FEV_1<80\%$ predicted, lack of reversibility (reversibility defined as increase in FEV_1 of 200mL and 15% from pre-BD FEV1) and presence of respiratory symptoms.	10 cases FEV_1 % predicted 50-80%: 14 (87.5%) 30-50%: 2 (12.5%) <30%: 0 (0%) (NB. FEV1 % predicted includes results from both study arms)
Haroon 2013 (28)	Eligible: 819 Invited: 258 Mean age: 55.3 Male: 67.6% Smoking status Current: 55.9% Former: 54.1%	Opportunistic questionnaire As above	As above	Questionnaire Total: 111 Positive: 81 Spirometry Total: 28 Acceptable: NR	As above	6 cases FEV_1 % predicted As above
Kotz 2008 (42)	Eligible: 1052 Invited: 1052 Data on subjects with spirometry: Mean age: 52.3 Male: 58.7% Smoking status Current: 100%	COPD Diagnostic Questionnaire (CDQ) Items: See Price 2006 Threshold ≥19.5	Device: Vitalograph 2120 Bronchodilator: 500 µg terbutaline Operator: Two qualified research assistants under supervision of a pulmonologist. Standard: ATS/ERS standards Quality control: All spirometry results were validated by a pulmonologist and specialised lung function laboratory assistant not involved in the trial- both were blinded to questionnaire scores.	Questionnaire Total: 1052 Positive: 554* Spirometry Total: 826 Acceptable: 716	Post-BD $FEV_1/FVC<0.7$	233 cases* FEV_1 % predicted See table S3.3
Kotz 2008 (42)	As above	As above Threshold ≥16.5	As above	Questionnaire Total: 1052 Positive: 844* Spirometry As above	As above	316 cases* FEV_1 % predicted See table S3.3

Study	Population	Questionnaire	Spirometry	Screened	Definition of COPD	New cases of COPD
Laniado-Laborin 2011 (61)	Eligible: NR Invited: NR Data on 2293 subjects with acceptable spirometry: Mean age: 57.6 Male: 39.8% Smoking status Current: 42.1%* Former: NR Never: NR	Items Smoking Exposure to biomass smoke and/or dusts Cough Sputum production Dyspnoea Threshold ≥1 symptom or risk factor	Device: EasyOne spirometer (ndd Medical Technologies) Bronchodilator: NR Operator: Certified respiratory therapist Standard: ATS/ERS standards Quality control: Poor quality results were excluded from analysis.	Questionnaire Total: NR Positive: NR Spirometry Total: 2617 Acceptable: 2293	Post-BD $FEV_1/FVC<0.7$ (Used reference equations from NHANES III for Mexican Americans)	472 cases FEV_1 % predicted ≥80%: 96 (20.3%) 50-79%: 217 (46.0%) 30-49%: 123 (26.1%) <30%: 36 (7.6%)
Mintz 2011 (62)	Eligible: NR Invited: 4956 Data on subjects who completed questionnaire: Mean age: 53.9* Male: 51.2% Smoking status Current: 57.6% Former: 42.4%	Lung Function Questionnaire Items See Hanania 2010 Threshold Score ≤18	Device: Biomedical Systems, St Louis, MO Bronchodilator: 360µg albuterol Operator: Trained site staff Standard: ATS standards Quality control: Only data collected from acceptable spirometry manoeuvres were included. Patients producing unacceptable spirometry were allowed to repeat this within seven days of study visit.	Questionnaire Total: 1575 Positive: 1228* Spirometry Total: 1225 Acceptable: 849	LFQ≤18 & post-BD $FEV_1/FVC<0.7$	315 cases* NB. restricted to subjects ≥40 years FEV_1 % predicted NR
Price 2006 (19)	Eligible: NR Invited: 17,361 Data on subjects with acceptable spirometry Mean age: 58.2 Male: 49.3% Smoking status Current: 44.5% Former: 55.5%	COPD Diagnostic Questionnaire Items Age Smoking pack-years Weather-affected cough Cough up phlegm in absence of a cold Early morning cough Wheeze Allergies Threshold ≥19.5	Device: EasyOne spirometer (NDD) Bronchodilator:2.5mg salbutamol/albuterol Operator: NR Standard: ATS standards Quality control: Principal investigators conducted blinded review of all spirometry loops. A pulmonologist not associated with the study reviewed all loops on which there was disagreement.	Questionnaire Total: 898 Positive: 243* Spirometry Total: 898 Acceptable: 818	Post-BD $FEV_1/FVC<0.7$	91 cases* FEV_1 % predicted See table S3.3

Study	Population	Questionnaire	Spirometry	Screened	Definition of COPD	New cases of COPD
Price 2006 (19)	As above	As above Threshold ≥16.5	As above	Questionnaire Total: 898 Positive: 406* Spirometry As above	As above	125 cases* FEV_1 % predicted NR
Sichletidis 2011 (63)	Eligible: 1250 Invited: 1250 Data on subjects with acceptable spirometry: Mean age: 65.3 Male:57.1% Smoking status Current/ex: 48.8% Never: 51.2%	COPD Diagnostic Questionnaire (referred to as "International Primary Airways Group Questionnaire") Items See Price 2006 Threshold Score ≥17	Device: Vitalograph Bronchodilator:400µg salbutamol Operator: Pulmonary specialists Standard: ATS/ERS standards Quality control: Spirometry performed and interpreted by pulmonary specialists according to ATS/ERS standards	Questionnaire Total: 1250 Positive: 693* Spirometry Total: NR Acceptable: 1078	Post-BD FEV_1/FVC<0.7	103 cases * FEV_1 % predicted See table S3.3

ATS=American Thoracic Society, ERS=European Respiratory Society, LFQ=Lung Function Questionnaire

Table S3.5 Results: studies evaluating handheld flow meters

Study	Population	Handheld spirometer	Spirometry	Screened	Definition of COPD	New cases of COPD
Duong-Quy 2009 (56)	Eligible: 2464 Invited: NR Data on 2397 screened subjects Mean age: 52 Male: 99.7% Smoking status Current: 88.9% Former: 11.1%	Pre-BD Piko-6® Best of three manoeuvres selected. All measures where FEV_1/FEV_6>1 were excluded. Operator: NR Threshold FEV_1/FEV_6<0.7	Device: SpiroLab II Bronchodilator: short-acting β_2-agonist (specific drug not specified) Operator: NR Standard: ATS/ERS standards. Quality control: Required at least three measures and at least two within 150mL	Handheld flow meter Total: 2464 Positive: 324 Spirometry Total:144 Acceptable: NR	Post-BD FEV_1/FVC<0.7 with <200mL or 12% reversibility	136 cases FEV_1 % predicted <80%: 65 50-79%: 63 30-49%: 8 <30%: 0
Frith 2011(20)	Eligible: 233 Invited: 237 Data on subjects with acceptable spirometry: Mean age: 61 Male: 69% Smoking status Current: 45% Former: 55% Never: <1%	Pre-BD Piko-6® Operator: Study nurse or GP Threshold: FEV_1/FEV_6<0.75 (optimal cut-point)	Device: EasyOne spirometer (ndd Medical Technologies) Bronchodilator: 360mcg salbutamol Operator: trained operators Standard: ATS/ERS standards. At least 3 adequate baseline and post-BD FVC manoeuvres performed. Quality control: spirometry quality monitored by a respiratory physiologist blinded to the questionnaire and Piko-6® results	Handheld flow meter Total: 233 Positive: 97* Spirometry Total: NR Acceptable: 204	Post-BD FEV_1/FVC<0.7	46 cases* FEV_1 % predicted: see table S3.3
Kaufmann 2009 (59)	Eligible: NR Invited: NR Data on subjects who used handheld flow meter: Mean age: 54.8* Male: 37.7% Smoking status Current: 30.4% Former: 4.1% Never: 65.5%	Pre-BD Piko-6® Operator: trained study nurses Threshold: FEV_1/FEV_6<80%	Device: NR Bronchodilator: Combivent (dose not reported) Operator: Trained study nurses Standard: NR Quality control: Study nurses were trained in a pulmonary function laboratory	Handheld flow meter Total: 507 Positive: 106 Spirometry Total: 74 Acceptable: NR	Reversibility of FEV_1≤200mL or <15% after administration of Combivent (dose NR)	14 cases FEV_1 % predicted ≥80%: 9 (64.3%) 50-80%: 5 (35.7%) <50%: 0 (NB. Study also included five patients with normal spirometry as having COPD)

Study	Population	Handheld spirometer	Spirometry	Screened	Definition of COPD	New cases of COPD
Sichletidis 2011 (63)	Eligible: 1250 Invited: 1250 Data on subjects with acceptable spirometry: Mean age:65.3 Male:57.1% Smoking status Current/ex: 48.8% Never: 51.2%	Post-BD Piko-6® Operator: GPs who had two hours training Bronchodilator: 400µg salbutamol Threshold Post-BD FEV_1/FEV_6<0.7	Device: Vitalograph Bronchodilator:400µg salbutamol Operator: Pulmonary specialists Standard: ATS/ERS standards Quality control: Spirometry performed and interpreted by pulmonary specialists according to ATS/ERS standards	Handheld flow meter Total: 1250 Positive: 147* Spirometry Total: NR Acceptable: 1078	Post-BD FEV_1/FVC<0.7	89 cases* FEV_1 % predicted See table S3.3
Sichletidis 2011 (63)	As above	Post-BD Piko-6® and COPD Diagnostic Questionnaire (see table 3)	As above	Handheld flow meter & screening questionnaire Total: 1250 Positive: 111* Spirometry: As above	As above	82 cases* FEV_1 % predicted See table S3.3
Thorn 2012 (46)	Eligible: NR Invited: NR Data on subjects with spirometry: Mean age: 61.2 Male:43.3% Smoking status Current/ex: 100%	Pre-BD COPD 6® Operator: Nurses Threshold FEV_1/FVC<0.73	Device: NR Bronchodilator: 0.5mg terbutaline Operator: Nurses Standard: ATS standards Quality control: NR	Handheld flow meter Total: 305 Positive: 106* Spirometry Total: 305 Acceptable: NR	Post-BD FEV_1/FVC<0.7	61 cases* FEV_1 % predicted See table S3.3

ATS=American Thoracic Society, ERS=European Respiratory Society, NR=not reported

3.7 References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
2. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-223.
3. Britton M. The burden of COPD in the U.K.: results from the Confronting COPD survey. Respiratory medicine. 2003;97 Suppl C:S71-9.
4. Soriano J, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. Lancet. 2009;374(9691):721 - 32.
5. Fromer L. Diagnosing and treating COPD: understanding the challenges and finding solutions. International journal of general medicine. 2011;4:729-39.
6. Kesten S, Ulrich J, Rich D. Public awareness of chronic obstructive pulmonary disease. Chest. 2003;124(4):167s-s.
7. Soriano JB, Calle M, Montemayor T, Alvarez-Sala JL, Ruiz-Manzano J, Miravitlles M. The General Public's Knowledge of Chronic Obstructive Pulmonary Disease and Its Determinants: Current Situation and Recent Changes. Arch Bronconeumol. 2012;48(9):308-15.
8. Jones RCM, Price D, Ryan D, Sims EJ, von Ziegenweidt J, Mascarenhas L, et al. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. The Lancet Respiratory Medicine. 2014.
9. Jordan R, Lam K-B, Cheng K, Miller M, Marsh J, Ayres J, et al. Case finding for chronic obstructive pulmonary disease: a model for optimizing a targeted approach. Thorax. 2010;65:492 - 8.
10. Calderon-Larranaga A, Carney L, Soljak M, Bottle A, Partridge M, Bell D, et al. Association of population and primary healthcare factors with hospital admission rates for chronic obstructive pulmonary disease in England: national cross-sectional study. Thorax. 2011;66(3):191-6.
11. Bastin AJ, Starling L, Ahmed R, Dinham A, Hill N, Stern M, et al. High prevalence of undiagnosed and severe chronic obstructive pulmonary disease at first hospital admission with acute exacerbation. Chronic respiratory disease. 2010;7(2):91-7.
12. Invisible lives: chronic obstructive pulmonary disease (COPD) — finding the missing millions. London: British Lung Foundation, 2007.
13. Bakke PS, Ronmark E, Eagan T, Pistelli F, Annesi-Maesano I, Maly M, et al. Recommendations for epidemiological studies on COPD. European Respiratory Journal. 2011;38(6):1261-77.
14. Buist AS. The US Lung Health Study. Respirology. 1997;2(4):303-7.
15. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. The Cochrane database of systematic reviews. 2006(4):CD003793.
16. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease, 2013.
17. Cartwright S. An evaluation of screening for COPD against the National Screening Committee criteria. 2012.
18. Lin K, Watkins B, Johnson T, Rodriguez JA, Barton MB, Force USPST. Screening for chronic obstructive pulmonary disease using spirometry: summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;148(7):535-43.
19. Price DB, Tinkelman DG, Nordyke RJ, Isonaka S, Halbert RJ, Group CQS. Scoring system and clinical application of COPD diagnostic questionnaires. Chest. 2006;129(6):1531-9.
20. Frith P, Crockett A, Beilby J, Marshall D, Attewell R, Ratnanesan A, et al. Simplified COPD screening: validation of the PiKo-6(R) in primary care. Prim Care Respir J. 2011;20(2):190-8, 2 p following 8.
21. Haroon SM, Adab PA, Jordan RE. Case finding for COPD in primary care: a systematic review. Prim Care Respir J. 2012;21(3):354-7.
22. PROSPERO: International prospective register of systematic reviews York: Centre for Reviews and Dissemination, University of York; 2014 [cited 2014]. Available from: http://www.crd.york.ac.uk/PROSPERO/.
23. Whiting P, Rutjes AW, Dinnes J, Reitsma J, Bossuyt PM, Kleijnen J. Development and validation of methods for assessing the quality of diagnostic accuracy studies. Health technology assessment. 2004;8(25):iii, 1-234.

24. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.
25. Higgins J, Green SP. Cochrane handbook for systematic reviews of interventions. Oxford: Wiley-Blackwell; 2008.
26. Bunker J, Hermiz O, Zwar N, Dennis SM. Feasibility and efficacy of COPD case finding by practice nurses. Aust Fam Physician. 2009;38(10):826-30.
27. Dirven J, Tange H, Muris J, van Haaren K, Vink G, van Schayck O. Early detection of COPD in general practice: patient or practice managed? A randomised controlled trial of two strategies in different socioeconomic environments. Prim Care Respir J. 2013;22(3):331 - 7.
28. Haroon S, Adab P, Griffin C, Jordan R. Case finding for chronic obstructive pulmonary disease in primary care: a pilot randomised controlled trial. Brit J Gen Pract. 2013;63(606).
29. Konstantikaki V, Kostikas K, Minas M, Batavanis G, Daniil Z, Gourgoulianis KI, et al. Comparison of a network of primary care physicians and an open spirometry programme for COPD diagnosis. Respiratory medicine. 2011;105(2):274-81.
30. Dirven JAM, Tange HJ, Muris JWM, van Haaren KMA, Vink G, van Schayck OCP. Early detection of COPD in general practice: patient or practice managed? A randomised controlled trial of two strategies in different socioeconomic environments. Prim Care Resp J. 2013;22(3):331-7.
31. Broekhuizen BD, Sachs AP, Hoes AW, Moons KG, van den Berg JW, Dalinghaus WH, et al. Undetected chronic obstructive pulmonary disease and asthma in people over 50 years with persistent cough. Br J Gen Pract. 2010;60(576):489-94.
32. Kogler H, Metzdorf N, Glaab T, Welte T. Preselection of patients at risk for COPD by two simple screening questions. Resp Med. 2010;104(7):1012-9.
33. Lokke A, Ulrik CS, Dahl R, Plauborg L, Dollerup J, Kristiansen LC, et al. Detection of previously undiagnosed cases of COPD in a high-risk population identified in general practice. COPD. 2012;9(5):458-65.
34. Ulrik CS, Lokke A, Dahl R, Dollerup J, Hansen G, Cording PH, et al. Early detection of COPD in general practice. Int J Chronic Obstr. 2011;6:123-7.
35. Sandelowsky H, Stallberg B, Nager A, Hasselstrom J. The prevalence of undiagnosed chronic obstructive pulmonary disease in a primary care population with respiratory tract infections - a case finding study. Bmc Fam Pract. 2011;12.
36. Al Ghobain M, Al-Hajjaj MS, Wali SO. Prevalence of chronic obstructive pulmonary disease among smokers attending primary healthcare clinics in Saudi Arabia. Ann Saudi Med. 2011;31(2):129-33.
37. Leuppi JD, Miedinger D, Chhajed PN, Buess C, Schafroth S, Bucher HC, et al. Quality of Spirometry in Primary Care for Case Finding of Airway Obstruction in Smokers. Respiration. 2010;79(6):469-74.
38. Vandevoorde J, Verbanck S, Gijssels L, Schuermans D, Devroey D, De Backer J, et al. Early detection of COPD: A case finding study in general practice. Resp Med. 2007;101(3):525-30.
39. van Schayck C, Loozen J, Wagena E, Akkermans R, Wesseling G. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. BMJ. 2002;324(7350):1370.
40. Freeman D, Nordyke RJ, Isonaka S, Nonikov DV, Maroni JM, Price D, et al. Questions for COPD diagnostic screening in a primary care setting. Respiratory medicine. 2005;99(10):1311-8.
41. Geijer RMM, Sachs APE, Hoes AW, Salome PL, Lammers JWJ, Verheij TJM. Prevalence of undetected persistent airflow obstruction in male smokers 40-65 years old. Fam Pract. 2005;22(5):485-9.
42. Kotz D, Nelemans P, van Schayck CP, Wesseling GJ. External validation of a COPD diagnostic questionnaire. Eur Respir J. 2008;31(2):298-303.
43. Stratelis G, Jakobsson P, Molstad S, Zetterstrom O. Early detection of COPD in primary care: screening by invitation of smokers aged 40 to 55 years. Brit J Gen Pract. 2004;54(500):201-6.
44. Dirven JAM, Tange HJ, Muris JWM, van Haaren KMA, Vink G, van Schayck OCP. Early detection of COPD in general practice: implementation, workload and socioeconomic status. A mixed methods observational study. Prim Care Resp J. 2013;22(3):338-43.
45. de Queiroz MCDAM, Moreira MAC, Rabahi MF. Underdiagnosis of COPD at primary health care clinics in the city of Aparecida de Goiania, Brazil. J Bras Pneumol. 2012;38(6):692-9.

46. Thorn J, Tilling B, Lisspers K, Jorgensen L, Stenling A, Stratelis G. Improved prediction of COPD in at-risk patients using lung function pre-screening in primary care: a real-life study and cost-effectiveness analysis. Prim Care Respir J. 2012;21(2):159-66.
47. Ulrik CS, Lokke A, Dahl R, Dollerup J, Hansen G, Cording PH, et al. Early detection of COPD in general practice. International journal of chronic obstructive pulmonary disease. 2011;6:123-7.
48. Jithoo A, Enright PL, Burney P, Buist AS, Bateman ED, Tan WC, et al. Case-finding options for COPD: results from the Burden of Obstructive Lung Disease study. Eur Respir J. 2013;41(3):548-55.
49. The Health Survey for England 2010. UK Data Service; 2010.
50. Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, managment, and prevention of chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease, 2013.
51. Bednarek M, Maciejewski J, Wozniak M, Kuca P, Zielinski J. Prevalence, severity and underdiagnosis of COPD in the primary care setting. Thorax. 2008;63(5):402-7.
52. Buffels J, Degryse J, Heyrman J, Decramer M, Study D. Office spirometry significantly improves early detection of COPD in general practice: the DIDASCO Study. Chest. 2004;125(4):1394-9.
53. Castillo D, Guayta R, Giner J, Burgos F, Capdevila C, Soriano JB, et al. COPD case finding by spirometry in high-risk customers of urban community pharmacies: A pilot study. Resp Med. 2009;103(6):839-45.
54. Clotet J, Gomez-Arbones X, Ciria C, Albalad JM. Spirometry is a good method for detecting and monitoring chronic obstructive pulmonary disease in high-risk smokers in primary health care. Arch Bronconeumol. 2004;40(4):155-9.
55. DeJong SR, Veltman RH. The effectiveness of a CNS-led community-based COPD screening and intervention program. Clinical nurse specialist CNS. 2004;18(2):72-9.
56. Duong-Quy S, Hua-Huy T, Mai-Huu-Thanh B, Doan-Thi-Quynh N, Le-Quang K, Nguyen-Van H, et al. [Early detection of smoking related chronic obstructive pulmonary disease in Vietnam]. Revue des maladies respiratoires. 2009;26(3):267-74.
57. 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 : JAPhA. 2012;52(5):e59-66.
58. Hanania NA, Mannino DM, Yawn BP, Mapel DW, Martinez FJ, Donohue JF, et al. Predicting risk of airflow obstruction in primary care: Validation of the lung function questionnaire (LFQ). Respiratory medicine. 2010;104(8):1160-70.
59. Kaufmann M, Hartl S, Geyer K, Breyer MK, Burghuber OC. Measuring FEV6 for Detecting Early Airway Obstruction in the Primary Care Setting. Respiration. 2009;78(2):161-7.
60. Kimura K, Kurosaki H, Wakabayashi R, Motegi T, Ishii T, Yamada K, et al. Concerns with the Health Check-up System for Chronic Obstructive Pulmonary Disease on two Japanese Islands. Internal Med. 2011;50(19):2135-41.
61. Laniado-Laborin R, Rendon A, Bauerle O. Chronic obstructive pulmonary disease case finding in Mexico in an at-risk population. Int J Tuberc Lung D. 2011;15(6):818-23.
62. Mintz ML, Yawn BP, Mannino DM, Donohue JF, Hanania NA, Grellet CA, et al. Prevalence of airway obstruction assessed by lung function questionnaire. Mayo Clinic proceedings. 2011;86(5):375-81.
63. Sichletidis L, Spyratos D, Papaioannou M, Chloros D, Tsiotsios A, Tsagaraki V, et al. A combination of the IPAG questionnaire and PiKo-6(R) flow meter is a valuable screening tool for COPD in the primary care setting. Prim Care Respir J. 2011;20(2):184-9, 1 p following 9.
64. Takahashi TU, Ichinose M, Inoue H, Shirato K, Hattori T, Takishima T. Underdiagnosis and undertreatment of COPD in primary care settings. Respirology. 2003;8(4):504-8.
65. Takemura H, Hida W, Sasaki T, Sugawara T, Sen T. Prevalence of chronic obstructive pulmonary disease in Japanese people on medical check-up. Tohoku J Exp Med. 2005;207(1):41-50.
66. van Schayck CP, Loozen JMC, Wagena E, Akkermans RP, Wesseling GJ. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. Brit Med J. 2002;324(7350):1370-3.
67. Vrijhoef HJM, Diederiks JPM, Wesseling GJ, Van Schayck CP, Spreeuwenberg C. Undiagnosed patients and patients at risk for COPD in primary health care: early detection with the support of non-physicians. J Clin Nurs. 2003;12(3):366-73.

CHAPTER 4: PREDICTING RISK OF COPD IN PRIMARY CARE: DEVELOPMENT AND VALIDATION OF A CLINICAL RISK SCORE

This chapter is based on a paper currently in press: Haroon S, Adab P, Riley RD, Marshall T, Lancashire R, Jordan RE. Predicting risk of COPD in primary care: development and validation of a clinical risk score. BMJ Open Respiratory Research. 2014.

4.1 Abstract

Objectives

To develop and validate a clinical risk score to identify patients at risk of chronic obstructive pulmonary disease (COPD) using clinical factors routinely recorded in primary care.

Design

Case-control study of patients containing one incident COPD case to two controls matched on age, sex, and general practice. Candidate risk factors were included in a conditional logistic regression model to produce a clinical score. Accuracy of the score was estimated on a separate external validation sample derived from 20 purposively selected practices.

Setting

UK general practices enrolled in the Clinical Practice Research Datalink (1st January 2000 to 31st March 2006).

Participants

The development sample included 340 practices containing 15,159 newly diagnosed COPD cases and 28,296 controls (mean age 70 years, 52% male). The validation sample included 2,259 cases and 4,196 controls (mean age 70 years, 50% male).

Main outcome measures

Area under the receiver operator characteristic curve (c-statistic), sensitivity, and specificity in the validation practices.

Results

The final model included four variables including smoking status, history of asthma, and lower respiratory tract infections, and prescription of salbutamol in the previous three years. It had a high average c-statistic of 0.85 [95% CI 0.83 to 0.86]) and yielded a sensitivity of 63.2% (95% CI 63.1 to 63.3) and specificity of 87.4% (95% CI 87.3 to 87.5).

Conclusions

Risk factors associated with COPD and routinely recorded in primary care have been used to develop and externally validate a new COPD risk score. This could be used to target patients for case finding.

4.2 Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of mortality.(1) However, population studies suggest that 50-90% of the disease burden remains undiagnosed.(2) A recent analysis of UK primary healthcare records showed that opportunities to diagnose COPD are frequently missed with up to 85% of patients presenting within five years of their diagnosis with indicative symptoms and clinical events.(3) There is now a drive to identify such patients in order to instigate early management and reduce disease progression.(4) A variety of screening tools have been proposed and evaluated including symptom-based questionnaires,(5) and use of handheld and diagnostic spirometry.(6) Although a variety of screening tools for COPD have been evaluated, as summarised in Chapters 2 and 3, mass screening is likely to be costly and a more targeted approach is required to improve their efficiency.

One potential way to achieve this is through the use of clinical prediction models. Several have already been developed to identify individuals at risk of undiagnosed COPD. These include two developed in the USA using administrative claims data,(7, 8) one in Denmark using primary and secondary care data,(9) and most recently in Scotland using routine primary healthcare data.(10) The first three models are unlikely to be implementable in a UK or similar primary care setting because of differences in healthcare structures as well as the included predictor variables, many of which are not routinely recorded. The Scottish model, while likely to be implementable, only considered a very limited number of potential risk factors, was

not externally validated, and used a country-specific index of socioeconomic deprivation as a predictor, which limits its use outside the UK.(10)

This chapter reports the development and external validation of a clinical prediction model that provides a score for identifying patients at high risk of undiagnosed COPD in primary care.

4.3 Methods

4.3.1 Study design

Electronic primary care records were available from a matched case-control dataset obtained from the General Practice Research Database (GPRD; now the Clinical Practice Research Datalink). Cases with incident COPD were matched by age, sex and general practice with controls without COPD (1:2).

4.3.2 Description of dataset

The GPRD is a computerised database of longitudinal anonymised patient records from a representative sample of 480 general practices across the UK, covering approximately 6% of the population.(11)

4.3.3 Selection of cases and controls

Cases consisted of all patients aged ≥35 years on 1st April 2006 with a new diagnosis of COPD recorded between 1st January 2000 and 1st April 2006 (see Table S4.1 for clinical codes). Cases had at least three years of up-to-standard data (i.e. data entry meeting set quality standards) prior to the date of COPD diagnosis (index date). Controls had no diagnosis of COPD, were registered on the index date and also had at least three years of up-to-standard data.

4.3.4 Identification of candidate risk factors

Risk factors associated with newly diagnosed COPD were identified from published epidemiological studies. Studies were identified from Medline, Embase and Google Scholar using “COPD” (and relevant synonyms) and “risk factor” as Medical Subject Headings and free text (Appendix 4). From 544 articles 46 candidate risk factors

were identified that were likely to be routinely recorded in primary care (Table 4.1). The final list included smoking history, comorbidities (including asthma, ischaemic heart disease and depression), lower and upper respiratory tract infections (LRTIs, URTIs), respiratory symptoms (including cough, dyspnoea, wheeze, and sputum production), systemic symptoms (including unintentional weight loss, chronic fatigue, and poor sleep), body mass index, and health service use including medication prescriptions (salbutamol, oral prednisolone, and antibiotics for a LRTI) and number of previous primary care consultations.

4.3.5 Data extraction

Clinical codes for each variable were identified using the CPRD medical and product dictionaries and the NHS Clinical Terminology Browser version 1.04.(12) Data on demographic characteristics, smoking, comorbidities, respiratory symptoms and health service use were extracted over the specified period (Table 4.1). Data recorded within 60 days prior to the index date were excluded since a clinical suspicion of COPD could have influenced clinical activity during this period.(7) Smoking status closest to the COPD diagnosis date (or matched time point) was used to reflect likely clinical practice.

4.3.6 Sample size and creation of derivation and validation datasets

The dataset was split into a development and external validation sample (whilst preserving matching of cases and controls) by purposively selecting 20 general practices that reflected the full range of practice and population characteristics where the risk score would be applicable. These practices each had at least 200 individuals to ensure validation statistics were estimated with high precision.

Table 4.1 Risk factors associated with COPD extracted for analysis

Category	Variable	Restriction*[1]
Demographic information	Age	At diagnosis
	Sex	N/A
	Socioeconomic status*[2]	N/A
Smoking history	Current smoker	Last recorded before diagnosis
	Ex-smoker	Last recorded before diagnosis
	Never smoked	Last recorded before diagnosis
Comorbidities	Asthma	Before diagnosis
	Ischaemic heart disease*[3]	Before diagnosis
	Heart failure	Before diagnosis
	Stroke	Before diagnosis
	Hyperlipidaemia	Before diagnosis
	Anaemia	Before diagnosis
	Polycythaemia	Within 3 years of diagnosis
	Pulmonary embolus	Within 3 years of diagnosis
	Deep vein thrombosis	Within 3 years of diagnosis
	Atrial fibrillation	Before diagnosis
	Lung cancer	Before diagnosis
	Cancer (excluding lung cancer)	Before diagnosis
	Depression	Within 3 years of diagnosis
	Anxiety	Within 3 years of diagnosis
	Allergic rhinitis	Before diagnosis
	Tuberculosis	Before diagnosis
	Obstructive sleep apnoea	Before diagnosis
	Gastric ulcer	Before diagnosis
	Helicobacter pylori	Before diagnosis
	Gastro-oesophageal reflux disease	Before diagnosis
	Osteoporosis	Before diagnosis
	Fractures	Before diagnosis
	Diabetes	Before diagnosis
	Rheumatoid arthritis	Before diagnosis
	Chronic kidney disease	Before diagnosis
	Underweight	Within 3 years of diagnosis
	Cachexia	Within 3 years of diagnosis
	Overweight	Within 3 years of diagnosis
	Obesity	Within 3 years of diagnosis
	Lower respiratory tract infection	Within 3 years of diagnosis
	Upper respiratory tract infection	Within 3 years of diagnosis
	Common cold	Within 3 years of diagnosis
	Allergies	Before diagnosis
Symptoms	Cough	Within 3 years of diagnosis
	Dyspnoea	Within 3 years of diagnosis
	Wheeze	Within 3 years of diagnosis
	Sputum	Within 3 years of diagnosis
	Unintentional weight loss	Within 3 years of diagnosis,
	Chronic fatigue or tiredness	Within 3 years of diagnosis
	Insomnia/poor sleep	Within 3 years of diagnosis
Clinical measurements and tests	Height	Last recorded before diagnosis
	Weight	Last recorded before diagnosis
	Body mass index	Last recorded before diagnosis
	Sputum culture	Within 3 years of diagnosis
	Chest X-ray	Within 3 years of diagnosis
Medications	Salbutamol	Within 3 years of diagnosis,
	Oral prednisolone	Within 3 years of diagnosis
	Antibiotics*[4]	Within 3 years of diagnosis
Consultations	GP consultations	Within 3 years of diagnosis
	Emergency hospital referrals	Within 3 years of diagnosis

*1. Excluding 60 days prior to COPD diagnosis or equivalent matched time point for controls.

*2. Socioeconomic status of general practice as measured by the Index of Multiple Deprivation Score.

*3. Including myocardial infarction, angina & coronary artery bypass graft.

*4. Antibiotics (combined): amoxicillin, clarithromycin, doxycyclin, benzylpenicillin, co-amoxiclav, cefuroxime, or rifampicin

4.3.7 Model development

Both the unadjusted and adjusted association between each factor and COPD were estimated using conditional logistic regression (to account for matching of cases and controls). Risk factors were included in the model based on statistical significance (adjusted odds ratio ≥1.5 and p-value <0.05) and clinical understanding, with the aim to achieve a parsimonious and clinically acceptable model (Figure 4.1). The final model was simplified by including only four risk factors that had the highest adjusted odds ratios and were most likely to be recorded in a range of primary care settings.

Missing smoking status was accounted for by including a missing value category in the regression model. Patients in primary care may have unknown smoking status and the model in practice may be applied to such patients. Missing data for other factors was assumed indicative of their true absence. Risk scores were computed for each individual by combining the estimated regression log odds ratios (beta coefficients) from the final model with the individual's risk factor values.

4.3.8 External validation and model performance

The accuracy of the risk score was evaluated in each of the 20 validation practices by producing the corresponding receiver operator characteristic (ROC) curve and estimating the area under it (c-statistic). To summarise the average performance across the 20 practices, the c-statistic estimates were synthesised in a random effects meta-analysis. The heterogeneity in performance was also summarised by estimating a 95% interval for the range of potential c-statistics.(13)

A score cut-point to define 'high risk' was selected by optimising the balance between the sensitivity and positive predictive value (PPV), assuming a prevalence of

undiagnosed COPD of 5.5% in the general population.(14) The total number screened was divided by the number of true positives to derive the number-needed-to-screen (NNS) to detect a single case of COPD. The number of diagnostic assessments needed to detect a single case of COPD (NND) was estimated as the reciprocal of the PPV.

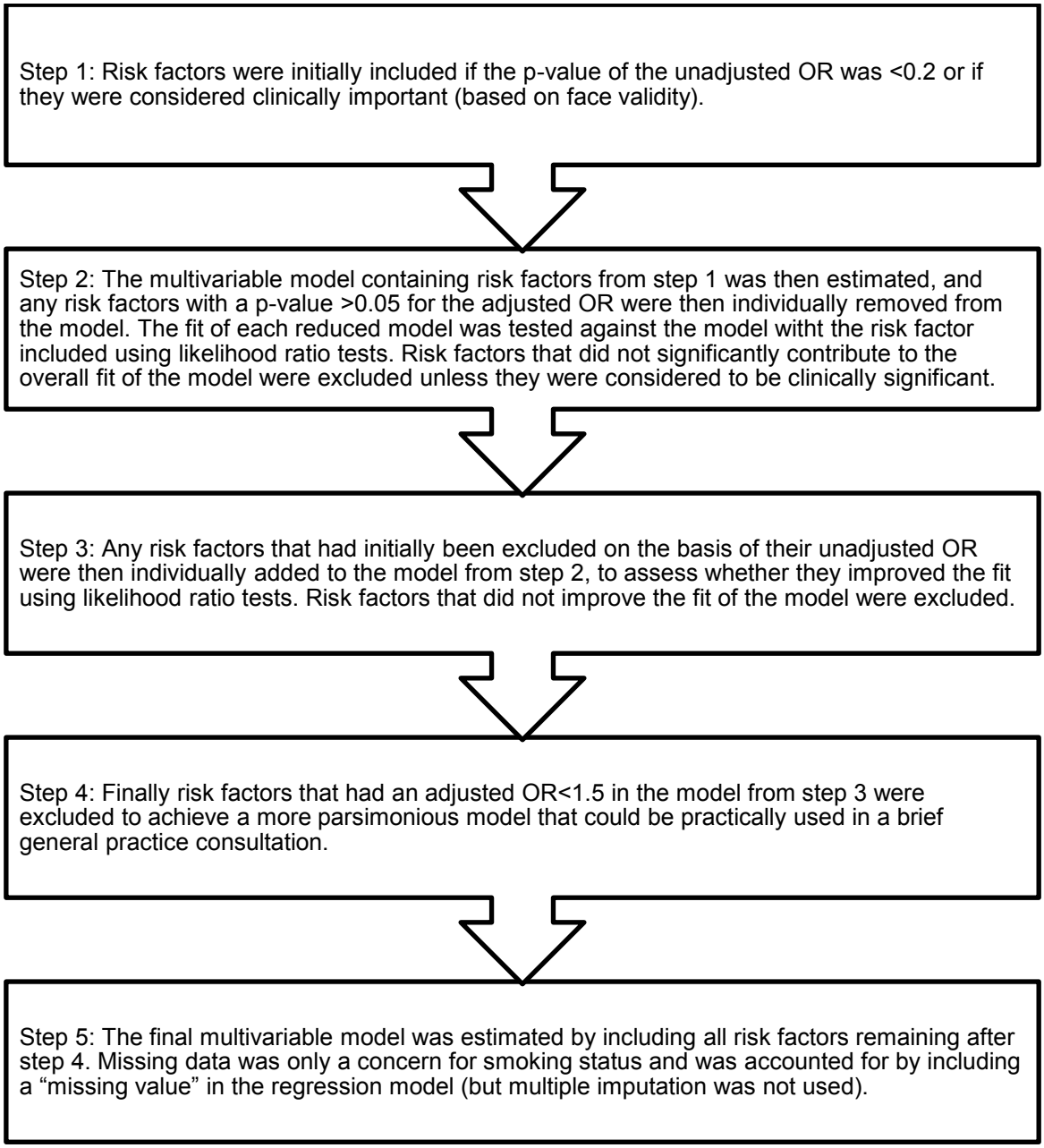

Figure 4.1 Model building strategy

4.4 RESULTS

4.4.1 Development sample: population characteristics

15,159 newly diagnosed COPD cases and 28,296 controls from 340 general practices were included in the development sample (Tables 4.2 and 4.3). Mean age was 70 years and 52% were male. Cases and controls were matched and therefore identical in age, sex, and socioeconomic status of registered practice. 27% were current smokers, 25% ex-smokers and 40% had never smoked. A significantly higher proportion of cases than controls had a positive smoking history (77% vs. 38%, respectively). All co-morbidities except hyperlipidaemia and diabetes mellitus were more common in cases than in controls. This was also true for respiratory and systemic symptoms, including fatigue and poor sleep, as well as health service use.

4.4.2 Model results

Details of the selection of predictors are shown in Table S4.2. The final model included history of smoking, asthma, and salbutamol prescriptions and number of lower respiratory tract infections (LRTIs) in the previous three years (Table 4.4). There was a significant drop in the model fit when removing asthma, salbutamol and LRTIs. The model was used to derive a clinical score ranging from 0 to 6.5 as shown below Table 4.4. This had a c-statistic in the development sample of 0.85 (95% CI 0.845 to 0.853). A more comprehensive model that incorporates additional variables, including symptoms, is provided in Table 4.5.

4.4.3 External validation sample: population characteristics

2259 newly diagnosed cases and 4196 controls from 20 general practices were included in the validation sample (Table 4.6). The mean age was 70 years, 50% were

male, and 26.6% were current smokers. A greater proportion of subjects in the validation sample than the development sample were from practice in the lowest socioeconomic quintile (42.4% vs. 26.8%, respectively).

4.4.4 External validation: discriminative ability

The final risk score had a c-statistic of 0.84 (95% CI 0.83 to 0.85) in the validation sample when analysing the data from all 20 practices combined (ignoring clustering of patients within practices; Figure 4.2). The c-statistic in each of the validation practices separately was consistently high (Figure 4.3) and a random effects meta-analysis (which takes into account clustering) produced a similar summary c-statistic of 0.85 (95% CI 0.83 to 0.86), with a 95% prediction interval of 0.80 to 0.90. The more comprehensive score had a marginally higher c- statistic (0.87, 95% CI 0.86 to 0.87).

Table 4.7 summarises the performance of the final score across a range of thresholds in the validation sample. A score threshold of ≥2.5 yielded a sensitivity of 63.2% (95% CI 63.1 to 63.3) and specificity of 87.4% (95% CI 87.3 to 87.5). Assuming a prevalence of undiagnosed COPD of 5.5%,(14) the score at the suggested threshold would have a PPV of 22.6%, NPV of 97.6%, and an overall screening yield of 3.5% when applied to patients over the age of 35 years. At this threshold the score would need to be applied to 29 patients, 5 of whom would require a clinical assessment, to identify one with COPD (Figure 4.4).

Table 4.2 General characteristics of subjects in the development sample

		Controls (n=28,296)		Cases (n=15,159)		Unadjusted OR	(95% CI)
		N	(%)	N	(%)		
Mean age (standard deviation)		69.7	(10.8)	69.7	(10.9)	-	
Males		14,655	(51.8)	7,849	(51.8)	-	
Socioeconomic quintile*[1]	1	5,035	(17.8)	2,698	(17.8)	-	
	2	4,156	(14.7)	2,237	(14.8)	-	
	3	5,079	(17.9)	2,733	(18.0)	-	
	4	6,386	(22.6)	3,429	(22.6)	-	
	5	7,640	(27.0)	4,062	(26.8)	-	
Smoking status*[2]	Never	14,693	(51.9)	2,758	(18.2)	1	
	Former	6,013	(21.3)	4,671	(30.8)	4.79	(4.49, 5.10)
	Current	4,831	(17.1)	6,961	(45.9)	8.99	(8.43, 9.59)
	Missing	2,759	(9.8)	769	(5.1)	1.37	(1.23, 1.51)
BMI*[2]	<18.5	5,810	(20.5)	2,917	(19.2)	0.80	(0.76, 0.85)
	18.5-25	8,651	(30.6)	5,232	(34.5)	1	
	25-30	9,299	(32.9)	4,475	(29.5)	0.79	(0.75, 0.83)
	>30	4,536	(16.0)	2,535	(16.7)	0.93	(0.87, 0.98)

Unadjusted odds ratio (OR) for association with COPD.

NB. Unadjusted ORs for age, sex and socioeconomic status of general practice were not estimated as cases and controls were matched on these variables.

*1. 1=least deprived, 5=most deprived. Based on Index of Multiple Deprivation score of general practice electoral ward.

*2. Closest to diagnosis

Table 4.3 Comorbidities, symptoms, and healthcare use (development sample)

			Controls (n=28,296)		Cases (n=15,159)		Unadjusted OR	(95% CI)
			N	(%)	N	(%)		
Comorbidities[1]	Asthma		2,438	(8.6)	5,669	(37.4)	6.61	(6.23, 7.02)
	Ischaemic heart disease		5,572	(19.7)	3,560	(23.5)	1.31	(1.25, 1.38)
	Heart failure		687	(2.4)	847	(5.6)	2.50	(2.24, 2.77)
	Stroke		850	(3.0)	539	(3.6)	1.23	(1.10, 1.37)
	Hyperlipidaemia		3,327	(11.8)	1,660	(11.0)	0.93	(0.87, 1.00)
	Anaemia		1,554	(5.5)	859	(5.7)	1.04	(0.95, 1.14)
	Pulmonary embolism		50	(0.2)	71	(0.5)	2.72	(1.89, 3.91)
	Deep vein thrombosis		139	(0.5)	107	(0.7)	1.44	(1.12, 1.86)
	Atrial fibrillation		980	(3.5)	690	(4.6)	1.37	(1.24, 1.51)
	Lung cancer		35	(0.1)	68	(0.4)	3.68	(2.45, 5.55)
	Cancer		3,805	(13.4)	2,098	(13.8)	1.05	(0.99, 1.11)
	Depression[2]		967	(3.4)	630	(4.2)	1.24	(1.12, 1.38)
	Anxiety[2]		2,056	(7.3)	1,816	(12.0)	1.77	(1.65, 1.90)
	Allergic rhinitis		1,917	(6.8)	1,152	(7.6)	1.13	(1.05, 1.22)
	Tuberculosis		421	(1.5)	365	(2.4)	1.66	(1.44, 1.91)
	Pulmonary tuberculosis		371	(1.3)	344	(2.3)	1.77	(1.52, 2.06)
	Chronic kidney disease		56	(0.2)	45	(0.3)	1.69	(1.11, 2.60)
	Helicobacter pylori		188	(0.7)	139	(0.9)	1.45	(1.16, 1.81)
	Gastric ulcer		545	(1.9)	472	(3.1)	1.63	(1.43, 1.85)
	Gastro-oesophageal reflux disease		1,897	(6.7)	1,229	(8.1)	1.25	(1.16, 1.35)
	Osteoporosis		713	(2.5)	569	(3.8)	1.58	(1.41, 1.78)
	Fractures		3,862	(13.6)	2,547	(16.8)	1.30	(1.23, 1.38)
	Diabetes		2,167	(7.7)	1,015	(6.7)	0.87	(0.81, 0.94)
	Rheumatoid arthritis		462	(1.6)	369	(2.4)	1.52	(1.32, 1.75)
	Lower respiratory tract infections[2]	0	25,128	(88.8)	9,344	(61.6)	1	
		1	2,205	(7.8)	2,947	(19.4)	4.02	(3.76, 4.29)
		>1	963	(3.4)	2,868	(18.9)	9.76	(8.93, 10.7)
	Upper respiratory tract infections[2]	0	22,355	(79.0)	10,623	(70.1)	1	
		1	3,917	(13.8)	2,702	(17.8)	1.47	(1.39, 1.56)
		>1	2,024	(7.2)	1,834	(12.1)	1.98	(1.85, 2.13)
	Allergy		7,614	(26.9)	5,045	(33.3)	1.40	(1.34, 1.46)
Symptoms*[2]	Presentations with cough	0	23,470	(82.9)	8,180	(54.0)	1	
		1	3,072	(10.9)	3,130	(20.6)	3.14	(2.96, 3.34)
		>1	1,754	(6.2)	3,849	(25.4)	7.12	(6.64, 7.63)
	Presentations with dyspnoea	0	26,789	(94.7)	11,294	(74.5)	1	
		1	1,014	(3.6)	2,220	(14.6)	5.57	(5.12, 6.06)
		>1	493	(1.7)	1,645	(10.9)	9.01	(8.05, 10.1)
	Wheeze		456	(1.6)	1,860	(12.3)	8.89	(7.96, 9.94)
	Sputum production		245	(0.9)	609	(4.0)	5.32	(4.52, 6.26)
	Weight loss		211	(0.7)	306	(2.0)	2.74	(2.30, 3.28)
	Fatigue		1,550	(5.5)	1,215	(8.0)	1.53	(1.42, 1.66)
	Poor sleep		977	(3.5)	810	(5.3)	1.59	(1.44, 1,75)
Health service use*[2]	Antibiotic courses	0	18,799	(66.4)	5,150	(34.0)	1	
		1	5,361	(18.9)	3,313	(21.9)	2.34	(2.21, 2.47)
		2	2,127	(7.5)	2,267	(15.0)	4.04	(3.76, 4.34)
		>2	2,009	(7.1)	4,429	(29.2)	8.64	(8.07, 9.25)
	Salbutamol		2,492	(8.8)	7,723	(50.9)	11.5	(10.8, 12.2)
	Prednisolone		1,800	(6.4)	4,358	(28.7)	6.17	(5.78, 6.58)
	GP consultations	<5	5,162	(18.2)	1,156	(7.6)	1	
		5-10	4,618	(16.3)	1,734	(11.4)	1.81	(1.66, 1.98)
		10-20	7,677	(27.1)	3,745	(24.7)	2.55	(2.36, 2.77)
		20-40	7,610	(26.9)	5,136	(33.9)	3.99	(3.68, 4.32)
		>40	3,229	(11.4)	3,388	(22.3)	6.91	(6.31, 7.57)
	Hospital referrals		703	(2.5)	687	(4.5)	2.08	(1.85, 2.34)

Unadjusted odds ratio (OR) for association with COPD.

1. Ever previously diagnosed

2. Within 3 years of COPD diagnosis or equivalent matched time point for controls

Table 4.4 Adjusted odds ratios (OR) and regression coefficients (β) for risk factors included in the final risk model

		OR*	(95% CI)	β	(95% CI)
Smoking status	Never	1		0	
	Former	4.72	(4.35, 5.12)	1.55	(1.47, 1.63)
	Current	11.7	(10.7, 12.7)	2.46	(2.37, 2.54)
	Missing	2.44	(2.16, 2.76)	0.89	(0.77, 1.02)
Asthma		2.11	(1.93, 2.31)	0.75	(0.66, 0.84)
Lower respiratory tract infection (LRTI)**	0	1		0	
	1	2.57	(2.36, 2.81)	0.94	(0.86, 1.03)
	>1	4.29	(3.83, 4.80)	1.46	(1.34, 1.57)
Salbutamol**		6.91	(6.33, 7.55)	1.93	(1.85, 2.02)

As this model was developed using case-control data, the intercept term is not applicable and has therefore not been presented.

*Estimated using a multivariable conditional logistic regression model

**Within 3 years of COPD diagnosis or equivalent matched time point for controls

Risk score=(former smoker*1.55)+(current smoker*2.46)+(unknown smoking status*0.89)+(asthma*0.75)+(1 episode of LRTI*0.94)+(>1 episode of LRTI*1.46)+(salbutamol*1.93)

NB. Each variable can either take the value 0 (not present) or 1 (present)

e.g. A former smoker with a history of asthma who presented with more than one lower respiratory tract infection in the last three years, and received salbutamol in the last three years would have the following risk score:

(1*1.55)+(0*2.46)+(0*0.89)+((1*0.75)+(0*0.94)+(1*1.46)+(1*1.93)=5.69

Table 4.5 Adjusted odds ratios (OR) and regression coefficients (β) for variables included in a more comprehensive risk score

		OR*	(95% CI)	β	(95% CI)
Smoking status	Never	1		0	
	Former	4.36	(4.00, 4.75)	1.47	(1.39, 1.56)
	Current	12.0	(10.97, 13.12)	2.48	(2.40, 2.57)
	Missing	2.87	(2.52, 3.26)	1.05	(0.92, 1.18)
Asthma		1.89	(1.71, 2.08)	0.64	(0.54, 0.73)
Lower respiratory tract infection (LRTI)**	0	1		0	
	1	1.81	(1.64, 1.99)	0.59	(0.49, 0.69)
	>1	2.23	(1.96, 2.54)	0.80	(0.67, 0.93)
Presentations with cough**	0	1		0	
	1	1.42	(1.30, 1.56)	0.35	(0.26, 0.44)
	>1	1.77	(1.59, 1.97)	0.57	(0.46, 0.68)
Presentations with dyspnoea**	0	1		0	
	1	3.17	(2.82, 3.57)	1.16	(1.04, 1.27)
	>1	4.53	(3.89, 5.28)	1.51	(1.36, 1.66)
Wheeze**		1.86	(1.60, 2.17)	0.62	(0.47, 0.77)
Sputum production**		1.49	(1.17, 1.90)	0.40	(0.16, 0.64)
Unintended weight loss**		1.75	(1.33, 2.31)	0.56	(0.29, 0.84)
Antibiotic courses for a LRTI**	0	1		0	
	1	1.33	(1.23, 1.44)	0.29	(0.21, 0.37)
	2	1.53	(1.38, 1.70)	0.43	(0.32, 0.53)
	>2	1.80	(1.62, 2.01)	0.59	(0.48, 0.70)
Salbutamol**		4.19	(3.81, 4.61)	1.43	(1.34, 1.53)
Prednisolone**		1.53	(1.38, 1.69)	0.42	(0.32, 0.52)

As this model was developed using case-control data, the intercept term is not applicable and has therefore not been presented. The *c* statistic for this model in the external validation sample was 0.87 (95% CI 0.86 to 0.87).

*Estimated using a multivariable conditional logistic regression model

**Within 3 years of COPD diagnosis or equivalent matched time point for controls

Risk score=(former smoker*1.47)+(current smoker*2.48)+(unknown smoking status*1.05)+(asthma*0.64)+(1 episode of LRTI*0.59)+(>1 episode of LRTI*0.80)+(1 episode of cough*0.35)+(>1 episode of cough*0.57)+(1 episode of dyspnoea*1.16)+(>1 episode of dyspnoea*1.15)+(wheeze*0.62)+(sputum*0.40)+(unintended weight loss*0.56)+(1 antibiotic course*0.29)+(2 antibiotic course*0.43)+(>2 antibiotic courses*0.59)+(salbutamol*1.43)+(prednisolone*0.42)

NB. Each variable can either take the value 0 (not present) or 1 (present)

e.g. A former smoker with a history of asthma who presented with more than one lower respiratory tract infection and episode of cough in the last three years, complained of unintended weight loss and received salbutamol and 2 course of antibiotics for a LRTI in the last three years would have the following risk score:

(1*1.47)+(0*2.48)+(0*1.05)+(1*0.64)+(0*0.59)+(1*0.80)+(0*0.35)+(1*0.57)+(0*1.16)+(0*1.15)+(0*0.62)+(0*0.40)+(1*0.56)+(0*0.29)+(1*0.43)+(0*0.59)+(1*1.43)+(0*0.42)=5.9

Table 4.6 Characteristics of subjects in the external validation sample (derived from 20 general practices)

		Controls (n=4196)		Cases (n=2259)	
		N	(%)	N	(%)
Mean age (SD)		69.8	(11.0)	70.0	(11.1)
Males		2,110	(50.3)	1,133	(50.2)
Socioeconomic quintile*	1 (least deprived)	475	(11.3)	258	(11.4)
	2	561	(13.4)	313	(13.9)
	3	1,072	(25.5)	574	(25.4)
	4	308	(7.3)	159	(7.0)
	5 (most deprived)	1,780	(42.4)	955	(42.3)
Smoking status	Never	1,858	(44.3)	374	(16.6)
	Former	799	(19.0)	674	(29.8)
	Current	751	(17.9)	966	(42.8)
	Missing	788	(18.8)	245	(10.8)
Body mass index	<18.5	1,234	(29.4)	623	(27.6)
	18.5-25	1,098	(26.2)	643	(28.5)
	25-29	1,246	(29.7)	624	(27.6)
	≥30	618	(14.7)	369	(16.3)

* Based on the Index of Multiple Deprivation score of electoral ward.

Table 4.7 Test accuracy of the final risk score in the external validation sample

	Discrimination characteristics					Application of the score assuming a 5.5% prevalence of undiagnosed COPD				
Score cut-point	**Sensitivity (%)**	**Specificity (%)**	**Correctly Classified (%)**	**LR+**	**LR-**	**PPV (%)**	**NPV (%)**	**Screening Yield (%)**	**NNS**	**NND**
≥0	100	0	35.0	1	-	5.5	-	5.50	19	19
≥0 .5	96.1	34.7	56.2	1.47	0.11	7.9	99.3	5.29	19	13
≥1.0	90.6	51.9	65.5	1.88	0.18	9.9	99.0	4.98	21	11
≥1.5	89.4	55.1	67.1	1.99	0.19	10.4	98.9	4.92	21	10
≥2.0	81.2	71.9	75.2	2.89	0.26	14.4	98.5	4.47	23	7
≥2.5	63.2	87.4	79.0	5.02	0.42	22.6	97.6	3.48	29	5
≥3.0	55.8	91.9	79.3	6.89	0.48	28.6	97.3	3.07	33	4
≥3.5	47.6	94.6	78.1	8.80	0.55	33.9	96.9	2.62	39	3
≥4.0	40.4	95.8	76.4	9.57	0.62	35.8	96.5	2.22	45	3
≥4.5	23.2	98.3	72.0	13.5	0.78	44.0	95.6	1.28	79	3
≥5.0	20.6	98.4	71.2	13.1	0.81	44.3	95.5	1.13	89	3
≥5.5	11.3	99.5	68.6	21.5	0.89	55.8	95.1	0.62	161	2
≥6.0	5.53	99.7	66.7	18.9	0.95	50.9	94.8	0.30	329	2
≥6.5	3.23	99.8	65.0	19.4	0.97	52.5	94.7	0.18	563	2

Correctly classified= proportion of subjects with disease status correctly classified

LR= likelihood ratio (i.e. the ratio by which the pre-test probability is altered by a positive or negative test result).

PPV=positive predictive value (proportion of all subjects with a positive test who have disease)

NPV=negative predictive value (proportion of all subjects with a negative test who are disease free)

Screening yield= proportion of all patients subjected to the risk score who would be correctly identified as having COPD

NNS=number-needed-to-screen (the number of patients or patient records the risk score would need to be applied to) to identify one patient with COPD

NND=number of diagnostic assessments needed to identify one patient with COPD

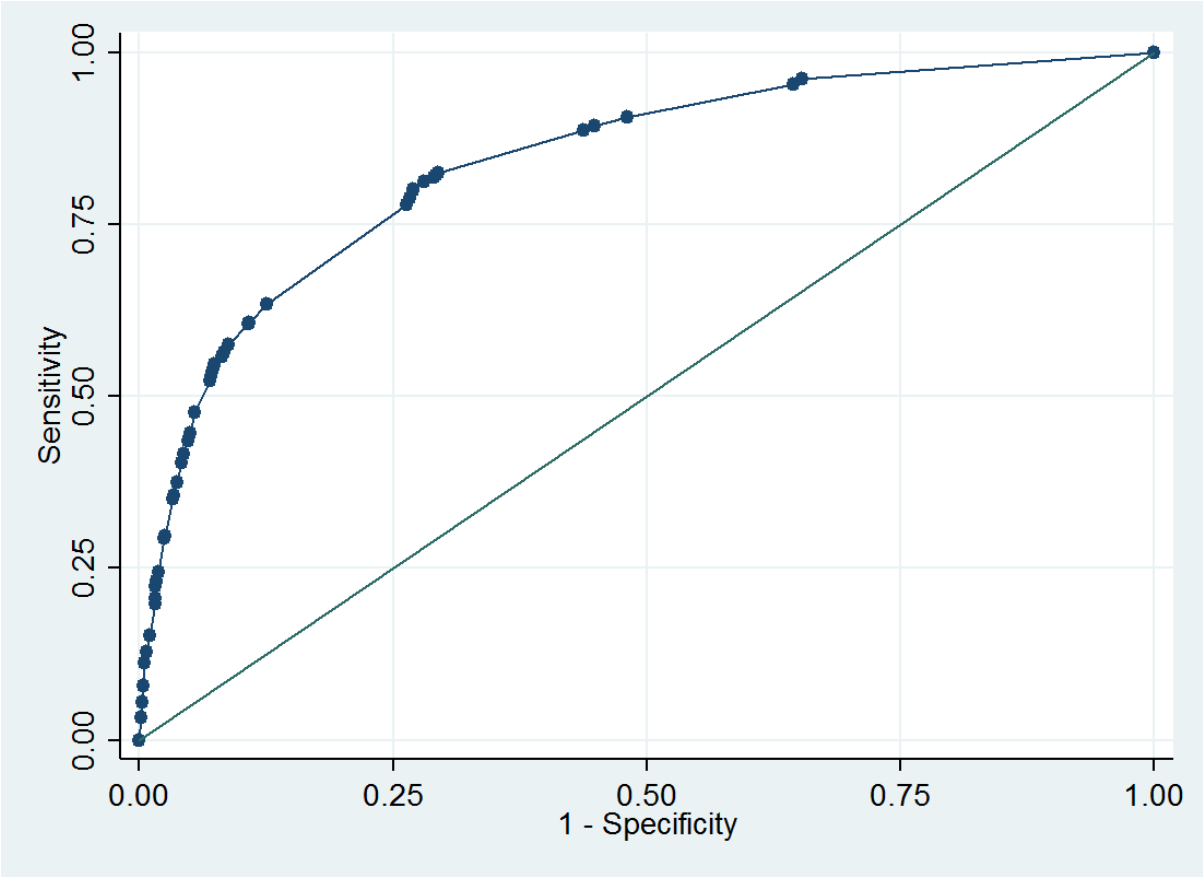

Figure 4.2 Receiver under the operator characteristic (ROC) curve for the test accuracy of the final risk score in the entire external validation sample (c-statistic=0.84, 95% CI 0.83 to 0.85), ignoring clustering of patients within practices.
Each point on the graph represents the performance (sensitivity and specificity) of the risk score at specific thresholds.

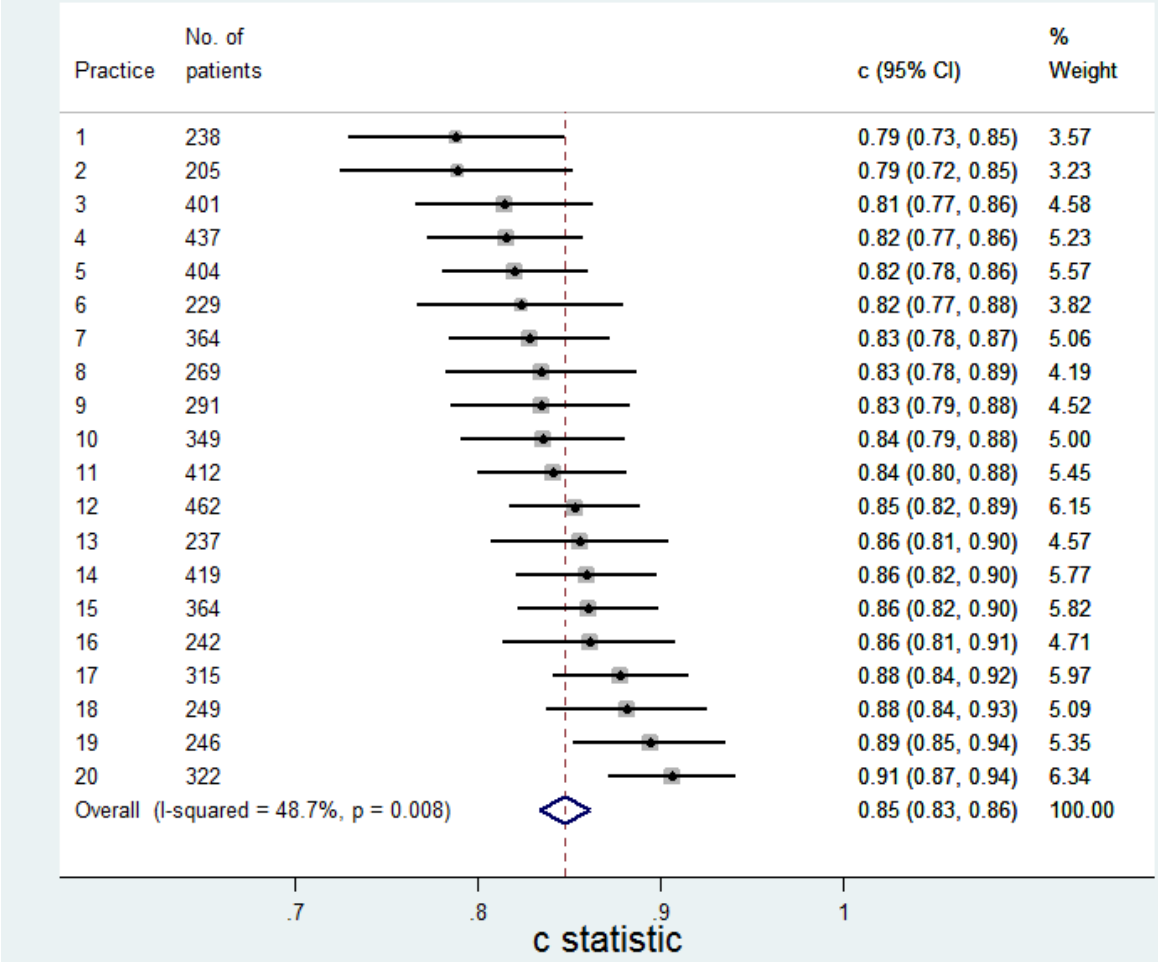

Figure 4.3 Random effects meta-analysis of the *c* statistics obtained for the final risk score when applied in each of the 20 validation practices separately. The summary result is the estimate of the average c-statistic across the validation practices.

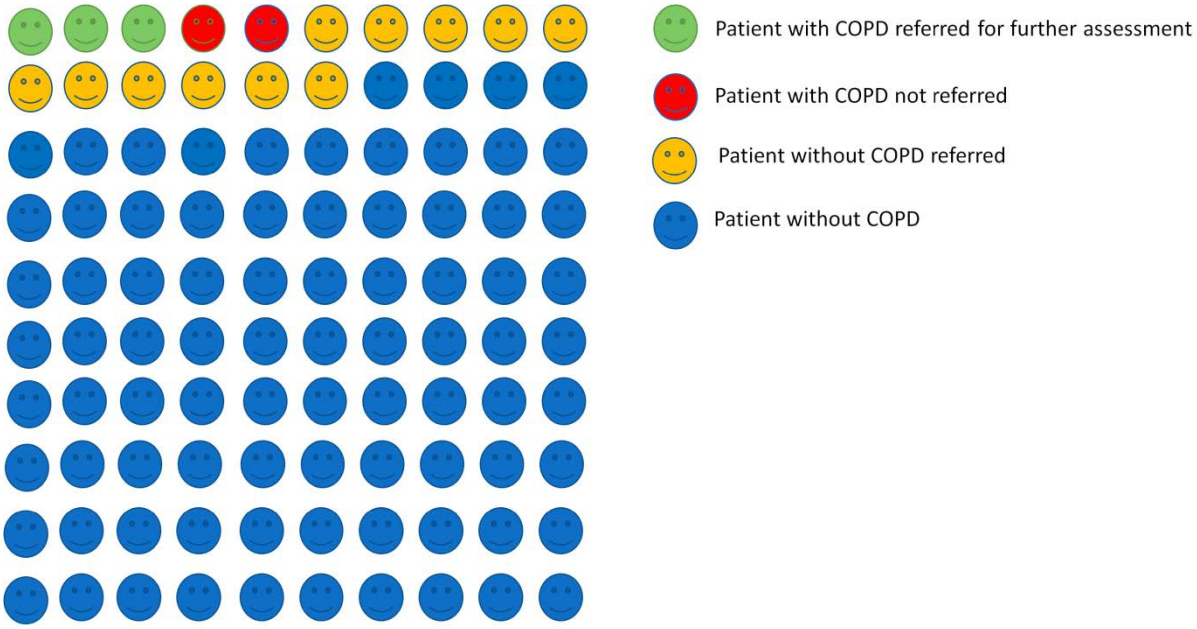

Figure 4.4 Screening test accuracy of the final risk score at a threshold of ≥2.5 when applied to 100 patients aged ≥35 years in primary care with an assumed prevalence of undiagnosed COPD of 5%.

4.5 DISCUSSION

4.5.1 Principal findings

A new clinical prediction model has been developed and validated for identifying patients at high risk of COPD in primary care. The clinical score incorporates smoking status, previous diagnosis of asthma and LRTIs, and prescriptions for salbutamol. The score showed good discrimination characteristics in the external validation population and the suggested cut-point to denote high risk yielded a relatively high sensitivity and specificity. It can potentially detect about three out of every five patients with undiagnosed COPD while also being able to effectively rule out patients at low risk of disease. The score cut-point however can be altered to either maximise sensitivity or specificity.

This builds on a previous published model (based on data from the Health Survey for England) which would require 19 patients to actively undertake a screening process (19 questionnaire responses and 7 clinical assessments) to identify one individual with COPD.(14) The new clinical score, which uses routine data from primary care health records, would significantly improve the efficiency of this process.

4.5.2 Comparison with existing literature

The first published risk model to identify patients with undiagnosed COPD was based on managed (predominantly secondary) care administrative claims data in the USA.(7) Using a case-control design, 19 health service utilisation characteristics were included, many of which are unlikely to be routinely recorded in primary care. In the current study a more parsimonious model was developed that uses data routinely

recorded in primary care and the study population had more complete data on smoking history. A further model was developed in the USA using outpatient pharmacy data.(8) This incorporated respiratory and cardiovascular medications and antibiotics, and had a sensitivity of 60.6% and specificity of 70.5% when externally validated. The risk score developed in the current study similarly included prior prescription of salbutamol as an important predictor. However the ROC curve and c-statistic for both US models were not reported, which makes it impossible to evaluate their discriminatory accuracy.

In Denmark, Smidth and colleagues used administrative data on hospital admissions for lung disorders, respiratory prescriptions and lung function tests to develop a model to identify COPD.(9) This had a much lower sensitivity (29.7-44.8%) but higher specificity (98.9%) than the score developed in the current study. While it had a high PPV in the Dutch population (65.0-72.9%; based on an overall COPD prevalence of 9%), it would be difficult to administer in a UK or similar primary care setting where primary and secondary care data are currently poorly linked. This model also relies on prior diagnoses of emphysema and chronic bronchitis at hospital admissions and would miss a significant number of patients due to the low sensitivity and high proportion of false negative results.

Kotz and colleagues recently developed and internally validated a COPD risk model using routine longitudinal data from primary care in Scotland,(10) including a very large (n=480,903 in the development cohort) and relatively young population (mean age 55.6 years). Their model demonstrated similar discrimination characteristics to that shown in the current study (c-statistic 0.85 [95% CI 0.84 to 0.85] in females and 0.83 [95% CI 0.83 to 0.84] in males), with good calibration. However this has only

been internally validated since the study population was randomly split into derivation and validation samples. Furthermore only a very limited range of risk factors were considered (age, sex, smoking status, socioeconomic status and history of asthma) and potentially important predictors such as respiratory infections were not. They constructed separate models for males and females since they found an interaction between smoking status and sex. We also stratified our model by sex and repeated our analysis but found the odds ratios to be broadly similar to those in the non-stratified model.

As described in Chapter 2, a variety of screening questionnaires have also been evaluated. For example Price and colleagues assessed the accuracy of a case finding questionnaire which included items on respiratory symptoms, smoking, and allergies and showed good discrimination characteristics.(15) This and other questionnaire-based tools can only be used in either face-to-face consultations or distributed by mail or online. If used in a population with a 5.5% prevalence of undiagnosed COPD, 26 patients would need to be screened to identify one case of COPD. The model developed in the current study has the advantage of being applicable in both face-to-face consultations as well as integrated with clinical information systems and used at a practice level to identify whole groups of high risk patients who could be invited to screening sessions. With the latter approach, only five patients would need to be invited for assessment to identify one case of COPD, thus improving its efficiency fivefold over the use of current screening questionnaires.

4.5.3 Strengths

Data were used from a large primary care population and a wide range of risk factors were explored, focusing on those routinely recorded in primary care. Both aspects

help ensure this clinical score will be widely applicable in primary care in the UK and other similar health systems. The score was also validated in a number of non-randomly selected practices allowing for assessment of the heterogeneity of its performance.

4.5.4 Weaknesses

Ideally previously undiagnosed COPD cases identified by case-finding/screening would have been used to derive the risk score since their characteristics may differ from incident cases identified through routine clinical practice. A coded diagnosis of COPD was used for the case definition. Given that the data are from a UK primary care setting, the diagnosis of COPD is likely to be based on NICE guidance. GPs would be expected to take a clinical history, perform a clinical examination, have the patient undertake pre- and post-bronchodilator spirometry as well as other clinical investigations (e.g. chest radiography) prior to making the diagnosis. Spirometry should be performed before and after the administration of a bronchodilator to help differentiate COPD from asthma and the diagnosis should be based on the presence of post-bronchodilator airflow obstruction.(16) However there is good evidence that COPD is both misdiagnosed and under-diagnosed in primary care,(2) a proportion of patients are likely to have undergone spirometry of variable quality,(17) and this may have led to some misclassification of cases and controls. Unfortunately there was insufficient spirometry data in the dataset to validate the diagnosis.

The analysis was performed on data that mostly preceded the Quality and Outcomes Framework, which is a pay-for-performance initiative in England that was introduced to the national GP contract in 2004. A number of COPD-related performance indicators were introduced into QOF, one of which requires post-bronchodilator

spirometry.(18) The quality of spirometry data for COPD diagnosis is thus likely to be of higher quality in more recent primary care data. Quint and colleagues recently demonstrated that clinical codes specific for COPD and emphysema have a high positive predictive value for validated COPD.(19) Clinical codes for COPD that were recommended by the GPRD (now CPRD) at the time of this analysis were used. Although these largely overlapped with those recommended by Quint et al. they also included codes specific for chronic bronchitis, which would not necessarily constitute a diagnosis of COPD (although may increase the likelihood of the development of airflow obstruction and risk of mortality.(20)

The mean age of the study population (70 years) was older than patients who would typically be targeted for case finding. Age and sex, which are likely to be predictors of COPD, could not be incorporated in the model because of the matched case-control data. This also prevented evaluation of the calibration of the model in the validation practices. 18.2% of cases were classed as never smokers. This was significantly higher than the proportion of never smokers among patients with diagnosed COPD (6.9%) but similar to the proportion of never smokers among patients with undiagnosed COPD (16.8%) in an analysis of the Health Survey for England.(14) Anecdotally the quality of smoking status coding in primary can be quite variable and often misclassified and it is likely that the proportion of never smokers among incident cases may in fact be lower than suggested in the current analysis. Another limitation of the matched case-control design is that c-statistics are generally downwardly biased when estimated in such data.(21, 22) Therefore, it is possible the true c-statistic may be closer to 1 upon application.

Some of the variables explored, such as hospitalisations were poorly recorded, and may actually be significant predictors of COPD. In addition the absence of a risk factor could be secondary to under-recording. However the aim was to produce a model that would be implementable in a common primary care setting drawing on routinely recorded data. If clinical coding improves over time some of these variables may need to be revisited as potential predictors and considered for inclusion in future revised models. Finally, the clinical score may not be applicable in health settings where exposure to risk factors other than cigarette smoking (e.g. biomass fuels) is a significant cause of COPD.

4.5.5 Implications for clinicians, policymakers and research

The newly developed clinical score once further validated, could be used by clinicians in primary care to stratify patients by risk of COPD. This could be achieved primarily with the aid of developed software applications that would automate the calculations. Since the model was based entirely on routinely collected data it could also be integrated into primary care clinical information systems to use data on risk factors to stratify all eligible patients. Patients predicted to be at high risk of COPD could then be referred for a clinical assessment including confirmatory spirometry testing.

However, further work is needed to validate or adapt this preliminary model in other populations, notably in case finding trials that have enrolled patients with previously undiagnosed COPD. This includes examining the matching factors (age and sex) as potential predictors. The cost-effectiveness of targeting patients at different thresholds should also be evaluated. Future studies should also address the impact of this tool on use and outcomes in general practice.

4.5.6 Conclusion

The newly developed risk score shows promising accuracy and increased efficiency over current methods for identifying patients with undiagnosed COPD in primary care. Use of an externally validated score could be used for risk stratification so that high risk patients can be efficiently identified and referred for confirmatory spirometry. However evidence that early identification of COPD results in improved patient outcomes must be robustly assessed before screening for COPD can be recommended as part of routine practice.

4.6 Supplementary tables

Table S4.1. Clinical codes (Read/OXMIS terms) used to define COPD

GPRD Medical Code	Read/OXMIS Code	Read/OXMIS Term
303970	491	Chronic bronchitis
303973	492	Emphysema pulmonary
303971	491 AC	Bronchitis acute on chronic
275013	491 BT	Bronchitis obstructive
303972	491 E	Chronic bronchitis with emphysema
306529	491 R	Bronchitis recurrent
265866	492 AB	Apical bullae
265867	492 AC	Emphysema apical bullae
306530	492 CM	Hyperinflation compensatory
256647	492 PP	Puffer pink
304065	5199C	Obstructive airways disease
304067	5199CL	Obstructive lung disease
304071	5199G	Obstructive airways disease chronic
304072	5199GE	Exacerbation coad
304073	5199GL	COLD (chronic obstructive lung disease)
304074	5199GP	COPD (chronic obstructive pulmonary disease)
305740	9906E	Radiological emphysema
280081	H3...00	Chronic obstructive pulmonary disease
243388	H3...11	Chronic obstructive airways disease
207194	H31..00	Chronic bronchitis
280085	H310.00	Simple chronic bronchitis
261743	H310000	Chronic catarrhal bronchitis
289195	H310z00	Simple chronic bronchitis NOS
280086	H311.00	Mucopurulent chronic bronchitis
252513	H311000	Purulent chronic bronchitis
271037	H311100	Fetid chronic bronchitis
225243	H311z00	Mucopurulent chronic bronchitis NOS
271038	H312.00	Obstructive chronic bronchitis
280087	H312000	Chronic asthmatic bronchitis
207195	H312011	Chronic wheezy bronchitis
261744	H312100	Emphysematous bronchitis
216142	H312200	Acute exacerbation of chronic obstructive airways disease
252514	H312z00	Obstructive chronic bronchitis NOS
261745	H313.00	Mixed simple and mucopurulent chronic bronchitis
261745	H313.00	Mixed simple and mucopurulent chronic bronchitis
298476	H31y.00	Other chronic bronchitis
261746	H31y100	Chronic tracheobronchitis
225244	H31yz00	Other chronic bronchitis NOS
261747	H31z.00	Chronic bronchitis NOS
234374	H32..00	Emphysema
280088	H320.00	Chronic bullous emphysema
225245	H320000	Segmental bullous emphysema
271039	H320100	Zonal bullous emphysema
225246	H320200	Giant bullous emphysema
271040	H320300	Bullous emphysema with collapse
252516	H320311	Tension pneumatocoele
280089	H320z00	Chronic bullous emphysema NOS

GPRD Medical Code	Read/OXMIS Code	Read/OXMIS Term
271041	H321.00	Panlobular emphysema
298477	H322.00	Centrilobular emphysema
280090	H32y.00	Other emphysema
280091	H32y000	Acute vesicular emphysema
225247	H32y100	Atrophic (senile) emphysema
298478	H32y111	Acute interstitial emphysema
216143	H32y200	MacLeod's unilateral emphysema
234375	H32yz00	Other emphysema NOS
234376	H32yz11	Sawyer - Jones syndrome
234377	H32z.00	Emphysema NOS
280094	H36..00	Mild chronic obstructive pulmonary disease
298483	H37..00	Moderate chronic obstructive pulmonary disease
289203	H38..00	Severe chronic obstructive pulmonary disease
207198	H3y..00	Other specified chronic obstructive airways disease
216150	H3y..11	Other specified chronic obstructive pulmonary disease
252524	H3y0.00	Chronic obstruct pulmonary disease with acute lower respiratory infection
252524	H3y0.00	Chronic obstruct pulmonary dis with acute lower respiratory infection
261758	H3y1.00	Chronic obstruct pulmonary dis with acute exacerbation, unspecified
216151	H3z..00	Chronic obstructive airways disease NOS
261759	H3z..11	Chronic obstructive pulmonary disease NOS

Table S4.2 Odds ratios (OR) of variables used to derive the risk score at each main step in the model selection process.

		Unadjusted[1]			Adjusted[2]			Adjusted[3]		Adjusted[4]	
Variable		**OR**	**(95% CI)**	**p**	**OR**	**(95% CI)**	**p**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Smoking status	Never	1			1			1		1	
	Former	4.87	(4.56, 5.20)	<0.001	4.50	(4.11, 4.93)	<0.001	4.50	(4.11, 4.92)	4.36	(4.00, 4.75)
	Current	9.25	(8.65, 9.89)	<0.001	11.89	(10.8, 13.1)	<0.001	11.80	(10.7, 13.0)	12.00	(11.0, 13.1)
	Missing									2.87	(2.52, 3.26)
BMI	<18.5	0.80	(0.76, 0.85)	<0.001	0.94	(0.85, 1.05)	0.296	0.95	(0.85, 1.06)		
	18.5-25	1			1			1			
	25-30	0.79	(0.75, 0.83)	<0.001	0.76	(0.70, 0.82)	<0.001	0.76	(0.70, 0.82)		
	>30	0.93	(0.87, 0.98)	0.014	0.76	(0.68, 0.84)	<0.001	0.76	(0.68, 0.84)		
Asthma		6.61	(6.23, 7.02)	<0.001	1.93	(1.74, 2.15)	<0.001	1.93	(1.74, 2.15)	1.89	(1.71, 2.08)
Ischaemic heart disease		1.31	(1.25, 1.38)	<0.001	0.99	(0.91, 1.09)	0.907				
Heart failure		2.50	(2.24, 2.77)	<0.001	1.35	(1.13, 1.61)	0.001	1.39	(1.17, 1.64)		
Stroke		1.23	(1.10, 1.37)	<0.001	1.14	(0.95, 1.37)	0.157				
Hyperlipidaemia		0.93	(0.87, 1.00)	0.039	0.82	(0.73, 0.91)	<0.001	0.82	(0.74, 0.91)		
Anaemia		1.04	(0.95, 1.14)	0.368							
Pulmonary embolism		2.72	(1.89, 3.91)	<0.001	1.42	(0.75, 2.69)	0.279				
Deep vein thrombosis		1.44	(1.12, 1.86)	0.005	0.78	(0.52, 1.18)	0.245				
Atrial fibrillation		1.37	(1.24, 1.51)	<0.001	1.05	(0.88, 1.24)	0.597				
Lung cancer		3.68	(2.45, 5.55)	<0.001	1.84	(0.95, 3.55)	0.071				
Cancer		1.05	(0.99, 1.11)	0.121	0.89	(0.81, 0.99)	0.024	0.90	(0.82, 0.99)		
Depression		1.24	(1.12, 1.38)	<0.001	0.89	(0.74, 1.07)	0.211				
Anxiety		1.77	(1.65, 1.90)	<0.001	1.00	(0.88, 1.12)	0.937				
Allergic rhinitis		1.13	(1.05, 1.22)	0.001	0.65	(0.56, 0.75)	<0.001	0.69	(0.60, 0.78)		
Tuberculosis		1.66	(1.44, 1.91)	<0.001	1.42	(1.12, 1.80)	0.003	1.43	(1.13, 1.80)		
Pulmonary tuberculosis		1.77	(1.52, 2.06)	<0.001							
Chronic kidney disease		1.69	(1.11, 2.60)	0.016	1.18	(0.58, 2.36)	0.65				
Helicobacter pylori		1.45	(1.16, 1.81)	0.001	0.90	(0.63, 1.28)	0.545				
Gastric ulcer		1.63	(1.43, 1.85)	<0.001	1.14	(0.94, 1.40)	0.19				
GORD		1.25	(1.16, 1.35)	<0.001	0.84	(0.74, 0.96)	0.01	0.85	(0.75, 0.97)		
Osteoporosis		1.58	(1.41, 1.78)	<0.001	1.04	(0.86, 1.26)	0.686				
Fractures		1.30	(1.23, 1.38)	<0.001	1.12	(1.02, 1.22)	0.021	1.12	(1.02, 1.23)		
Diabetes		0.87	(0.81, 0.94)	0.001	0.74	(0.65, 0.85)	<0.001	0.74	(0.65, 0.84)		
Rheumatoid arthritis		1.52	(1.32, 1.75)	<0.001	1.19	(0.95, 1.51)	0.137				
LRTI	0	1			1					1	
	1	4.02	(3.76, 4.29)	<0.001	1.70	(1.53, 1.89)	<0.001	1.72	(1.55, 1.91)	1.81	(1.64, 1.99)
	>1	9.76	(8.93, 10.7)	<0.001	2.08	(1.81, 2.39)	<0.001	2.10	(1.83, 2.42)	2.23	(1.96, 2.54)
URTI	0	1									
	1	1.47	(1.39, 1.56)	<0.001	0.94	(0.85, 1.03)	0.184	0.94	(0.85, 1.03)		
	>1	1.98	(1.85, 2.13)	<0.001	0.83	(0.73, 0.95)	0.005	0.83	(0.73, 0.94)		
Allergy		1.40	(1.34, 1.46)	<0.001	1.09	(1.00, 1.18)	0.055				

		Unadjusted[1]			Adjusted[2]			Adjusted[3]		Adjusted[4]	
Variable		**OR**	**(95% CI)**	**p**	**OR**	**(95% CI)**	**p**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Presentations with cough	0	1			1			1		1	
	1	3.14	(2.96, 3.34)	<0.001	1.37	(1.25, 1.51)	<0.001	1.37	(1.24, 1.50)	1.42	(1.30, 1.56)
	>1	7.12	(6.64, 7.63)	<0.001	1.78	(1.59, 2.00)	<0.001	1.78	(1.59, 1.99)	1.77	(1.59, 1.97)
Presentations with dyspnoea	0	1			1			1		1	
	1	5.57	(5.12, 6.06)	<0.001	3.11	(2.74, 3.53)	<0.001	3.11	(2.74, 3.52)	3.17	(2.82, 3.57)
	>1	9.01	(8.05, 10.1)	<0.001	4.27	(3.63, 5.02)	<0.001	4.28	(3.65, 5.03)	4.53	(3.89, 5.28)
Wheeze		8.89	(7.96, 9.94)	<0.001	1.88	(1.60, 2.21)	<0.001	1.85	(1.58, 2.18)	1.86	(1.60, 2.17)
Sputum production		5.32	(4.52, 6.26)	<0.001	1.55	(1.20, 2.00)	0.001	1.56	(1.21, 2.02)	1.49	(1.17, 1.90)
Weight loss		2.74	(2.30, 3.28)	<0.001	1.52	(1.13, 2.03)	0.005	1.53	(1.14, 2.04)	1.75	(1.33, 2.31)
Fatigue		1.53	(1.42, 1.66)	<0.001	1.06	(0.93, 1.22)	0.371				
Poor sleep		1.59	(1.44, 1.75)	<0.001	0.87	(0.73, 1.02)	0.086				
Antibiotic courses	0	1			1			1		1	
	1	2.34	(2.21, 2.47)	<0.001	1.32	(1.21, 1.44)	<0.001	1.31	(1.20, 1.44)	1.33	(1.23, 1.44)
	2	4.04	(3.76, 4.34)	<0.001	1.54	(1.37, 1.73)	<0.001	1.54	(1.37, 1.73)	1.53	(1.38, 1.70)
	>2	8.64	(8.07, 9.25)	<0.001	1.91	(1.69, 2.17)	<0.001	1.89	(1.67, 2.14)	1.80	(1.62, 2.01)
Salbutamol		11.45	(10.8, 12.2)	<0.001	4.27	(3.86, 4.73)	<0.001	4.25	(3.84, 4.71)	4.19	(3.81, 4.61)
Prednisolone		6.17	(5.78, 6.58)	<0.001	1.49	(1.34, 1.67)	<0.001	1.51	(1.36, 1.69)	1.53	(1.38, 1.69)
GP consultations	<5	1			1			1			
	5-10	1.81	(1.66, 1.98)	<0.001	1.26	(1.10, 1.45)	0.001	1.27	(1.10, 1.45)		
	10-20	2.55	(2.36, 2.77)	<0.001	1.27	(1.11, 1.45)	<0.001	1.28	(1.13, 1.46)		
	20-40	3.99	(3.68, 4.32)	<0.001	1.34	(1.16, 1.54)	<0.001	1.37	(1.20, 1.57)		
	>40	6.91	(6.31, 7.57)	<0.001	1.31	(1.10, 1.56)	0.002	1.37	(1.17, 1.61)		
Hospital referrals		2.08	(1.85, 2.34)	<0.001	1.20	(0.99, 1.46)	0.065				

1. All risk factors
2. Risk factors with p<0.2 for unadjusted ORs
3. Risk factors with p<0.05 for adjusted ORs or significantly contributed to the model fit (as defined by statistically significant likelihood ratio tests)
4. Risk factors with adjusted OR>1.5

4.7 References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
2. Soriano J, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. Lancet. 2009;374(9691):721 - 32.
3. Jones R, Price D, Ryan D, Sims E, von Ziegenweidt J, Mascarenhas L, et al. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. The Lancet Respiratory Medicine. 2014;2(4):267 - 76.
4. An outcomes strategy for people with chronic obstructive pulmonary disease (COPD) and asthma in England London: Department of Health; 2011 [cited 2013 29/10/2013]. Available from: https://www.gov.uk/government/publications/an-outcomes-strategy-for-people-with-chronic-obstructive-pulmonary-disease-copd-and-asthma-in-england.
5. Price DB, Tinkelman DG, Halbert RJ, Nordyke RJ, Isonaka S, Nonikov D, et al. Symptom-based questionnaire for identifying COPD in smokers. Respiration. 2006;73(3):285-95.
6. Frith P, Crockett A, Beilby J, Marshall D, Attewell R, Ratnanesan A, et al. Simplified COPD screening: validation of the PiKo-6(R) in primary care. Prim Care Respir J. 2011;20(2):190-8, 2 p following 8.
7. Mapel D, Frost F, Hurly J, Petersen H, Roberts M, Marton J, et al. An algorithm for the identification of undiagnsoed COPD cases using administrative claims data. J Manag Care Pharm. 2006;12(6):458 - 65.
8. Mapel DW, Petersen H, Roberts MH, Hurley JS, Frost FJ, Marton JP. Can Outpatient Pharmacy Data Identify Persons With Undiagnosed COPD? Am J Manag Care. 2010;16(7):505-12.
9. Smidth M, Sokolowski I, Kaersvang L, Vedsted P. Developing an algorithm to identify people with Chronic Obstructive Pulmonary Disease (COPD) using administrative data. Bmc Med Inform Decis. 2012;12.
10. Kotz D, Simpson CR, Viechtbauer W, van Schayck OC, Sheikh A. Development and validation of a model to predict the 10-year risk of general practitioner-recorded COPD. NPJ primary care respiratory medicine. 2014;24:14011.
11. Clinical Practice Research Database London: The Medicines and Healthcare products Regulatory Agency; 2013 [cited 2013 29/10/2013]. Available from: http://www.cprd.com/home/.
12. Read Codes London: NHS Connecting for Health; 2013 [cited 2013 29/10/2013]. Available from: http://www.connectingforhealth.nhs.uk/systemsandservices/data/uktc/readcodes.
13. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011;342:d549.
14. Jordan R, Lam K-B, Cheng K, Miller M, Marsh J, Ayres J, et al. Case finding for chronic obstructive pulmonary disease: a model for optimizing a targeted approach. Thorax. 2010;65:492 - 8.
15. Price DB, Tinkelman DG, Nordyke RJ, Isonaka S, Halbert RJ, Group CQS. Scoring system and clinical application of COPD diagnostic questionnaires. Chest. 2006;129(6):1531-9.
16. Chronic obstructive pulmonary disease : management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Institute for Health and Clinical Excellence; 2010.
17. Eaton T, Withy S, Garrett JE, Mercer J, Whitlock RM, Rea HH. Spirometry in primary care practice: the importance of quality assurance and the impact of spirometry workshops. Chest. 1999;116(2):416-23.
18. Quality and Outcomes Framework- 2011-12, England level: Clinical domain, chronic obstructive pulmonary disease data tables: Health and Social Care Information Centre; 2013 [cited 2013 29/10/2013]. Available from:

http://www.hscic.gov.uk/searchcatalogue?productid=9548&q=qof&topics=0%2fPrimary+care+services&sort=Relevance&size=10&page=1#top.
19. Quint JK, Mullerova H, DiSantostefano RL, Forbes H, Eaton S, Hurst JR, et al. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). BMJ open. 2014;4(7):e005540.
20. Pelkonen M, Notkola IL, Nissinen A, Tukiainen H, Koskela H. Thirty-year cumulative incidence of chronic bronchitis and COPD in relation to 30-year pulmonary function and 40-year mortality: a follow-up in middle-aged rural men. Chest. 2006;130(4):1129-37.
21. Ganna A, Reilly M, de Faire U, Pedersen N, Magnusson P, Ingelsson E. Risk prediction measures for case-cohort and nested case-control designs: an application to cardiovascular disease. American journal of epidemiology. 2012;175(7):715-24.
22. Janes H, Pepe MS. Matching in studies of classification accuracy: implications for analysis, efficiency, and assessment of incremental value. Biometrics. 2008;64(1):1-9.

CHAPTER 5: PREDICTING RISK OF UNDIAGNOSED COPD IN PRIMARY CARE: DEVELOPMENT AND VALIDATION OF THE TARGETCOPD MODEL

5.1 Abstract

Background

Previous prediction models have been developed for assessing the risk of undiagnosed COPD. These used data from patients who received a diagnosis through routine care, which may be inaccurate because of widespread underdiagnosis and misdiagnosis. This chapter reports the development and external validation of a primary care-based model using data from a unique case finding trial.

Methods

Patients aged 40-79 years with no prior diagnosis of COPD received a screening questionnaire either by post or opportunistically at primary care attendances through a large case finding trial based in primary care in the West Midlands, UK. Those reporting chronic respiratory symptoms were assessed with spirometry. COPD was defined as presence of respiratory symptoms with post-bronchodilator FEV_1/FVC<lower limit of normal. A prediction model was then developed using logistic regression with predictor variables available from electronic health records from subjects who returned a postal questionnaire (n=2398, mean age 59.9 years, 52% male). The model was internally validated in the development sample, and then

externally validated among subjects who returned an opportunistic questionnaire (n=1097, mean age 60.1 years, 51.6% male).

Results

A model containing age, smoking status, dyspnoea, and prescriptions of salbutamol and antibiotics discriminated reasonably well between patients with and without undiagnosed COPD (external validation c-statistic 0.74 [95% CI 0.68 to 0.80]), and provided predicted risks that calibrate well up to 10%, but slightly overestimate observed risks up to 30%. Using a cut-point of ≥7.5% predicted risk to prompt referral for diagnostic assessment has a sensitivity of 68.8% (95% CI 57.3 to 78.9%) and a specificity of 68.8% (95% CI 65.8.1 to 71.6%), and requires seven diagnostic assessments (95% CI 6 to 10) to identify one patient with undiagnosed COPD.

Conclusion

A simple and readily applicable risk prediction model that uses routine data from electronic health records in primary care has been developed and externally validated for undiagnosed COPD. This could improve the efficiency of targeting patients for case finding but should be validated in other populations and its impact on patient outcomes evaluated in RCTs.

5.2 Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of mortality worldwide (1) and it is estimated that 50-90% of the disease burden is undiagnosed.(2) Primary care has a key role to play in improving the diagnosis of COPD (3) and the clinical strategy is now shifting towards earlier identification to improve access to care and prevent disease progression.(4) To achieve this, a number of case finding tools have been evaluated including screening questionnaires (5) and handheld flow meters.(6) However mass screening with systematic invitation of all potentially at-risk individuals has resource implications and is reliant on patient response.(7) A more efficient approach is needed.

A number of risk prediction models have been developed to help identify patients at high risk of undiagnosed COPD. This includes the clinical score reported in Chapter 4 and another developed using longitudinal data from general practices in Scotland.(8) Both used a new diagnosis of COPD in primary healthcare records as the outcome. The models demonstrated good discrimination characteristics when validated but were limited by their case definition, which lacked standardised, objective measures. This has two important implications. Firstly, COPD is often both underdiagnosed (9) as well as misdiagnosed,(10) so a proportion of patients classed as being disease-free in the previous analyses may in fact have had undiagnosed COPD, and some patients with a record of COPD may have been misdiagnosed. Secondly, the clinical characteristics of patients diagnosed with COPD through case finding may differ from incident cases identified through routine care, thus potentially differing in their predictors of disease.

This chapter reports the development and external validation of a new prediction model for identifying patients at high risk of undiagnosed COPD in primary care using data from a large cluster randomised controlled case finding trial.(11)

5.3 Methods

5.3.1 Study design

This is a retrospective cohort analysis of data from the case finding arm of the TargetCOPD trial (12) to develop and validate a risk prediction model for undiagnosed COPD. TargetCOPD was a pragmatic cluster randomised controlled case finding trial for COPD based in primary care that recruited eligible participants from August 2012 to June 2014. Subjects within the case finding arm were randomised to receive a screening questionnaire (Appendix 6), either opportunistically at routine clinical appointments or to additionally receive it by post. This captured information on respiratory symptoms, smoking history, occupational exposures to vapours, gases, dust, and fumes (VGDF), and demographic characteristics. Participants reporting relevant respiratory symptoms were offered a diagnostic assessment with post-bronchodilator spirometry. Data were used from their primary care health records (recorded at any time prior to the trial start date at each practice), and spirometry assessment to develop and validate a risk prediction model for undiagnosed COPD.

5.3.2 Population

Participants were aged 40 to 79 years with no prior diagnosis of COPD (Table S5.1 provides the clinical codes used for exclusion). There were no other specific eligibility criteria and subjects were excluded at the discretion of their GP. This analysis was restricted to participants who returned a screening questionnaire.

5.3.3 Setting

The TargetCOPD trial was based in primary care practices in the West Midlands, UK.(11) Data from electronic health records were available for a subset of 13 of the 26 participating practices allocated to the case finding arm, which broadly reflected the diversity of the population in terms of age, ethnicity and socioeconomic status, and practice characteristics.

5.3.4 Outcome

COPD was defined as the presence of at least one chronic respiratory symptom (chronic cough or phlegm for three or more months of the year for two or more years, wheeze in the previous 12 months or dyspnoea of MRC grade 2 or higher) together with airflow obstruction measured by post-bronchodilator spirometry. Spirometry was performed to ERS standards (13) by trained research assistants using EasyOne spirometers (ndd Medical Technologies, Zurich) 20 minutes after the inhalation of 400mcg of salbutamol delivered through a metered dose inhaler and volumatic spacer. Spirometers were calibrated on a daily basis and all research assistants were trained for one week at a lung function laboratory followed by training days held every 3-6 months. All spirometry traces were reviewed by a lung function specialist. For this analysis airflow obstruction was defined as a forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC) less than the lower limit of normal (<5^{th} percentile) adjusted for age, sex, height, and ethnic group using the Global Lung Initiative 2012 equations.(14)

5.3.5 Data extraction

Data (clinical codes) selected for extraction from electronic health records were initially based on those predictors identified as important in the previous analysis reported in Chapter 4. These included demographic characteristics, smoking status, respiratory symptoms, comorbidities, lower respiratory tract infections (LRTIs), and respiratory medication prescriptions (see Table S5.2 for the corresponding clinical codes). Data from residential postcodes were used to estimate socioeconomic status using the Index of Multiple Deprivation (IMD, higher scores represent greater levels of socioeconomic deprivation).(15) Data on antibiotics that are indicated for treating LRTIs were extracted- this included amoxicillin, clarithromycin, co-amoxiclav, erythromycin, doxycycline, and cephalexin. All data were stored on an encrypted database.

5.3.6 Sample size

Subjects with missing outcome (COPD) status (predominantly those invited but who did not attend a spirometry assessment) were excluded from the analysis (n=755) but their characteristics were described. Data from 2398 subjects who returned a postal questionnaire were used for model development (development sample) and from 1097 subjects who returned a questionnaire provided opportunistically for external validation (external validation sample). This non-random splitting of the data was considered important, to ensure the developed model could be checked in new data from a different part of the intended population.(16) 7.9% of all subjects were newly diagnosed with COPD through the trial (198 in the development and 77 in the external validation samples). At least 10 outcome events are recommended per candidate predictor considered for inclusion in a logistic regression model.(17) There

was therefore sufficient power to consider up to 19 candidate predictors in the developed model.

5.3.7 Model development

The model was developed using multivariable logistic regression considering the following candidate predictors for inclusion: age, sex, latest smoking status, history of asthma, and lower respiratory tract infections (LRTIs), complaints of cough, dyspnoea, wheeze, and sputum, and prescriptions of salbutamol, prednisolone, and antibiotics, within the previous three years. Since there was very little (<1%) missing data for these candidate predictors, multiple imputation was not used and a complete-case analysis was performed.(18) Interactions were tested for with a particular focus on age, sex, and smoking status. The best-fitting terms for continuous variables were determined using fractional polynomial regression.(19) Predictors that were not statistically significant at the $p<0.05$ level were removed from the model (although age and smoking status were forced in) and the fit of the reduced model was compared to that of the full model using a likelihood ratio test.

To improve the calibration of the model predictions and adjust for over fitting, the model's calibration slope coefficient was estimated in 1000 bootstrap samples to determine the shrinkage factor (the average calibration slope), which was multiplied against predictor coefficients in the developed model.(20) This produced the final model equation.

5.3.8 Internal validation performance

To examine the discrimination performance of the final model, the sensitivity and specificity of the predicted probabilities from the final model were plotted on a

receiver operator characteristic (ROC) curve. The model was internally validated using bootstrap resampling (with 1000 replications) to estimate the c-statistic (area under the ROC curve) corrected for over-fitting.(21) Calibration was assessed by grouping subjects into deciles of predicted risk and comparing the observed with the expected number diagnosed with COPD.

5.3.9 External validation performance

The c-statistic and calibration of the final model were then assessed in the external validation sample. Again, since there was very little missing data, multiple imputation was not used for externally validating the model. As a comparator, the discrimination performance of the previously developed clinical score (Chapter 4) was assessed in the external validation sample.

5.3.10 Implementation of the model in clinical practice

For implementation of the model as a screening tool, cut-points were evaluated for dichotomising the predicted probabilities into low and high risk. Across a range of cut-points, the sensitivity and specificity were calculated in the external validation sample, alongside the positive and negative predictive values, positive and negative likelihood ratios, and number of diagnostic assessments required to identify one individual with undiagnosed COPD (NND). All analyses were performed using Stata version 13.1 (StataCorp, Texas).

5.3.11 Ethical approval

Ethical approval for the TargetCOPD trial was received (IRAS, reference 11/WM/0403).

5.4 Results

5.4.1 Practice characteristics

Practices varied in size with the majority having a patient list size below 10,000 (Table 5.1). Most practices served populations in socioeconomically deprived areas with a wide range in the proportion of ethnic minorities. The mean prevalence of established COPD was 1.3% (range 0.8 to 2.9%).

Table 5.1 Practice characteristics

		N	(%)
Practices		13	(100)
Patient list size	<5000	5	(38.5)
	5000-10,000	6	(46.2)
	>10,000	2	(15.4)
IMD quintile	1 (most deprived)	8	(61.5)
	2	1	(7.7)
	3	3	(23.1)
	4	1	(7.7)
	5 (least deprived)	0	(0)
Mean proportion of white patients (range)		71.8%	(26.3-98.7%)
Mean COPD prevalence (range)		1.3%	(0.8-2.9%)

IMD=Index of Multiple Deprivation (measure of socioeconomic deprivation derived from practice postcodes)

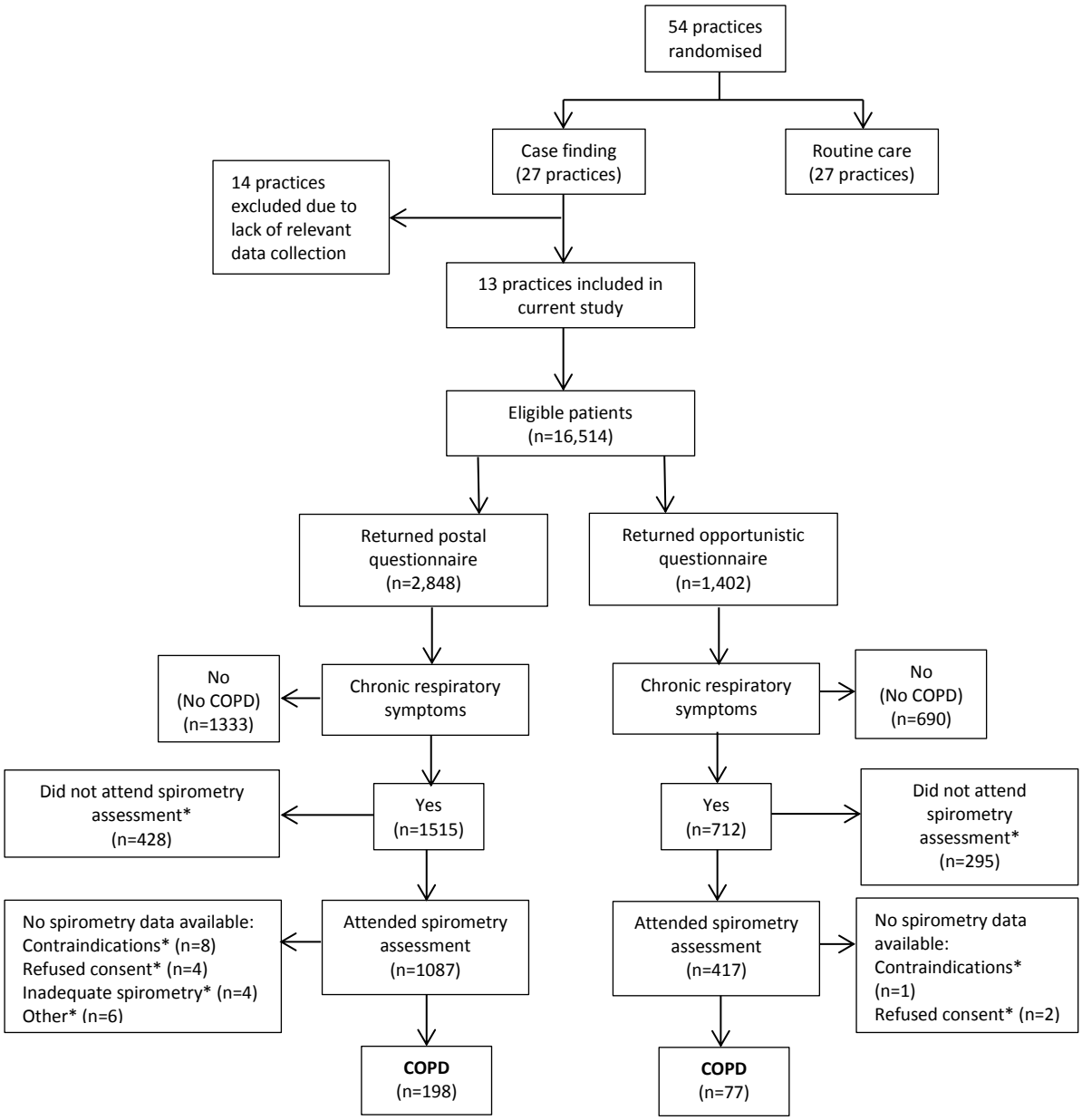

Figure 5.1 Participant selection
*Disease status unknown

5.4.2 Development sample: population characteristics

The development sample included 2,398 subjects, of whom 198 (8.3%) were diagnosed with COPD during the study (Figure 5.1). The mean age was 59.6 years, 51.6% were male and the majority (85.0%) were of white ethnicity. The severity of COPD was: 77.7% mild (FEV_1 ≥80% predicted), 21.1% moderate (FEV_1 50-79%), 1.0% severe (FEV_1 30-49%), and 0.2% very severe (FEV_1 <30%).

Based on data extracted from electronic health records (Table 5.2), current smoking was significantly more common among subjects with COPD than those without (32.8% versus 14.1%, respectively). There was also a higher prevalence of asthma and a slightly higher prevalence of anxiety and depression among those with COPD but the prevalence of other chronic conditions was similar in both groups. Records of cough, dyspnoea, sputum production, LRTIs, and respiratory prescriptions were all also more common among subjects with COPD. Based on data from returned screening questionnaires (Table 5.3), subjects with COPD were also more likely to report dyspnoea-related limitation of activities, being unable to lay flat at night, symptoms of chronic rhinitis, higher pack years of smoking (median 24.8 versus 12.9, respectively) and prior exposure to occupational VGDF (40.4% versus 31.3%).

There was very little (<1%) missing data for candidate predictors (Table 5.2). However there was a large amount of missing data for self-reported characteristics including ethnic group (4.7%), smoking pack years (55.3%), and BMI (28.2%; Table 5.3). It was not possible to quantify the amount of missing data for symptoms or comorbidities since these could either have been truly absent or could have been under-recorded.

Subjects with unknown COPD-status (predominantly those who did not attend an assessment) differed from those in the derivation sample across a number of demographic characteristics (Table 5.4) - they were generally younger (mean age 55.8 years versus 59.6, respectively), a higher proportion were female (52.5% versus 48.4%), of unknown ethnic group, and current smokers (33.5% versus 15.8%), and had a slightly higher mean body mass index (28.1 versus 27.1) and lower socioeconomic status.

Table 5.2 Characteristics extracted from electronic health records (development sample)

		COPD (n=198 [8.3%])		Non-COPD (n=2200 [91.7%])		Missing data	
		n	(%)	n	(%)	n	(%)
Age (years)	Mean (SD)	60.8	(9.6)	59.5	(10.7)	7	(0.3)
	40-49	30	(15.2)	528	(24.0)		
	50-59	54	(27.3)	621	(28.2)		
	60-69	74	(37.4)	595	(27.0)		
	70-79	40	(20.2)	456	(20.7)		
Sex	Male	107	(54.0)	1,128	(51.3)	4	(0.2)
Smoking status	Never	37	(18.7)	744	(33.8)	11	(0.5)
	Former	95	(48.0)	1,135	(51.6)		
	Current	65	(32.8)	311	(14.1)		
IMD score	Median (IQR)	37.4	(19.8-41.3)	23.3	(19.8-41.3)	0	(0.0)
Comorbidities	Asthma	10	(5.1)	29	(1.3)	Unknown**	
	IHD	11	(5.6)	146	(6.6)		
	Heart failure	3	(1.5)	20	(0.9)		
	Diabetes	17	(8.6)	192	(8.7)		
	Stroke	2	(1.0)	18	(0.8)		
	Tuberculosis	3	(1.5)	11	(0.5)		
	Osteoporosis	4	(2.0)	37	(1.7)		
	Depression/anxiety*	36	(18.2)	335	(15.2)		
	LRTIs*	41	(20.7)	233	(10.6)		
Symptoms*	Cough	61	(30.8)	385	(17.5)	Unknown**	
	Dyspnoea	23	(11.6)	78	(3.5)		
	Wheeze	30	(15.2)	362	(16.5)		
	Sputum	11	(5.6)	43	(2.0)		
	Unintended weight loss	2	(1.0)	9	(0.4)		
Prescriptions*	Salbutamol	74	(37.4)	251	(11.4)	Unknown**	
	Prednisolone	40	(20.2)	138	(6.3)		
	Antibiotics ǂ	116	(58.6)	783	(35.6)		

IMD=Index of Multiple Deprivation (a measure of socioeconomic status based on participants' residential postcodes- higher scores indicate higher levels of socioeconomic deprivation), IQR=interquartile range, LRTI=lower respiratory tract infection, OR=odds ratio, SD=standard deviation
*Recorded within previous three years of commencing case finding at the registered practice
**It was unknown whether absence of a record of comorbidities, symptoms and prescriptions in electronic health records was due to true absence of those factors or due to under-recording.
ǂ Antibiotics=amoxicillin, clarithromycin, co-amoxiclav, erythromycin, doxycycline, and cefalexin

Table 5.3 Self-reported characteristics (development sample)

			COPD (n=198 [8.3%])		Non-COPD (n=2,200 [91.7])		Missing data	
			n	(%)	n	(%)	n	(%)
Ethnic group	White		173	(87.4)	1,864	(84.7)	112	(4.7)
	Mixed		2	(1.0)	16	(0.7)		
	Asian		9	(4.5)	100	(4.5)		
	Black		4	(2.0)	98	(4.5)		
	Other		3	(1.5)	17	(0.8)		
Smoking pack years	Median (IQR)		24.8	(8-38)	12.9	(5.25-26.25)	1327	(55.3)
Occupational exposures (VGDF)			80	(40.4)	688	(31.3)	69	(2.9)
Body mass index (BMI)	Mean (SD)		27.4	(5.1)	27.0	(4.6)	677	(28.2)
	<18.5		3	(1.5)	6	(0.3)		
	18.5-24		39	(19.7)	582	(26.5)		
	25-29		49	(24.7)	656	(29.8)		
	>=30		34	(17.2)	352	(16.0)		
Self-reported symptoms							Unknown*	
Chronic cough			84	(42.4)	272	(12.4)		
Weather-induced cough			59	(29.8)	217	(9.9)		
Chronic phlegm			58	(29.3)	195	(8.9)		
MRC dyspnoea score		1	63	(31.8)	1,627	(74.0)		
		2	59	(29.8)	318	(14.5)		
		3	30	(15.2)	105	(4.8)		
		4	27	(13.6)	98	(4.5)		
		5	19	(9.6)	52	(2.4)		
Activities limited by dyspnoea			88	(44.4)	297	(13.5)		
Unable to lie flat at night			78	(39.4)	480	(21.8)		
Chronic rhinorrhoea			74	(37.4)	511	(23.2)		

IQR=interquartile range, OR=odds ratio, SD=standard deviation, VGDF=previous exposure to vapours, gas, dust or fumes

* It was unknown whether absence of self-reported symptoms on returned screening questionnaires was due to them being truly absent or due to under-reporting.

Table 5.4 Characteristics of subjects with known and unknown COPD status

		COPD status known		COPD status unknown	
		(n=2398)		(n=752)	
		n	**(%)**	**n**	**(%)**
Age (years)	Mean (SD)	59.6	(10.6)	55.8	(10.1)
Sex	Male	1235	(51.6)	356	(47.2)
	Missing	4	(0.2)	2	(0.3)
Ethnic group	White	2037	(85.0)	521	(69.0)
	Mixed	18	(0.8)	7	(0.9)
	Asian	109	(4.6)	48	(6.4)
	Black	102	(4.3)	51	(6.8)
	Other	20	(0.8)	8	(1.1)
	Missing	112	(4.7)	120	(15.9)
Smoking status	Never	781	(32.6)	105	(13.9)
	Former	1230	(51.3)	279	(37.0)
	Current	376	(15.7)	268	(33.5)
	Missing	11	(0.5)	103	(13.6)
Smoking pack years	Median (IQR)	13.5	(6-27)	17.1	(7-29)
	Missing	1327	(55.3)	533	(70.9)
Occupational exposures	(VGDF)	768	(32.0)	268	(35.5)
	Missing	69	(2.9)	49	(6.5)
Body Mass Index (BMI)	Mean (SD)	27.1	(4.7)	28.1	(5.9)
	<18.5	9	(0.5)	5	(0.66)
	18.5-25	621	(36.1)	144	(19.1)
	25-30	705	(41.0)	178	(23.6)
	≥30	386	(22.4)	137	(18.2)
	Missing	677	(28.2)	291	(38.5)
IMD score	Median (IQR)	23.3	(20-41)	37.4	(20-45)

IMD= Index of Multiple Deprivation (a measure of socioeconomic status based on postcodes), IQR=interquartile range, SD=standard deviation

5.4.3 Model results

Complete data for candidate predictors was available for 2380 patients (99.2%) in the development sample (Table 5.5). The final model of GP-recorded factors included smoking status, age, dyspnoea, and salbutamol and antibiotic prescriptions. Age was included as two fractional polynomial terms since it was not linear in the logit scale. A likelihood ratio test comparing the final model to the full model with all candidate predictors was not statistically significant (p=0.185). No significant interactions were found. The shrinkage factor was 1, which indicates that there was no evidence of over-fitting in the final model (Table 5.6).

5.4.4 Internal validation

When applied to the development sample the apparent c-statistic was 0.76 (95% CI 0.73 to 0.80), and was 0.76 (95% 0.72 to 0.79) after correcting for over-fitting using bootstrapping. Although smoking status and age were the most important predictors in the model, restricting the model to just these variables reduced the c-statistic to 0.65 (95% CI 0.60 to 0.69).

5.4.5 External validation: population characteristics

Among 1097 subjects in the external validation population, 77 (7.0%) had COPD (Table 5.7). The mean age was 60.1 years and 51.6% were male, which was similar to the development sample. Again, a significantly greater proportion of subjects with COPD were current smokers (31.2% versus 17.1%, respectively). However, participants in the external validation sample had a slightly higher socioeconomic status than those in the development sample (median IMD score 20.2 versus 23.3, respectively). 1083 subjects (98.7%) had complete data on all candidate predictors.

5.4.6 External validation: model performance

The developed model demonstrated similar discrimination characteristics when applied to the external validation sample (c-statistic 0.74 [95% CI 0.68 to 0.80]; Figure 5.2) and performed better than our previously developed clinical score (c-statistic 0.70 [95% CI 0.64 to 0.76] in the external validation sample). In the external validation sample the final model showed excellent calibration of observed to predicted COPD risk up to 10%, but slightly over-estimated the predicted risk from 10% to 30%, beyond which comparisons were unreliable due to small sample sizes (Table 5.8).

5.4.7 Implementation in clinical practice

As the cut-point to define high risk is increased the number of assessments needed for each new diagnosis of COPD falls, although this is also accompanied by a reduction in sensitivity (Table 5.9). The optimum cut-point should balance both sensitivity and specificity, taking into consideration costs and resource availability. At a cut-point of 7.5% (i.e. classing subjects with a predicted risk ≥7.5% as high risk), the model is estimated in the external validation sample to have a sensitivity of 68.8% (95% CI 57.3 to 78.9%), specificity of 68.8% (95% CI 65.8 to 71.6%) and would require seven patients (95% CI 6 to 10) to undergo a diagnostic assessment to identify one with COPD.

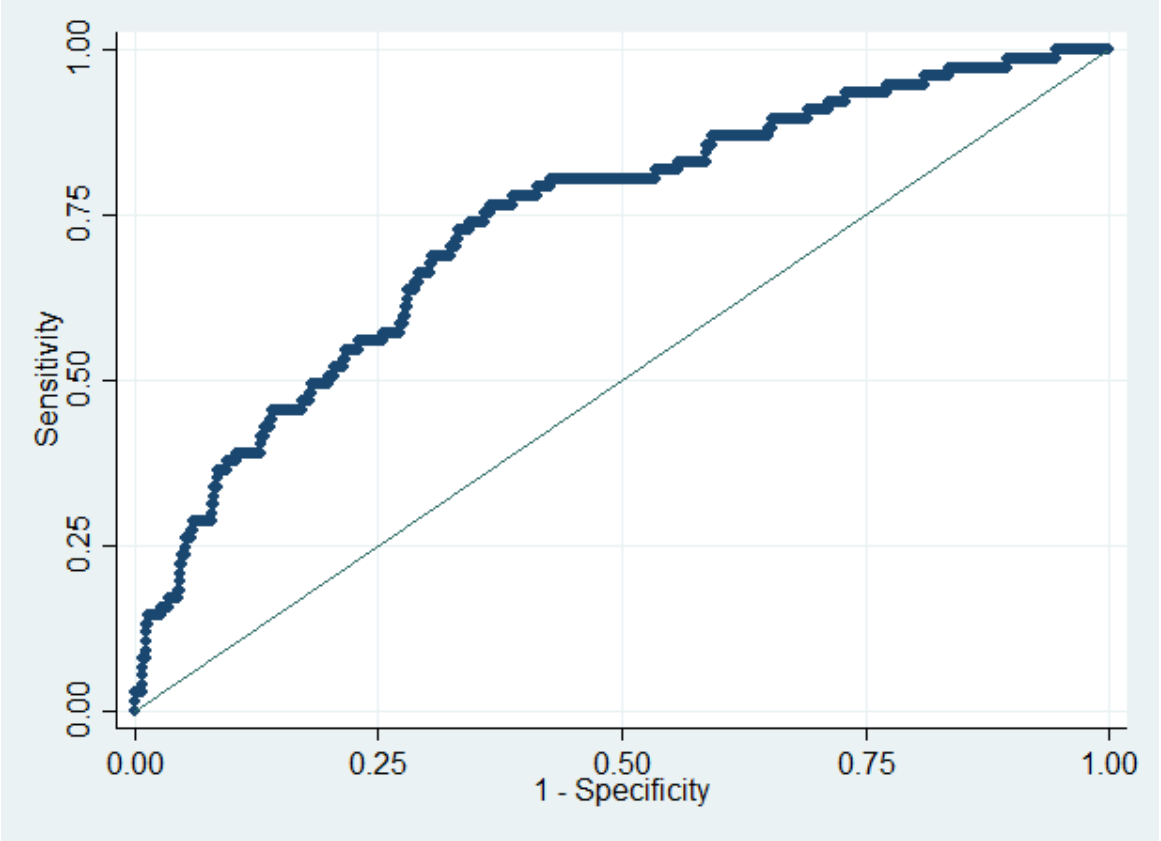

Figure 5.2 Receiver operator characteristic curve for the TargetCOPD model in the external validation sample (c-statistic 0.74 [95% CI 0.68 to 0.80])

Table 5.5 Candidate predictors evaluated in the multivariable logistic regression model

		Unadjusted			Adjusted		
		OR	**(95% CI)**	**p**	**OR**	**(95% CI)**	**p**
Age (years)	40-49	Reference category			Reference category		
	50-59	1.53	(0.97, 2.43)	0.070	1.66	(1.02, 2.70)	0.043*
	60-69	2.19	(1.41, 3.40)	<0.001*	2.63	(1.64, 4.23)	<0.001*
	70-79	1.54	(0.95, 2.52)	0.082	1.72	(1.01, 2.93)	0.044*
Sex	Male	1.11	(0.83, 1.49)	0.471	1.04	(0.76, 1.43)	0.800
Smoking status	Never smoked	Reference category			Reference category		
	Ex-smoker	1.68	(1.14, 2.49)	0.009*	1.71	(1.13, 2.59)	0.012*
	Current smoker	4.20	(2.75, 6.43)	<0.001*	5.58	(3.50, 8.89)	<0.001*
Asthma		3.98	(1.91, 8.30)	<0.001*	1.44	(0.62, 3.37)	0.400
LRTIs**		2.20	(1.52, 3.19)	<0.001*	1.00	(0.84, 1.19)	0.977
Symptoms**	Cough	2.10	(1.52, 2.89)	<0.001*	1.00	(0.68, 1.47)	0.986
	Dyspnoea	3.58	(2.19, 5.84)	<0.001*	2.19	(1.27, 3.76)	0.005*
	Wheeze	0.91	(0.61, 1.36)	0.635	1.14	(0.73, 1.76)	0.564
	Sputum	2.95	(1.50, 5.82)	0.002*	1.55	(0.71, 3.37)	0.270
Prescriptions**	Salbutamol	4.63	(3.38, 6.36)	<0.001*	3.05	(2.01, 4.62)	<0.001*
	Prednisolone	3.78	(2.57, 5.57)	<0.001*	1.76	(1.09, 2.84)	0.020*
	Antibiotics ǂ	2.56	(1.90, 3.44)	<0.001*	1.52	(1.06, 2.18)	0.023*

Based on data extracted from electronic health records for 2380 subjects in the development sample.
Candidate predictors are presented as binary variables unless specified otherwise.
LRTI=lower respiratory tract infection, OR=odds ratio
*Statistically significant at the p<0.05 level
**Recorded within previous 3 years
ǂ Antibiotics=amoxicillin, clarithromycin, co-amoxiclav, erythromycin, doxycycline, and cefalexin

Table 5.6 Final model

Predictor	**β***	**(95% CI)**	**p**
Age^3	1.43×10^{-4}	(6.11×10^{-5}, 2.26×10^{-4})	0.001
Age^3 x ln[age]	-3.18×10^{-5}	(-5.02×10^{-5}, -1.34×10^{-5})	0.001
Ex-smoker	0.51	(0.10, 0.91)	0.015
Current smoker	1.60	(1.14, 2.05)	<0.001
Dyspnoea**	0.72	(0.18, 1.26)	0.010
Number of salbutamol prescriptions**	0.045	(0.015, 0.075)	0.003
≥1 salbutamol prescription**	0.99	(0.56, 1.42)	<0.001
≥1 antibiotic prescription**	0.47	(0.13, 0.80)	0.007
Constant	-6.16	(-7.63, -4.70)	<0.001

*Regression coefficient
**Recorded within the previous three years
Predicted probability of undiagnosed COPD= $e^x/(1+e^x)$
Where x= ($1.43 \times 10^{-4} \times age^3$) – ($3.18 \times 10^{-5} \times$ ln[age]) + (0.51 x ex-smoker [Y/N]) + (1.60 x current smoker [Y/N]) + (0.72 x dyspnoea [Y/N]) + (0.045 x no. of salbutamol prescriptions) + (0.99 x salbutamol prescriptions [Y/N]) + (0.47 x antibiotic prescriptions [Y/N]) -6.16

Table 5.7 Demographic characteristics (external validation sample)

		COPD (n=77 [7.0%])		Non-COPD (n=1020 [93.0%])		Missing data	
		n	(%)	n	(%)	n	(%)
Age*	Mean (SD)	62.2	(10.1)	59.9	(10.8)	6	(0.5
Sex*	Male	39	(50.6)	484	(47.5)	2	(0.2)
Ethnic group**	White	72	(93.5)	855	(83.8)	79	(7.2)
	Mixed	1	(1.3)	9	(0.9)		
	Asian	1	(1.3)	45	(4.4)		
	Black	2	(2.6)	26	(2.5)		
	Other	1	(1.3)	6	(0.6)		
Smoking status*	Never	21	(27.3)	456	(44.7)		
	Former	32	(41.6)	382	(37.5)		
	Current	24	(31.2)	174	(17.1)		
Pack years**	Median (IQR)	28.5	(9-40)	15	(5.5-25)	685	(62.4)
BMI**	Mean (SD)	27.5	(5.05)	27.2	(4.8)	367	(33.5)
	<18.5	0	(0.0)	12	(1.2)		
	18.5-24	16	(20.8)	203	(19.9)		
	25-29	19	(24.7)	304	(29.8)		
	>=30	13	(16.9)	163	(16.0)		
IMD score*	Median (IQR)	20.2	(10.9-37.4)	20.2	(10.9-37.4)	0	(0.0)

IMD=Index of Multiple Deprivation (a measure of socioeconomic status- higher scores represent higher levels of socioeconomic deprivation), IQR=interquartile range
*Recorded on electronic health records
**Self-reported

Table 5.8 Model calibration

	Development sample (n=2380)			External validation sample (n=1083)		
Predicted Risk (%)	**COPD**	**Non-COPD**	**Observed Risk (%)**	**COPD**	**Non-COPD**	**Observed Risk (%)**
0-9	84	1,781	4.5	35	780	4.3
10-19	53	271	16.4	20	158	11.2
20-29	33	89	27.0	11	51	17.7
30-39	11	17	39.3	6	9	40.0
40-49	8	15	34.8	3	4	42.9
50-59	4	6	40.0	0	2	0.0
60-69	1	3	25.0	0	0	0.0
70-79	2	0	100.0	1	2	33.3
80-89	1	0	100.0	0	0	0.0
90-100	0	1	0.0	1	0	100.0
Total	197	2183	8.3	77	1006	7.1

Table 5.9 Diagnostic accuracy of the final model in the external validation sample (n=1083)

Cut-point (%)	Sensitivity (%) (95% CI)		Specificity (%) (95% CI)		Correctly Classified (%)	LR+	(95% CI)	LR-	(95% CI)	PPV (%)	(95% CI)	NPV (%)	(95% CI)	NND	(95% CI)
≥2.5	97.4	(90.9, 99.7)	12.5	(10.5, 14.7)	18.6	1.11	(1.07, 1.16)	0.21	(0.05, 0.82)	7.9	(6.2, 9.8)	98.4	(94.5, 99.8)	13	(11, 17)
≥5.0	80.5	(69.9, 88.7)	48.4	(45.3, 51.5))	50.7	1.56	(1.38, 1.77)	0.40	(0.25, 0.64)	10.7	(8.3, 13.5)	97.0	(95.1, 98.3)	10	(8, 13)
≥7.5	68.8	(57.3, 78.9)	68.8	(65.8, 71.6)	68.8	2.21	(1.85, 2.63)	0.45	(0.32, 0.63)	14.4	(11.0, 18.5)	96.6	(95.1, 97.8)	7	(6, 10)
≥10.0	54.5	(42.8, 65.9)	77.5	(74.8, 80.1)	75.9	2.43	(1.92, 3.07)	0.59	(0.46, 0.75)	15.7	(11.5, 20.6)	95.7	(94.1, 97.0)	7	(5, 9)
≥12.5	46.8	(35.3, 58.5)	82.3	(79.8, 84.6)	79.8	2.64	(2.01, 3.47)	0.65	(0.52, 0.80)	16.8	(12.1, 22.5)	95.3	(93.7, 96.6)	6	(5, 9)
≥15.0	41.6	(30.4, 53.4)	87.0	(84.7, 89.0)	83.8	3.19	(2.34, 4.35)	0.67	(0.56, 0.81)	19.6	(13.8, 26.6)	95.1	(93.5, 96.4)	6	(4, 8)
≥17.5	33.8	(23.4, 45.4)	91.9	(90.0, 93.5)	87.7	4.14	(2.85, 6.03)	0.72	(0.61, 0.85)	24.1	(16.4, 33.3)	94.8	(93.2, 96.1)	5	(3, 7)
≥20.0	28.6	(18.8, 40.0)	93.2	(91.5, 94.7)	88.6	4.23	(2.77, 6.44)	0.77	(0.66, 0.88)	24.4	(16.0, 34.6)	94.5	(92.9, 95.8)	5	(3, 6)
≥22.5	20.8	(12.4, 31.5)	95.2	(93.7, 96.5)	89.9	4.36	(2.60, 7.30)	0.83	(0.74, 0.93)	25.0	(15.0, 37.4)	94.0	(92.4, 95.4)	4	(3, 7)
≥25.0	14.3	(7.4, 24.1)	97.1	(95.9, 98.1)	91.2	4.96	(2.58, 9.53)	0.88	(0.81, 0.97)	27.5	(14.6, 43.9)	93.7	(92.0, 95.1)	4	(3, 7)
≥30.0	14.3	(7.4, 24.1)	98.3	(97.3, 99.0)	92.3	8.45	(4.11, 17.4)	0.87	(0.80, 0.96)	39.3	(21.5, 59.4)	93.7	(92.1, 95.1)	3	(2, 5)
≥35.0	10.4	(4.6, 19.4)	98.8	(97.9, 99.4)	92.5	8.71	(3.67, 20.7)	0.91	(0.84, 0.98)	40.0	(19.1, 63.9)	93.5	(91.9, 94.9)	3	(2, 6)
≥40.0	6.5	(2.1, 14.5)	99.2	(98.4, 99.7)	92.6	8.17	(2.74, 24.4)	0.94	(0.89, 1.00)	38.5	(13.9, 68.4)	93.3	(91.6, 94.7)	3	(2, 8)
≥45.0	2.6	(0.3, 9.1)	99.3	(98.6, 99.7)	92.4	3.73	(0.79, 17.7)	0.98	(0.95, 1.02)	22.2	(2.8, 60.0)	93.0	(91.3, 94.5)	5	(2, 36)
≥50.0	2.6	(0.3, 9.1)	99.6	(99.0, 99.9)	92.7	6.53	(1.22, 35.1)	0.98	(0.94, 1.01)	33.3	(4.3, 77.7)	93.0	(91.3, 94.5)	3	(2, 23)

LR=likelihood ratio, PPV=positive predictive value, NPV=negative predictive value, NND=number of diagnostic assessments needed per case detected

5.5 Discussion

5.5.1 Principal findings

From a large case finding trial in primary care (11) the TargetCOPD model has been developed and externally validated to predict patients' risk of having undiagnosed COPD using data from electronic health records. The model incorporates five factors commonly recorded in general practice- smoking status, age, dyspnoea, and prescriptions of salbutamol and antibiotics commonly prescribed for LRTIs. When externally validated, the model discriminated reasonably well between patients with and without COPD and performed better than the previously developed clinical score (Chapter 4), which relied on incident COPD from routine records rather than actively case found patients. In the newly developed model, a cut-point of ≥7.5% would expect to identify about 70% of patients with undiagnosed COPD, needing seven diagnostic assessments to identify one patient with undiagnosed COPD (although use of higher cut-points could reduce this number at the expense of reducing sensitivity).

5.5.2 Comparison with existing literature

Several models have previously been developed for assessing risk of undiagnosed COPD (Table 5.10). Most recently, a clinical score was developed and externally validated in Chapter 4 of this thesis using routine case control data from a large primary care dataset. This differed from the newly developed model in that it included LRTIs and history of asthma but not age (since this was used as a matching factor in the study design), history of dyspnoea or prescriptions of antibiotics as predictors. The exclusion of age was a particularly important limitation in the previous model

since it is well established that risk of COPD rises with this factor.(22) A history of asthma and LRTIs were both found to be strong predictors of incident COPD in the previous study but were not statistically significant in the full multivariable model used in the current analysis (although they were highly significant in the unadjusted analysis). A likely explanation is that prescriptions of salbutamol and antibiotics are closely associated with asthma and LRTIs, respectively, and are possibly better documented in electronic health records. Thus they may be reflecting similar clinical features.

Kotz and colleagues also recently developed and internally validated a prediction model for COPD using longitudinal data from general practices in Scotland.(8) Their model included age, smoking status, socioeconomic deprivation, and history of asthma but only considered a limited range of risk factors and was not externally validated. Furthermore, use of a UK-specific index of socioeconomic deprivation limits its applicability to other health systems. Unfortunately the final model was not reported so it was not possible to externally validate it in the current dataset. Their model, like the clinical score in Chapter 4, was developed on incident cases of COPD diagnosed through routine care, the disease status of which may have been misclassified because of underdiagnosis (9) and misdiagnosis.(10) The TargetCOPD model has the advantage of having been developed on case found patients based on a standardised definition of COPD that included quality assured spirometry confirmation. Also the characteristics of patients included in the current analysis are more likely to be representative of those that would be identified through a case finding process.

Both previous models however were based on a large sample size using nationally representative data and demonstrated good discrimination characteristics for identifying incident GP-diagnosed COPD. The newly developed TargetCOPD model partially overlaps with these previous models, notably including age, smoking status and possible proxies for asthma (salbutamol prescriptions) and LRTIs (antibiotics prescriptions) as important predictors. The previously developed model (Chapter 4) also showed reasonably good discrimination characteristics in the current analysis (c-statistic 0.70 [95% CI 0.64 to 0.76]), although this was lower than that for the newly developed model and significantly lower than that shown in the previous external validation (c-statistic 0.85 [95% CI 0.83 to 0.86]), which was based entirely on data from electronic health records. This highlights that the performance of prediction models should be interpreted cautiously when validated solely on routine data without adequate verification of disease status.

Price and colleagues developed a screening questionnaire for COPD using data from a case finding study involving two general practices.(5, 23) Their questionnaire included eight self-reported risk factors (age, smoking exposure in pack years, BMI, symptoms of wheeze, weather-affected cough, phlegm without a cold, morning phlegm and history of allergies) and has been widely validated, demonstrating a combined sensitivity of 64.5% (95% CI 59.9 to 68.8) and specificity of 65.2% [95% CI 52.9 to 75.8%; Chapter 2]). This requires 22 patients to complete the questionnaire and 8 to undergo a diagnostic assessment to identify one patient with undiagnosed COPD. The TargetCOPD model showed higher discrimination characteristics, incorporates fewer variables (five versus eight, respectively), and has the important advantage of not relying on patients to respond to a questionnaire.

Finally, other models have also been developed for COPD using routine healthcare data (24-26) but are unlikely to be applicable in a primary care setting due to the predictors included, many of which are not routinely recorded (Table 5.10).

5.5.3 Strengths

A range of risk factors were investigated and the model developed and validated on a population with no prior diagnosis of COPD that was screened in a wide range of general practices. A robust case definition was employed which is likely to be representative of clinically significant, undiagnosed COPD. The analysis adjusted for over-fitting using bootstrapping and shrinkage of coefficients, and the developed model was externally validated, which increases the likelihood of its validity in other primary care populations. The final model incorporates a small number of commonly recorded factors which should ensure its applicability in routine primary care.

5.5.4 Weaknesses

A smaller sample size was used than several other studies reporting the development of COPD risk models from routine healthcare data,(8, 24) including the model developed in Chapter 4. Although the study was adequately powered for the number of risk factors considered for the model selection, a larger sample size would have enabled estimation of the parameters with greater precision. Ideally a larger sample size would have been used for external validation of the model since simulation-based estimates suggest at least 100 outcome events are required.(27) The model showed excellent calibration up to 10% but slight over-prediction from 10 to 30%, in the external validation sample, in which the sample size was too small to provide reliable comparisons. .

It was unclear whether the lower than expected predictive ability of risk factors previously shown to identify patients with COPD, such as a history of LRTIs, was due to variability in clinical coding, limitations in the range of clinical codes extracted, or differences in the outcome being predicted (i.e. truly undiagnosed COPD versus GP-diagnosed COPD). Also there are potential limitations in the use of antibiotics as a predictor since the included antibiotics may well have been prescribed for suspected infections other than LRTIs. However the included antibiotics were chosen to reflect those most likely to be prescribed for a LRTI in primary care and the aim was to evaluate whether these prescriptions were associated with the presence of undiagnosed COPD independent of records of previous LRTIs.

Finally, the response to the questionnaire was low (25.7%), which is likely to have introduced response bias. Subjects who did not respond to the questionnaire may have felt untroubled by respiratory symptoms (either because such symptoms were absent or unrecognised) and therefore deemed the questionnaire not relevant to them. Conversely they may simply belong to a more hard-to-reach population who are unlikely to respond to questionnaires either because of cultural or socioeconomic factors. Furthermore a significant proportion (32.5%) of subjects who responded to the questionnaire and reported symptoms did not attend a spirometry assessment. They differed from those included in the analysis across a number of demographic characteristics and the validity of the model in such patients could not be determined. Thus the model is best considered applicable to populations of individuals that are likely to respond to questionnaire surveys and are willing to attend subsequent clinical assessment.

5.5.5 Implications for clinicians, policymakers and research

The TargetCOPD model has been developed to help primary care services stratify patients according to their risk of undiagnosed COPD for targeted systematic case finding (Figure 5.3). It could be used to help prioritise referral for diagnostic assessment, including spirometry, or for further screening (e.g. using handheld flow meters). Since it relies entirely on routinely recorded data from electronic health records, it could be fully integrated with clinical information systems. Finally, the TargetCOPD model should be externally validated in other primary care populations and its effectiveness in practice evaluated in RCTs, where the impact of using the model on patient outcomes can be evaluated as well as the associated costs.(28)

5.5.6 Conclusion

The TargetCOPD model has been developed and externally validated for assessing the risk of undiagnosed COPD among patients in primary care. This is the first risk prediction model for COPD that has been derived from patients identified through systematic case finding and uses routine data from electronic health records. It should be readily applicable in primary care and can be used to help identify patients at high risk of COPD to improve access to appropriate clinical care. The model should be externally validated in further populations and its impact on clinical care and outcomes evaluated in RCTs.

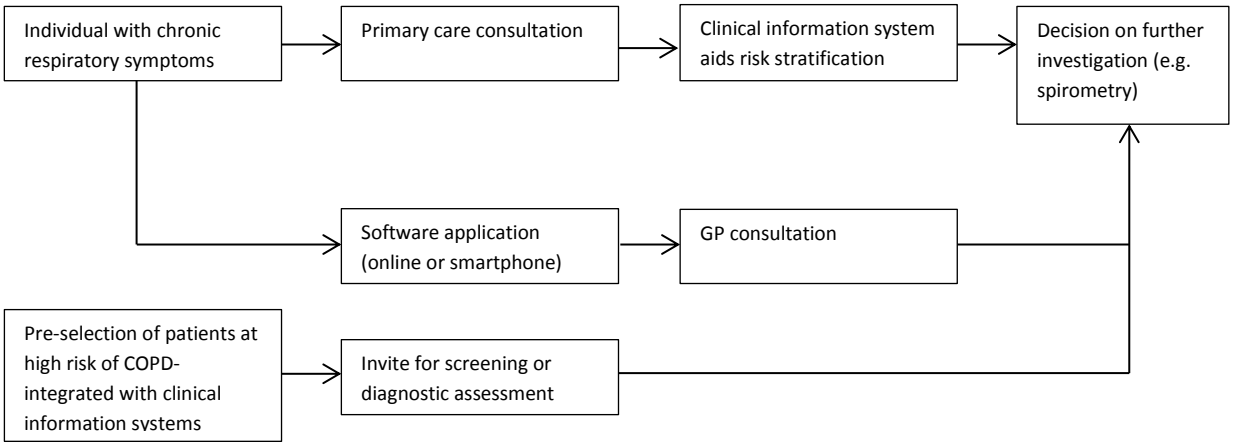

Figure 5.3 Potential strategies for applying the TargetCOPD risk model

Table 5.10 Comparison of existing risk prediction models for COPD

Model/clinical score	Development	Validation	Predictors	c-statistic (95% CI)	Strengths	Limitations
TargetCOPD*	Retrospective cohort analysis of a case finding cluster RCT & routine data from 13 general practices	Internal and external validation using data from subjects who completed a screening questionnaire and performed spirometry	Age Smoking Dyspnoea Salbutamol Antibiotics	External 0.74 (0.68-0.80)	Developed and validated on subjects with previously undiagnosed COPD confirmed by quality controlled spirometry. Can be integrated with clinical information systems. Good discrimination performance.	Dependent on quality of clinical coding
Haroon 2014* (Chapter 4)	Case control study using routine data from 360 general practices.	Internal and external validation using routine data	Smoking Salbutamol Asthma Lower respiratory tract infections	External 0.85 (0.83-0.86) in original study 0.70 (0.64-0.76) in current study	Developed on large sample size. Can be integrated with clinical information systems. High discrimination performance. Considered wide range of risk factors.	**Predicts physician-diagnosed COPD.‡** Excluded age and sex as predictors. Dependent on quality of clinical coding
Kotz 2014(8)*	Retrospective cohort study using routine data from 239 general practices.	Internal validation using routine data	Age Smoking Socioeconomic status Asthma	Internal 0.85 (0.84-0.85) in males 0.83 (0.83-0.84) in females	Developed on large sample size. Can be integrated with clinical information systems. High discrimination performance. Estimates 10 year risk of incident COPD.	**Predicts physician-diagnosed COPD. ‡** Limited range of risk factors explored. Includes a UK-specific index of socioeconomic deprivation (limiting applicability to other health systems). Dependent on quality of clinical coding
Smidth 2012(26)	Cross-sectional analysis of routine data from seven general practices, secondary care registers and an RCT.	Internal and external validation using routine data and data from an RCT	Chronic lung disease Respiratory medication Previous spirometry	Not reported	High positive predictive value.	**Predicts physician-diagnosed COPD. ‡** Requires prior diagnosis of chronic lung disease. Requires data linkage between primary and secondary care. Difficult to administer.
Mapel 2010(25)	Case control study using routine data from four hospitals and 18 general practices.	Internal and external validation using routine data	Antibiotics Respiratory & cardiovascular medications	Not reported	Only used data on medication prescriptions, which are likely to be well recorded. Developed on large sample size.	**Predicts physician-diagnosed COPD. ‡**
Mapel 2006(24)	Case control study using routine data from secondary care	Internal and external validation using routine data	19 healthcare utilization characteristics including cor pulmonale and asthma	Not reported	Developed on large sample size. Can be integrated with clinical information systems.	**Predicts physician-diagnosed COPD. ‡** Model includes large number of predictors. Includes predictors unlikely to be routinely recorded in primary care. Excluded smoking status as a predictor.

* Likely to be readily applicable in primary care. **‡ Potential misclassification of disease (COPD) status during model development and validation.**

5.6 Supplementary Tables

Table S5.1 Clinical codes used to exclude patients with COPD

Read Code (version 2)	Description
H31	Chronic bronchitis
H32	Emphysema
H36	Mild chronic obstructive pulmonary disease
H37	Moderate chronic obstructive pulmonary disease
H38	Severe chronic obstructive pulmonary disease
H39	Very severe chronic obstructive pulmonary disease
H3A	End stage chronic obstructive airways disease
H3y	Other specified chronic obstructive airways disease
H3z	Chronic obstructive airways disease NOS

Table S5.2 Clinical codes used for data extraction

Variables	Read code (version 2)	Read code (version 3)
Cough	171..	XE0qn
Dyspnoea	173.., excl. 1731, 1737, 173A, 173E, 173c, 173d, 173e	XE0qq, R060A, excl. 1731
Wheeze	1737.	XE0qs, X76If, excl. XaCH9
Sputum/phlegm	4E…, 1716., 4JF5.00	X76I2, X7ABC, XE26N, X76Hy, Xa0Yb, X76I5, excl. X76I9
Unintended weight loss	1625.., 1D1A.00	XE0qb, XaKwR, YA081, XaXTs
LRTI	H06z0, H06z1, H2…	X1004, X100E, XE0Xt
Asthma	H33..	H33..

LRTI=lower respiratory tract infection

5.7 References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
2. Soriano J, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. Lancet. 2009;374(9691):721 - 32.
3. Jones RC, Price D, Ryan D, Sims EJ, von Ziegenweidt J, Mascarenhas L, et al. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. The lancet Respiratory medicine. 2014;2(4):267-76.
4. Bakke PS, Ronmark E, Eagan T, Pistelli F, Annesi-Maesano I, Maly M, et al. Recommendations for epidemiological studies on COPD. European Respiratory Journal. 2011;38(6):1261-77.
5. Price DB, Tinkelman DG, Halbert RJ, Nordyke RJ, Isonaka S, Nonikov D, et al. Symptom-based questionnaire for identifying COPD in smokers. Respiration. 2006;73(3):285-95.
6. Frith P, Crockett A, Beilby J, Marshall D, Attewell R, Ratnanesan A, et al. Simplified COPD screening: validation of the PiKo-6(R) in primary care. Prim Care Respir J. 2011;20(2):190-8, 2 p following 8.
7. Jordan RE, Lam KB, Cheng KK, Miller MR, Marsh JL, Ayres JG, et al. Case finding for chronic obstructive pulmonary disease: a model for optimising a targeted approach. Thorax. 2010;65(6):492-8.
8. Kotz D, Simpson CR, Viechtbauer W, van Schayck OC, Sheikh A. Development and validation of a model to predict the 10-year risk of general practitioner-recorded COPD. NPJ primary care respiratory medicine. 2014;24:14011.
9. Soriano JB, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. Lancet. 2009;374(9691):721-32.
10. Walters JA, Walters EH, Nelson M, Robinson A, Scott J, Turner P, et al. Factors associated with misdiagnosis of COPD in primary care. Prim Care Respir J. 2011;20(4):396-402.
11. Jordan RE, Adab P, Jowett S, Marsh J, Riley R, Enocson A, et al. TargetCOPD: a pragmatic randomised controlled trial of targeted case finding for COPD versus routine practice in primary care: protocol. BMC pulmonary medicine. 2014;14(1):157.
12. Jordan R, Adab P, Jowett S, Marsh J, Riley R, Enocson A, et al. TargetCOPD: a pragmatic randomised controlled trial of targeted case finding for COPD versus routine practice in primary care: protocol. BMC Pulmonary Medicine. 2014;14(1):157.
13. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. European Respiratory Journal. 2005;26(2):319-38.
14. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. The European respiratory journal. 2012;40(6):1324-43.
15. McLennan D, Barnes H, Noble M, Davies J, Garratt E, Dibben C. The English indices of deprivation 2010. In: Government DfCaL, editor. London2011.
16. Collins GS, de Groot JA, Dutton S, Omar O, Shanyinde M, Tajar A, et al. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. BMC Med Res Methodol. 2014;14:40.
17. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9.
18. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-99.
19. Royston P, Altman DG. Approximating statistical functions by using fractional polynomial regression. Statistician. 1997;46(3):411-22.
20. Steyerberg EW, Eijkemans MJC, Habbema JDF. Application of shrinkage techniques in logistic regression analysis: a case study. Stat Neerl. 2001;55(1):76-88.
21. Efron B, Tibshirani R. Improvements on cross-validation: The .632+ bootstrap method. J Am Stat Assoc. 1997;92(438):548-60.
22. Fletcher C, Peto R. The natural history of chronic airflow obstruction. British medical journal. 1977;1(6077):1645-8.
23. Price DB, Tinkelman DG, Nordyke RJ, Isonaka S, Halbert RJ, Grp CQS. Scoring system and clinical application of COPD diagnostic questionnaires. Chest. 2006;129(6):1531-9.

24. Mapel DW, Frost J, Hurley JS, Petersen H, Roberts M, Marton JP, et al. An algorithm for the identification of undiagnosed COPD cases using administrative claims data. J Manag Care Pharm. 2006;12(6):458-65.
25. Mapel DW, Petersen H, Roberts MH, Hurley JS, Frost FJ, Marton JP. Can Outpatient Pharmacy Data Identify Persons With Undiagnosed COPD? Am J Manag Care. 2010;16(7):505-12.
26. Smidth M, Sokolowski I, Kaersvang L, Vedsted P. Developing an algorithm to identify people with Chronic Obstructive Pulmonary Disease (COPD) using administrative data. Bmc Med Inform Decis. 2012;12.
27. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Habbema JD. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. J Clin Epidemiol. 2005;58(5):475-83.
28. Steyerberg EW, Moons KG, van der Windt DA, Hayden JA, Perel P, Schroter S, et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. PLoS medicine. 2013;10(2):e1001381.

CHAPTER 6: CASE FINDING FOR COPD IN PRIMARY CARE: A QUALITATIVE STUDY OF THE VIEWS OF HEALTH PROFESSIONALS

6.1 Abstract

Introduction

COPD is common but largely underdiagnosed. A number of case finding initiatives have been evaluated in primary care but few studies have explored the views of service providers on implementing this in practice.

Methods

20 semi-structured interviews were conducted from March to September 2014 among GPs, nurses and managers from practices participating in a large COPD case finding trial based in primary care in the West Midlands, UK. Participants' views were sought to explore perceived benefits, harms, barriers and facilitators to implementing case finding for COPD in practice. Interviews were transcribed and analysed using the framework method.

Results

Participants felt that case finding improves patient care, including smoking cessation and access to healthcare but also acknowledged potential harms to providers (increase in workload) and to patients (overdiagnosis). Insufficient resources, poor

knowledge of COPD, and limited access to diagnostic services were viewed as barriers to diagnosis while provision of community respiratory services, including COPD specialist nurses, and support from secondary care were thought to be facilitators. Participants also expressed a need for more education on COPD for both patients and clinicians.

Conclusion

Care providers believe early detection of COPD improves patient care but also has accompanying harms. Barriers to diagnosing COPD, such as insufficient expertise in primary care and limited access to diagnostic services in the community should be explored and addressed. The knowledge and attitudes of the public about COPD and its symptoms should also be investigated to inform future education and awareness-raising strategies.

6.2 Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality (1) and represents a significant cost to health services and society.(2) However, much of the disease burden remains undiagnosed (3) and there has been a policy drive to identify COPD early through systematic case finding.(4) This has been accompanied by the evaluation of a number of case finding strategies (5, 6) as described in the previous chapters of this thesis. However there has been a paucity of research exploring the views of primary care practitioners on these initiatives or factors influencing the ability of health services to screen for and diagnose COPD.

A study in Tasmania conducted semi-structured interviews and focus groups to explore the views of patients with COPD and their general practitioners (GPs) on factors influencing the diagnosis of COPD.(7) This found that GPs intentionally avoided early diagnosis as a result of harbouring nihilistic attitudes towards COPD and misperceiving patient expectations. Patients reported receiving the diagnosis from other sources and were frustrated by delayed diagnosis.

Another study by the same authors randomly assigned eight practices to either deliver optimised usual care or opportunistic assessment with spirometry for over 35 year old ever smokers routinely attending primary care.(8) At the end of the study, focus groups were conducted with participating GPs to explore their views on each approach. They felt that organised follow-up, especially with spirometry was essential but would increase an already high workload and increase costs for patients. They also expressed a need for assistance with interpreting spirometry but felt its use prompted them to record their patients' smoking status and initiate discussions about

smoking cessation. Some also questioned the value of diagnosing COPD in the absence of a cure.

54 general practices were recently enrolled in a large pragmatic cluster randomised controlled trial (RCT) in the West Midlands, UK comparing the effectiveness and cost-effectiveness of targeted case finding for COPD against routine care.(9). Interviews were undertaken with participating healthcare providers to gain insights into their views on case finding for COPD, and to discern factors that might influence their ability to make a diagnosis.

6.3 Methods

6.3.1 Study design

I conducted semi-structured interviews with primary care service providers. Interviews were conducted from March to September 2014 and were audio-recorded and transcribed verbatim. Memos were made shortly after each interview to summarise key points and reflections.

6.3.2 Participants

One GP, nurse and manager was invited from each of the 54 general practices participating in the TargetCOPD trial.(9) Practices were selected to represent a wide range of population and practice characteristics. Eligible participants were posted an invitation letter as well as up to two reminders.

6.3.3 Sample size

The aim was to recruit 5-10 participants of each profession across at least five general practices with a minimum sample size of 20. Eventual sample size was determined by the reaching of theoretical saturation (i.e. no new concepts arising from the data).(10, 11)

6.3.4 Interviews

One-to-one semi-structured interviews were conducted either at practices (n=9) or over the telephone (n=11) using a topic prompt (see Box) and had a mean duration of 23 minutes (range 13 to 38 minutes). Repeat interviews were not conducted and transcripts were not returned to participants for comment.

Box 1. Topic prompt

- Please tell me about any experience you have had looking after patients with COPD.
- What are your thoughts on screening or case finding for COPD?
- How do you think it would be best to identify undiagnosed patients with COPD in the community?
- Does your practice take part in any COPD case-finding activities? Please tell me about this.
- What might be the barriers to case finding and identifying patients with COPD?
- What would help primary care services identify patients with COPD?
- We are developing an electronic tool for GPs which will help them identify which of their patients are at high risk of undiagnosed COPD. Do you think such a tool would be useful? Do you think it would be used in practice and if so in what way?
- Is there anything else you would like to comment about screening or case finding for COPD?

6.3.5 Analysis

Interviews were analysed using the framework method.(12) In brief, transcripts were read to identify codes or themes referring to specific topics. Two transcripts considered to be particularly rich and informative were independently coded by myself and my supervisors and compared to create an initial coding framework. I coded all subsequent transcripts and built on this framework. A framework matrix was then constructed, tabulating quotes by their associated codes and participant type. Emergent themes were then discussed and finalised. The analysis was performed using NVivo version 10.

6.3.6 Ethical approval

Ethical approval was provided by the Solihull National Research Ethics Service committee (reference: 11/WM/0403). All identifiable data were held on an encrypted database.

6.4 Results

6.4.1 Practice and participant characteristics

162 care providers were invited to participate, from which 20 participants (ten GPs, seven practice nurses, and three practice managers) from 16 practices were interviewed (Tables 6.1 and 6.2). Practices had a range of patient list sizes with most having 5-10,000 patients and the majority serving relatively socioeconomically deprived populations. Approximately one third of practices had been in the case finding arm of the trial and all had been involved in recruiting patients for a large COPD cohort study (the Birmingham COPD Study). Most GPs (70%) interviewed were male and all practice nurses and managers were female. Participants had been in practice on average for thirteen or more years.

Table 6.1 Practice characteristics

		N	(%)
Total number of practices		16	(100)
Patient list size	0-5000	5	(31.3)
	5000-10,000	8	(50.0)
	>10,000	3	(18.8)
IMD quintile	1 (most deprived)	8	(50.0)
	2	1	(6.3)
	3	3	(18.8)
	4	4	(25.0)
	5 (least deprived)	0	(0)
Intervention arm	Targeted case finding	6	(37.5)
	Routine care	10	(62.5)

IMD=Index of Multiple Deprivation (measure of socioeconomic deprivation based on postcodes)

Table 6.2 Participant characteristics

	GP		**Nurse**		**Practice manager**		**Total**	
Number (%)	10	(50)	7	(35)	3	(15)	20	(100)
Mean age in years (range)	44.7	(31-73)	46.7	(33-54)	57.7	(55-61)	47.4	(31-73)
Male (%)	7	(70)	0	(0)	0	(0)	7	(35)
Mean years in practice (range)	13.7	(2-35)	15.7	(10-25)	16.7	(12-25)	14.9	(2-35)

6.4.2 Views on case finding

Participants were generally of the opinion that early detection of COPD was beneficial for both patients and health services. Several felt that early detection improved smoking cessation, helped instigate positive changes to other lifestyle behaviours (e.g. exercise), and improved quality of life and disease prognosis by enabling earlier access to care. Some also felt that it would be cost-saving for health services in the long term.

> *I guess the main advantage of screening is presumably to pick up the disease early so that… I mean COPD is to some extent preventable and particularly if you treat it early and I guess the biggest advantage is… you can encourage them to stop smoking… if we treat it early, treat it effectively then hopefully there'll be fewer hospital admissions and therefore reducing the costs.* (GP 8)

Several potential harms were also highlighted including the impact on health services, such as increased workload, resources and costs, as well as patients, including the risk of overdiagnosis, the implications of diagnostic labelling on insurance costs and creating anxiety.

> *…it's just that impact on workload really, whether primary care would just be overwhelmed if we started screening… you could end up labelling people, which can have a huge impact, and they are fine.* (Nurse 6)

6.4.3 Diagnostic strategies

Participants mainly reported that patients were investigated for COPD on an opportunistic basis when consulting the health services, particularly when presenting with suggestive symptoms. Others discussed using a more active approach such as

screening at smoking cessation clinics. A wide range of factors were considered to be important triggers for considering COPD such as smoking status and a history of asthma. Participants also highlighted the potential of clinical information systems to help identify and flag high risk patients.

> *Also looking at computer data, we can set up searches on our computers, but it depends on how active people are at putting the information on the computer, then we can pull that information…* (Nurse 4)

Spirometry was described as essential for making a diagnosis of COPD while screening tests such as handheld flow meters and respiratory questionnaires were discussed as potentially useful for assessing risk prior to diagnostic assessment. Some handheld flow meters were reported to feedback lung age which was highlighted by several participants as being useful for promoting smoking cessation. Handheld flow meters were also described as quick and easy to use within a consultation.

> *If someone has got appropriate symptoms, a smoking history, and a low FEV_1 over V_6, then we'll bring them in for formal spirometry… overall I think it's not an unreasonable way to triage the people into proper spirometry. I think the key thing is not to make the diagnosis on the handheld stuff.* (GP 7)

Most participants felt that use of electronic risk prediction tools would be useful for identifying patients at high risk of undiagnosed COPD and even to help communicate risk to patients. Ease of use, provision of technical support, integration with existing clinical information systems, and the generation of automated prompts on electronic health records were seen as important factors for their implementation.

I think it's because we (nurses) always like something to refer to and we like to use tools, and I think sometimes that helps just to show the patient as well. Because we use a tool to assess cardiovascular risk… I found it useful, because it illustrates to them for example if they're a smoker you can calculate their risk as a smoker, and then show them if you weren't a smoker it would be this… So that's a visual thing for them to see. (Nurse 5)

A number of participants also highlighted the importance of being able to refer to secondary care, particularly for more challenging clinical presentations. One single-handed GP also commented on the need to refer patients to secondary care for medico-legal protection.

6.4.4 Barriers to case finding for COPD

Limitation of time, finances and resources were seen as important barriers to implementing case finding and diagnosing COPD. Participants felt that primary care services were already stretched to capacity managing patients with established COPD and a lack of additional funding and resources would prohibit the implementation of case finding.

…just managing the patients who are already on the COPD register is a hell of an onerous task anyway so going out and case finding… there's a cost implication, there's a man-time implication so unless it's well-resourced it's not going to happen. (GP 6)

There was also felt to be a significant lack of knowledge and expertise on COPD in primary care. This included poor understanding of spirometry, difficulties

distinguishing between COPD, asthma and COPD-asthma overlap disease, and under recognition of the signs of COPD.

> *I suspect as a profession, we're not very good at picking up early signs of COPD either… Partly because we, again, attribute a lot of their symptoms to their social habits- smoking, lack of activity, environment.* (GP 3)

Limited access to diagnostic services was also cited as a barrier, particularly in smaller practices, which often lack provision of in-house spirometry. Challenges to providing spirometry included costs of equipment and training, quality assurance, and availability of appropriately trained staff.

> *…you can't refer for spirometry, the only thing we could possibly do is buddy up with other practices, but not every practice has a practice nurse available to do spirometry or has a spirometry machine.* (Practice Manager 1)

However some participants did comment on the gradual improvement of diagnostic testing for COPD in the community.

> *It's getting better I think. I think there was a phase where people were just doing spirometry willy-nilly without necessarily having the right equipment, the training to use it properly. I think there has been a lot of improvement, particularly over the last couple of years with the accreditation…* (GP 3)

Several patient-related factors were also described as barriers to diagnosing COPD. This included poor attendance at primary care, and late presentation with advanced disease. Patients were perceived to sometimes try to cope with symptoms for as long as possible without consulting the health services until suffering an acute

exacerbation. Some felt that patients often under-recognised the significance of their symptoms or were not always forthcoming about them or their smoking habits.

> *…a lot of patients have symptoms but they just think that's what they should have because they're smokers so they don't often seek advice.* (Nurse 7)

There was also a view that awareness of COPD among the general public was low, that patients were more likely to be aware of the more severe stages of the disease, and that smokers with undiagnosed COPD often have low expectations of their health. They also felt that communicating information about COPD was challenging.

> *If you said to the average man on the street, 'What's COPD?' they wouldn't even know what it was… when you do try to explain it to them, you get people going into panic mode then because it doesn't sound very nice… there's just not enough educational publicity surrounding it.* (Practice Manager 1)

Cultural barriers were also discussed, which present both challenges to communicating risk as well as making a diagnosis because of under-recognition of exposures more common in the developing world such as indoor air pollution from cooking fuels.

> *I think there is a linguistic barrier; increasing numbers of patients are from ethnic minorities and getting them up and looking at them, and actually understanding where their exposure has been…. You get all the little Asian ladies who cooked on open fires indoors and have COPD from that, but then they're not smokers… So I think there's a lot of cultural things going on here.* (GP 7)

6.4.5 Facilitators for diagnosing COPD

Training of health professionals was seen as one of the key facilitators for case finding and diagnosing COPD. Particular importance was attributed to spirometry training and acquiring a diploma in COPD, which several participating nurses had already achieved.

> *…two of our nurses are going to do a spirometry course to become more up-to-date and obviously qualified in doing spirometry, then we could offer more access to spirometry and possibly set up a breathing clinic…* (Nurse 4)

Access to community respiratory services, including specialist COPD nurses, and support from secondary care and community outreach were also seen as important, particularly since expertise on respiratory medicine in primary care was generally perceived to be low. Participants also discussed the importance of sharing diagnostic services between practices, which was especially important for smaller practices with limited service capacity.

> *…if say a patient was suspected with COPD and I've sent them off for spirometry, we normally send them off to a local service where they have this spirometry, and I guess luckily for us we do have a respiratory consultant reporting the spirometry findings as well which gives us recommendations.* (GP 8)

The importance of educating patients and the public about COPD, including ethnic minority populations, was also discussed. This included communicating the symptoms of COPD, disseminating information at a community level, and use of social marketing and mass publicity.

I think more patient education, more information out there, more publicity… I think it's got to be in the media really… If you've got these sort of symptoms then see your GP, get it checked… (Practice Manager 1)

6.4.6 Perceptions of patients' responses to receiving a diagnosis of COPD

Patients' responses to being diagnosed with COPD were perceived to be quite variable. Most participants felt that patients accepted their diagnosis and worked with their clinicians to improve their lifestyle behaviours, particularly in relation to smoking. Patients were perceived to sometimes even be relieved by the diagnosis since this allows them to attribute a cause to their chronic symptoms.

I've not really had any genuine reluctance to accept a diagnosis… I think they take on board what they have been told… take on board the fact that by making lifestyle changes, they can significantly slow the progress of the process they have started. (GP 4)

However it was acknowledged that patients were often shocked and upset by the diagnosis, particularly if they had family members who had severe disease, and also that there were implications for insurance costs and potentially employment. Some felt that patients were occasionally very reluctant to accept the diagnosis, particularly when they had no wish to give up smoking.

I think because it is a big shock, it is a big diagnosis, as I said it's got lots of implications with insurance. I think it frightens patients as well because they look at the worst case scenario and associations with oxygen… (GP 2)

6.5 Discussion

6.5.1 Main findings

Case finding for COPD is to some extent already occurring in primary care and some healthcare providers believe that this will benefit patient care at the expense of applying high workload and cost pressures on the health service, as well as risking overdiagnosis and creating anxiety among patients (Figure 6.1). Primary care providers are opportunistically diagnosing patients when presented with a suggestive clinical history while others are keen to undertake active case finding using a range of approaches.

However, some important barriers to case finding were identified- limited service capacity, insufficient expertise on COPD and interpretation of spirometry, and restricted (but improving) access to diagnostic services were highlighted. Perceived poor awareness of COPD and its symptoms among the public and the difficulty of communicating a diagnosis of COPD were also seen as barriers.

Investing in the training of healthcare professionals on COPD and spirometry, improving access to community respiratory services including specialist COPD/respiratory nurses, and education campaigns to improve awareness of COPD in the general population, were all suggested to improve the identification of patients with undiagnosed COPD.

Finally, healthcare professionals recognise that receiving a diagnosis of COPD can be an upsetting and life-changing event and patients' health beliefs and their response to the diagnosis can play an important role in subsequent management.

Effective communication of the diagnosis is thus an important component of patient care.

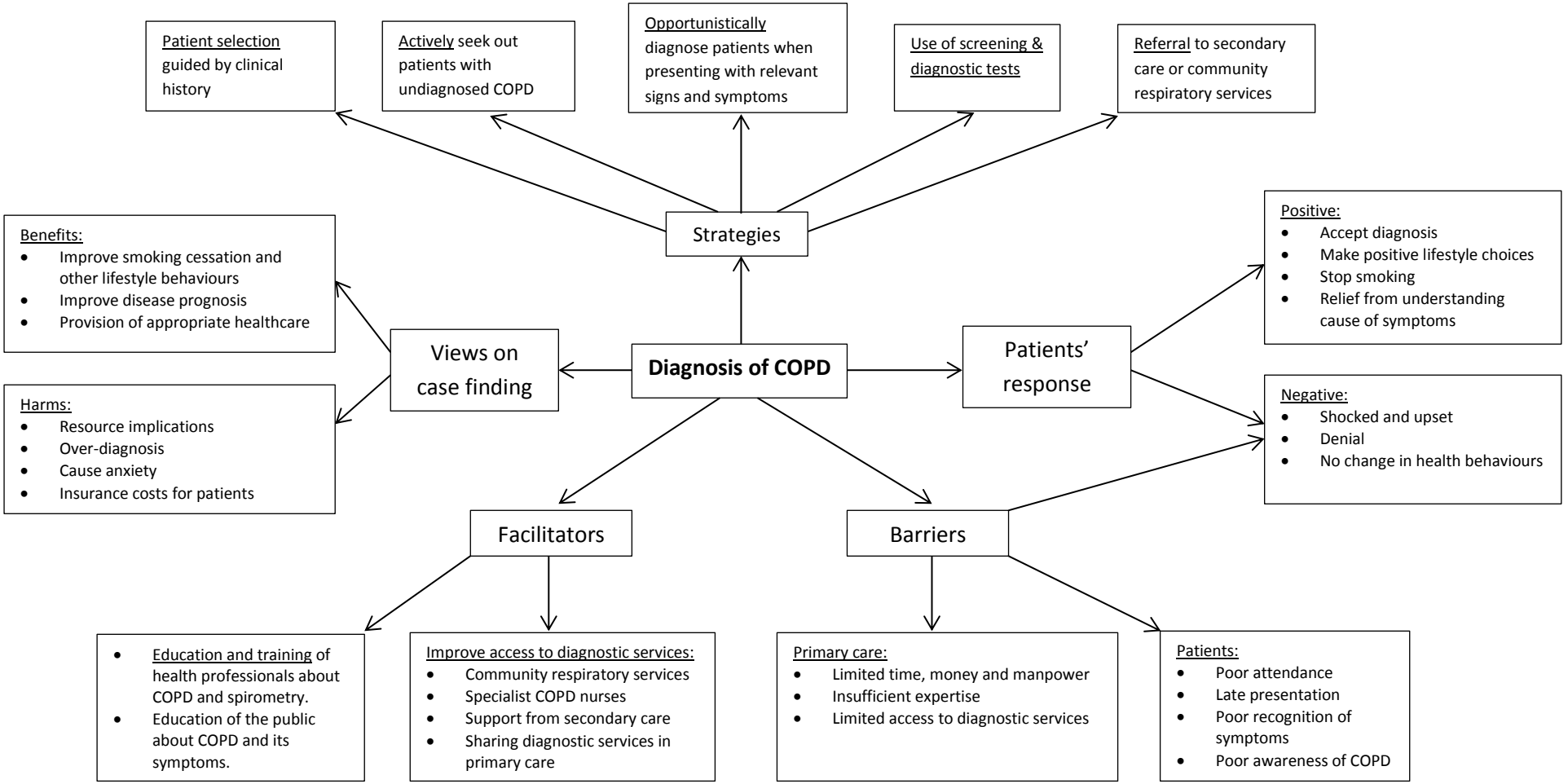

Figure 6.1 Summary of themes discussed by participants

6.5.2 Relationship to other studies

Like Walters and colleagues (7, 8) the current study found that additional workload and resource requirements associated with case finding, as well as poor knowledge and confidence with spirometry interpretation, are likely to be barriers to diagnosing COPD in primary care. However unlike their study, participants in the current study did not express views of therapeutic nihilism. Instead they largely felt that early intervention was likely to improve patient outcomes. Patients with COPD participating in a qualitative study in Sweden that explored their perspectives on receiving a diagnosis suggested that they would prefer the diagnosis to be given at an early stage.(13) This also aligns with findings by Walters and colleagues (7) and the views expressed by health professionals in the current study.

A recent analysis of a large primary care database showed that opportunities to diagnose COPD in primary care are frequently missed.(14) This was also acknowledged by participants in the current study and a number of reasons for this were postulated including health service and patient-related factors, such as under-recognition of symptoms. Also participants felt that there is a low awareness of COPD among primary care users and the general public and this has previously been shown in a number of surveys.(15-17)

6.5.3 Strengths and limitations

A variety of stakeholders were sampled to acquire a range of both clinical and nonclinical perspectives. Participants were from a number of practices with a wide range of characteristics, including those that had participated in both the case finding and routine care arms of the TargetCOPD trial.(9) However, only a small proportion

(12.3%) of health professionals who were invited agreed to participate, despite receiving a written invitation and two reminder letters. This is likely to have introduced a response bias from a more select group of primary care providers who may potentially be more engaged with COPD care. The views expressed by the participants may therefore not fully reflect those among all healthcare providers who participated in the TargetCOPD trial. Also patients were not interviewed as part of this study so the views expressed were from a care provider perspective and may not necessarily reflect what patients personally experience. Transcripts were not returned to participants for validation of the themes and the interpretation of the transcripts could have been influenced by the prior beliefs of the author who is involved in the evaluation of COPD case finding. The findings of this study should therefore be interpreted in that light.

6.5.4 Implications for policy, practice, and research

Improving the diagnosis of COPD in primary care may require investment in community respiratory services and training of health professionals on COPD and performance and interpretation of spirometry. Further research should explore public perceptions of COPD, including awareness of symptoms, and understanding of the full spectrum of disease. Greater awareness may improve the likelihood that patients with undiagnosed disease access the appropriate services.

The benefits and harms of case finding highlighted in this study should be evaluated empirically in the long term follow-up of case finding trials. The findings of this study should also be compared to the views of patients and explore the issues and implications surrounding the receipt of a diagnosis, addressing both the benefits and harms. The acceptability and feasibility of case finding strategies should be

qualitatively evaluated among care providers and patients alongside clinical trials evaluating their effectiveness.

6.5.5 Conclusion

The diagnosis of COPD in primary care may be improved by increasing access to community respiratory services and investing in the training of health professionals on COPD and spirometry. The benefits and harms of case finding should be empirically assessed in longitudinal studies to evaluate the overall effectiveness of detecting COPD early. Finally, the knowledge and attitudes of the public about COPD and its symptoms should be investigated to inform future education and awareness-raising initiatives and help those with undiagnosed disease access the appropriate care.

6.6 References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
2. Gibson GJe, Loddenkemper Re, Sibille Ye, Lundbäck Be. The European lung white book. [New edition]. ed.
3. Buist A, McBurnie M, Vollmer W, Gillespie S, Burney P, Mannino D, et al. International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. Lancet. 2007;370:741 - 50.
4. An outcomes strategy for people with chronic obstructive pulmonary disease (COPD) and asthma in England London: Department of Health; 2011 [cited 2013 29/10/2013]. Available from: https://www.gov.uk/government/publications/an-outcomes-strategy-for-people-with-chronic-obstructive-pulmonary-disease-copd-and-asthma-in-england.
5. Dirven J, Tange H, Muris J, van Haaren K, Vink G, van Schayck O. Early detection of COPD in general practice: patient or practice managed? A randomised controlled trial of two strategies in different socioeconomic environments. Prim Care Respir J. 2013;22(3):331 - 7.
6. Haroon S, Adab P, Griffin C, Jordan R. Case finding for chronic obstructive pulmonary disease in primary care: a pilot randomised controlled trial. Brit J Gen Pract. 2013;63(606):26 - 7.
7. Walters JA, Hansen EC, Walters EH, Wood-Baker R. Under-diagnosis of chronic obstructive pulmonary disease: a qualitative study in primary care. Respiratory medicine. 2008;102(5):738-43.
8. Walters JA, Hansen EC, Johns DP, Blizzard EL, Walters EH, Wood-Baker R. A mixed methods study to compare models of spirometry delivery in primary care for patients at risk of COPD. Thorax. 2008;63(5):408-14.
9. Jordan R, Adab P, Jowett S, Marsh J, Riley R, Enocson A, et al. TargetCOPD: a pragmatic randomised controlled trial of targeted case finding for COPD versus routine practice in primary care: protocol. BMC Pulmonary Medicine. 2014;14(1):157.
10. Mason M. Sample Size and Saturation in PhD Studies Using Qualitative Interviews2010.
11. Morse JM. Determining Sample Size. Qualitative Health Research. 2000;10(1):3-5.
12. Gale N, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Medical Research Methodology. 2013;13(1):117.
13. Arne M, Emtner M, Janson S, Wilde-Larsson B. COPD patients perspectives at the time of diagnosis: a qualitative study. Prim Care Respir J. 2007;16(4):215-21.
14. Jones R, Price D, Ryan D, Sims E, von Ziegenweidt J, Mascarenhas L, et al. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. The Lancet Respiratory Medicine. 2014;2(4):267 - 76.
15. de Castro MC, auxiliadora Carmo M, r Jardim J, alves Barbosa M, Velasco FC, Carmo MV. Knowledge about COPD among users of primary health care services. International Journal of COPD. 2015;10:1-6.
16. Kesten S, Ulrich J, Rich D. Public awareness of chronic obstructive pulmonary disease. Chest. 2003;124(4):167s-s.
17. Soriano JB, Calle M, Montemayor T, Alvarez-Sala JL, Ruiz-Manzano J, Miravitlles M. The General Public's Knowledge of Chronic Obstructive Pulmonary Disease and Its Determinants: Current Situation and Recent Changes. Arch Bronconeumol. 2012;48(9):308-15.

CHAPTER 7: DISCUSSION

7.1 Summary of principal findings

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality (1, 2) but is widely underdiagnosed.(3) A significant proportion of people with undiagnosed COPD are likely to benefit from interventions such as smoking cessation support, pulmonary rehabilitation, and influenza vaccination.(4) Although there is a policy drive to identify people with undiagnosed COPD, (5) the most effective approach is currently unknown.(6) The interlinked studies reported in this thesis have examined the evidence, developed tools, and explored views on strategies to improve case finding for COPD in primary care. Chapters 2 and 3 report two systematic reviews evaluating the accuracy and effectiveness of screening tests and diagnostic strategies. Chapters 4 and 5 report the development and external validation of two readily applicable prediction models for assessing the risk of undiagnosed COPD using routine healthcare data. Finally, Chapter 6 reports a qualitative study exploring the views of healthcare professionals on case finding for COPD.

7.1.1 Chapter 2

Case finding is likely to be resource intensive, potentially requiring the clinical assessment of a large number of patients. The efficiency of case finding could be improved by using screening tests that can accurately discriminate between patients with and without disease to identify those most likely to benefit from further diagnostic

assessment. The accuracy of screening tests for COPD had not previously been formally summarised and their relative accuracy was therefore unknown.

The systematic review in Chapter 2 evaluated the diagnostic accuracy of screening tests for COPD, incorporating evidence from ten studies. Only studies assessing screening questionnaires (the most widely evaluated of which was the COPD Diagnostic Questionnaire [CDQ] (7, 8)) and handheld flow meters met the inclusion criteria. There were very few comparative studies which meant that the review largely relied on indirect comparisons, which could potentially be biased because of differences in population and study characteristics. However the two studies that directly compared screening tests (9, 10) gave similar results to the indirect comparisons. There were also methodological limitations with inadequate blinding between index and reference tests, and a physiological definition of COPD was mostly used, relying on the presence of airflow limitation, which may not be truly representative of clinical disease. However the one study that only included subjects with respiratory symptoms (11) produced estimates of sensitivity and specificity for the CDQ that were broadly similar to studies that did not explicitly recruit subjects with respiratory symptoms. Meta-analyses of similar studies suggested that handheld flow meters are significantly more accurate than the CDQ for identifying patients with undiagnosed airflow limitation and potentially clinical COPD. The review highlighted the need for further diagnostic accuracy studies that directly compare alternative screening tests (including those not evaluated in the review such as peak flow meters) and use a clinical definition of COPD that requires the presence of relevant symptoms (see 1.3) as well as airflow limitation.

7.1.2 Chapter 3

Knowledge of the accuracy of screening tests does not in itself provide information on the overall effectiveness of case finding strategies since this also depends on the uptake of screening and diagnostic tests by the target population. A number of studies have evaluated the effectiveness of case finding approaches for COPD but had not been previously summarised. The second systematic review in this thesis (Chapter 3) summarised the effectiveness of alternative approaches to case finding for COPD, incorporating data from 39 primary studies. Again these were largely non-comparative (mostly single arm before-after studies) and were highly heterogeneous in terms of study design, target population, recruitment methods, screening tests, and diagnostic criteria. It therefore relied on indirect comparisons to identify factors associated with the yield from different case finding approaches, such as the patient population, method of recruitment, and use of screening tests. The included studies were of variable methodological quality, mainly used physiological definitions of COPD and often did not report the size and characteristics of the eligible population, which are important for making inferences about the overall effectiveness of case finding initiatives in primary care populations.

The findings show that any case finding approach is likely to identify a substantial burden of previously undiagnosed disease. The findings from comparative studies suggest that nurse-led case finding using written invitations for spirometry may be more effective than usual care, that screening questionnaires should ideally be scored and further follow-up arranged by practices rather than directed by patients, and that opportunistic case finding among patients clinically suspected to have COPD is likely to be more effective than more widespread public invitation for

spirometry testing. The findings from indirect comparisons suggest that uptake of spirometry testing is likely to be higher when this is offered opportunistically at routine primary care visits than when offered through a mailed invitation, that the yield may be higher when targeting ever smokers with a history of respiratory symptoms, and that use of screening tests such as questionnaires or handheld flow meters prior to spirometry may reduce the number of diagnostic assessments needed per case detected. The review highlighted the need for well conducted RCTs comparing the relative effectiveness of alternative case finding strategies, and addressing the methodological limitations found in previous studies, such as reporting of eligible populations and indeterminate results. The review did not consider the costs of each approach, which ideally should be modelled alongside RCTs.

7.1.3 Chapters 4 and 5

Case finding is likely to involve the invitation of a large number of patients for assessment, and is therefore likely to be costly and resource intensive. One way to potentially improve the efficiency of the process is to risk stratify patients in order to identify those most likely to benefit from further clinical assessment. This could reduce the number of clinical assessments needed to identify each additional case. This is already part of routine practice in certain clinical domains such as cardiovascular disease (12) and could potentially be incorporated for COPD using routine healthcare data.(13) Use of routinely recorded healthcare data to risk stratify patients has the advantage of being less dependent on patient response (unlike screening questionnaires) and is likely to require less resources than the application of screening tests (such as handheld flow meters).

The next two chapters in this thesis (Chapters 4 and 5) report the development and validation of two models that use routine healthcare data to estimate the risk of undiagnosed COPD among patients in primary care. The first model was developed using case control data from a large primary care database drawn from general practices in England. The main derived model included only four routinely recorded risk factors- smoking status, and history of lower respiratory tract infections (LRTIs), salbutamol prescriptions, and asthma. This showed high discrimination characteristics when externally validated and at a score cut-point of ≥2.5 was estimated to require only five diagnostic assessments to identify one patient with COPD (although this did not consider nonresponse), which is potentially far fewer than would be required than when inviting all ever smokers for diagnostic spirometry (~19 diagnostic assessments required per case detected). However the study was limited by the case definition used which was a diagnosis of COPD documented through routine care. Cases and controls may have been misclassified because of the underdiagnosis and misdiagnosis of COPD known to exist in primary care (3, 14) and cases identified through routine care may not necessarily be representative of those that would be identified through case finding.

Nevertheless this analysis was highly informative for the development of a second model (the TargetCOPD model) which was derived from a large cluster RCT for COPD in primary care (the TargetCOPD trial).(15) This has the advantage over previous models of having been developed on data from patients who had been diagnosed through systematic case finding using quality controlled spirometry and the most up-to-date and comprehensive lung function reference equations.(16) The final model incorporated five predictors that are routinely recorded in electronic health

records- age, smoking status, history of dyspnoea, and prescriptions of salbutamol and antibiotics indicated for lower respiratory tract infections. This model was able to discriminate reasonably well between patients with and without COPD when externally validated (c-statistic 0.74 [95% CI 0.68 to 0.80]). The calibration (matching of predicted and observed risk) was good up to 10%, but slightly overestimated observed risks up to 30%, although this may have been affected by the small sample size in the external validation population. The previously developed model was also externally validated in this dataset and showed slightly worse discrimination characteristics than the TargetCOPD model (c-statistic 0.70 [95% CI 0.64 to 0.76]). Unlike the TargetCOPD model, the previous model cannot be used to estimate absolute risk of COPD since it was developed on case control data. Also the previous model did not include age since this had been used as a matching factor in the study design. Both models are probably incorporating markers of overlapping clinical factors since prescriptions of salbutamol are more likely in patients with asthma, and prescriptions of relevant antibiotics more likely in those with a history of LRTIs.

Using the TargetCOPD model at the suggested cut-point of ≥7.5% to prompt referral for further clinical assessment, seven patients would require a diagnostic assessment (including spirometry) to identify one with undiagnosed COPD (although this could be reduced by raising the cut-point at the expense of lowering sensitivity). This is the first prediction model derived from patients with COPD who were diagnosed exclusively through systematic case finding and uses routine data from electronic health records. It is likely to be readily applicable and integrated with clinical information systems to risk stratify patients for undiagnosed COPD and help prioritise further diagnostic assessment. However the model still needs to be validated in other

populations and its impact on clinical practice and patient outcomes evaluated in RCTs before its routine use can be recommended.

7.1.4 Chapter 6

Finally, to contextualise the findings of the previous chapters to everyday general practice and understand the potential barriers and facilitators to identifying patients with undiagnosed COPD, 20 primary care providers, including GPs, nurses and managers, were interviewed. Findings from these interviews suggest that healthcare professionals view case finding as beneficial for improving patient outcomes but may also risk overstretching healthcare resources, as well as potentially causing overdiagnosis, and creating anxiety among patients. Healthcare providers appear to be keen to use novel methods for assessing risk of COPD, such as using handheld flow meters and risk prediction software. However there was felt to be a lack of expertise on COPD and the use and interpretation of spirometry as well as the healthcare capacity to undertake case finding. The findings suggest that improving access to community respiratory services, including specialist COPD/respiratory nurses, increasing education on COPD and spirometry for primary care health professionals, and increasing awareness of COPD and its symptoms among the general public may help improve the timely diagnosis of COPD and the implementation of case finding for COPD in primary care. These factors should be empirically evaluated in ongoing and future case finding studies and as part of respiratory service evaluations.

7.2 Relationship to other reports

The National Institute for Health and Care Excellence (NICE) recommend that a diagnosis of COPD should be considered in ever smokers aged over 35 years who have chronic respiratory symptoms in the absence of clinical features of asthma,(17) and that opportunistic case finding should be based on the presence of risk factors (age and smoking) and symptoms. Using a simple decision tree model, they surmised that this approach was likely to be cost-effective. The model focused exclusively on the benefits of smoking cessation therapy, incorporated evidence from a limited number of studies, and relied on a number of basic assumptions including differences in treatment compliance between patients diagnosed early versus late (although sensitivity analyses were performed to account for some of these variables).

The systematic reviews presented in Chapters 2 and 3 of this thesis should help inform policy on case finding for COPD and should be considered in future guideline reviews. Their findings support the effectiveness of opportunistically targeting ever smokers with respiratory symptoms to optimise the diagnostic yield but additionally highlight potential improvements in the efficiency of this process by screening with either respiratory questionnaires or handheld flow meters prior to performing diagnostic spirometry. Future guidelines should also consider the potential benefits of using risk prediction models or clinical scores to improve the efficiency of case finding and their utility for triaging patients for further diagnostic assessment.

The Outcomes Strategy for COPD and Asthma in England advocated early recognition of COPD through opportunistic and active case finding although it did not

provide specific guidance on optimal approaches.(5) The systematic review in Chapter 3 provides some evidence that opportunistically inviting patients at high risk of COPD for assessment may improve the uptake. However this was based on indirect comparisons and needs to be empirically tested in adequately powered and well conducted RCTs. The findings from the qualitative study in Chapter 6 of this thesis also suggest that policy on case finding must consider the current capacity within primary care to diagnose and manage patients with COPD, including the need for good access to community respiratory services and education and training on community respiratory medicine.

In 2008 the US Preventive Service Task Force conducted a systematic review on screening for COPD using spirometry and recommended against it because they estimated that hundreds of patients would need to be screened in order to prevent a single exacerbation and that screening would largely uncover patients with early disease for whom there are limited therapeutic options.(18) However this review looked at screening asymptomatic individuals for airflow obstruction, which is not equivalent to identifying clinical COPD, the latter requiring a compatible clinical presentation including the presence of relevant symptoms.(17) The systematic reviews in Chapters 2 and 3 provide evidence on alternative strategies for identifying clinical COPD that are likely to be more efficient than performing spirometry on a population-wide basis. They also highlight that although the majority of patients identified through case finding have mild disease, a significant proportion (~20%) actually have moderate-to-severe disease who would likely benefit from evidence based interventions recommended in national and international guidelines.(17, 19)

An analysis of the Health Survey for England suggested that targeted case finding among symptomatic smokers aged over 40 years would be more efficient than general population screening and over three quarters of those diagnosed with COPD could benefit from further treatment such as smoking cessation support, pulmonary rehabilitation, immunisations and inhaled therapies.(4) There is also some limited evidence from subgroup analyses of RCTs that patients with mild-to-moderate disease may benefit from inhaled pharmacotherapy, (20, 21) including reductions in exacerbations and improved health status compared to placebo, although this is currently an area of ongoing research. Patients with mild-to-moderate COPD have impaired health status,(22) reduced physical activity,(23) and a higher mortality risk than people without COPD.(24) Early intervention among these patients may improve COPD-related morbidity and mortality (25) and this should be evaluated prospectively in RCTs that primarily recruit patients with mild-to-moderate disease (GOLD stage I-II).

The UK National Screening Committee recently reviewed and recommended against screening for COPD due to a lack of RCTs, insufficient evidence on outcomes from early intervention, uncertainty on the comparative effectiveness of alternative screening tests, and incomplete implementation of current prevention activities.(6) The report however also concluded that case finding among symptomatic individuals with more developed COPD is cost-effective and should continue. The findings from the systematic reviews in this thesis agree that there are indeed a lack of RCTs and those that have been conducted are highly heterogeneous. However they also offer suggestions for the design of future trials evaluating the effectiveness of alternative case finding strategies and partly bridge the evidence gap by synthesising the

findings of previous case finding studies, summarising evidence on target populations, recruitment methods, and screening tests. This is currently the most comprehensive evaluation of alternative strategies for COPD case finding in primary care and should offer important information to be considered in future policy reviews.

7.3 Implications for policy, practice and research

The findings from this thesis suggest that handheld flow meters (e.g. COPD-6®) are a more accurate screening test than the CDQ for detecting patients with airflow limitation and potentially clinical COPD. Opportunistic invitation of ever smokers with a history of respiratory symptoms (or lower respiratory tract infections) to a screening assessment using either a respiratory questionnaire (e.g. CDQ) or handheld flow meter, and referring those with a positive test for diagnostic assessment, may be more efficient for identifying patients with undiagnosed COPD than directly inviting all ever smokers for diagnostic spirometry. However this should be evaluated in rigorously conducted RCTs that address the methodological limitations highlighted in the systematic reviews (Chapters 2 and 3), particularly ensuring that COPD is defined clinically (as opposed to just physiologically).

Another way to potentially improve the efficiency of case finding is to stratify patients according to their risk of undiagnosed COPD using routinely recorded data from electronic health records. This could enable primary care services to select patients at the highest risk of undiagnosed disease who would most likely benefit from further clinical assessment. The newly developed and externally validated TargetCOPD model can be used to estimate the risk of undiagnosed COPD among patients in primary care using routine data from electronic health records. Use of this model may

further improve the efficiency of case finding although this should first be validated in other populations and empirically tested in RCTs to evaluate its impact on clinical outcomes and costs before recommendations on its use in routine practice can be made.

Modelled estimates suggest that use of the TargetCOPD model to identify and select high risk patients could significantly reduce the number of screening and diagnostic assessments needed for each new case detected (Table 7.1). For example, use of the model to select high risk patients and invitation of those with a predicted risk of ≥7.5% for a screening assessment with handheld flow meters may reduce the number of screening assessments from 23 to 9 and diagnostic assessments from 5 to 3 per case detected. This could be empirically tested in a cluster RCT (clustering by general practices) comparing routine care against targeted case finding using the TargetCOPD model to identify high risk patients before offering a screening or diagnostic assessment. The effectiveness of this approach could be measured by the number of new diagnoses of COPD, cost per additional case detected, impact on clinical care (e.g. access to smoking cessation services and pulmonary rehabilitation), and clinical outcomes such as smoking quit rates, hospitalisations, and health related quality of life. If shown to be clinically useful, the TargetCOPD model could be readily applied by integrating it with clinical information systems. The cut-point used by the model to prompt referral for further clinical assessment could be determined by the available service capacity within primary care and by cost-effectiveness analyses.

The capacity within primary care to undertake case finding for COPD needs to be evaluated, including access to community respiratory services, diagnostic spirometry,

and education and training on community respiratory medicine. This may be particularly important for contextualising the findings of the ongoing National COPD Audit programme.(26) More must also be done to gauge the general public's awareness of COPD, including its symptoms, and gain a patient perspective on case finding. This could help inform future strategies for improving awareness of the condition, which may help patients with undiagnosed disease access the appropriate care in a timelier manner.

The findings of this thesis can only be used to comment on the effectiveness of approaches to case finding in terms of their accuracy and yield, as well as the views of health professionals. However they cannot be used to comment on the clinical benefits of case finding such as impact on health-related quality of life and disease prognosis. These must first be evaluated through long-term prospective studies before firm recommendations on the early detection of COPD can be made.

Table 7.1 Modelled estimates of screening for COPD among patients aged over 40 years with no prior diagnosis

Patient selection	Screening test	Diagnostic test	Sensitivity	Specificity	NNS*	NND*
Ever smokers	None	Spirometry	100	100	N/A	19
Ever smokers	COPD Diagnostic Questionnaire (cut-point ≥19.5)**	Spirometry	64.5	65.2	29	11
Ever smokers	Handheld flow meter**	Spirometry	79.9	84.4	23	5
TargetCOPD model (cut-point ≥7.5%)	None	Spirometry	68.8	68.8	N/A	7
TargetCOPD model (cut-point ≥7.5%)	Handheld flow meter**	Spirometry	45.5	96.8	9	3

NNS=number-needed-to-screen to identify one patient with undiagnosed COPD
NND=number of diagnostic assessments needed for each new case of COPD detected
*Based on a prevalence of undiagnosed COPD of 5.5%
**Based on the meta-analyses in Chapter 2
NB. Estimates do not consider patient response/uptake

7.4 Strengths and limitations

Evidence on the diagnostic accuracy of screening tests for COPD and the effectiveness of case finding approaches were evaluated in two systematic reviews. Each review followed a robust peer reviewed protocol (27) which should minimise bias in the inclusion, appraisal and synthesis of the evidence. However the test accuracy review (Chapter 2) only included evidence on screening questionnaires and handheld flow meters since studies evaluating other screening tests such as peak flow meters and chest radiography did not meet the pre-specified inclusion criteria. The findings of both reviews should be interpreted in light of the quality of the included evidence. As was previously highlighted, included studies were largely non-comparative and were highly heterogeneous with several important limitations in design such as poor reporting of eligible populations and indeterminate results, and lack of blinding between index and reference tests. Importantly, studies often used a physiological definition of COPD, most commonly using the fixed ratio of FEV_1/FVC to define airflow obstruction, whereas clinical guidelines recommend using a definition that also includes presence of compatible symptoms, and/or relevant risk factors.(17)

The clinical score reported in Chapter 4 was developed from a large primary care database and explored a wide range of risk factors that was informed by an extensive literature search. The main limitation of this score was that it was based on predicting COPD that had been diagnosed through routine practice. The accuracy of this case definition was likely to be affected by both under-diagnosis and misdiagnosis.(3, 14) Another important limitation was that age and sex were not

examined as predictors since these had been used as matching factors in the case control data. Nevertheless the findings from this chapter were instrumental in informing the development of the TargetCOPD model. The latter attempted to overcome these limitations by using data from a large cluster randomised case finding trial (15) that performed quality controlled spirometry assessments among symptomatic patients with no prior diagnosis of COPD and used a strict definition of airflow obstruction that accounted for age, sex and ethnicity biases in lung function.(16) This also allowed evaluation of age and sex as potential predictors. Key strengths of the model are that it showed good discrimination characteristics when externally validated, and relies entirely on routinely recorded data from electronic health records to estimate absolute risk of undiagnosed COPD, enabling its potential integration with primary care clinical information systems.

Another strength of this programme of work has been the mixed methods approach to evaluating the question of how to improve case finding for COPD in primary care. In addition to the quantitative research conducted through the systematic reviews and the risk prediction modelling studies, a qualitative study was also conducted to gain a health services perspective on the potential benefits and harms of case finding as well as the barriers and facilitators encountered in everyday general practice.

7.5 Further planned research

I began my academic journey on the epidemiology of COPD by conducting a pilot RCT comparing two approaches to case finding in primary care (Figure 7.1).(28) This led to the development of the series of interlinked studies incorporated in this thesis. Undertaking this programme of work has similarly sparked ideas for ongoing

research which I hope to achieve in collaboration with the Birmingham Lung Improvement Studies (BLISS) programme. Below is an outline of some of the future projects I am considering.

Although findings from the systematic review in Chapter 3 suggest that screening symptomatic ever smokers with either questionnaires or handheld flow meters may improve the efficiency of case finding, it did not consider the use of risk prediction models to select high risk patients, or consider costs. Although the NICE guidelines did include a cost-effectiveness analysis of opportunistic case finding, this included a fairly simple model using limited assumptions.(17) Therefore a robust economic model incorporating evidence from the systematic reviews in chapters 2 and 3 as well as future trials, and that includes detailed sensitivity analyses, is needed to further help inform policy makers on the optimal approach to case finding for COPD.

Data on a subset of 13 practices enrolled in the TargetCOPD trial (29) were used for the development and validation of the TargetCOPD model. The BLISS programme intends to extract data on all 26 practices enrolled in the case finding arm of the trial, which offers an opportunity to validate and revise the model using a larger sample size, and potentially investigate a wider range of risk factors.

Healthcare providers participating in the TargetCOPD trial were informed of patients meeting the study definition of COPD. The BLISS programme plans to collect data relevant to the management of these patients, which will enable their quality of care to be audited against clinical guideline recommendations and NICE standards.(30) This is a critical aspect of case finding since one of its main purposes is to enable early access to care in order to improve quality of life and disease prognosis.

Associations between practice and patient factors and the quality of care received can also be explored. In addition, patients identified with COPD through the TargetCOPD trial have been entered into a large cohort study (the Birmingham COPD Cohort), which will enable comparison of their clinical outcomes with those identified through routine care.

The COPD Assessment Test (CAT) has been widely evaluated for the assessment of health-related quality of life in patients with COPD (31) and was completed by participants attending spirometry assessments in the TargetCOPD trial.(29) This offers an opportunity to assess the accuracy of the CAT questionnaire as a potential screening tool for COPD, although this can only be tested among patients who explicitly reported experiencing chronic respiratory symptoms.(32)

Finally, the feasibility and effectiveness of the TargetCOPD model should be evaluated in a cluster RCT to assess its impact on clinical practice and patient outcomes. One potential trial suggested above could involve evaluating the effectiveness of a multistage screening process in which high risk patients are initially identified using the TargetCOPD model, and then invited for screening assessments using handheld flow meters and/or screening questionnaires, before referral for a full diagnostic assessment.

7.6 Conclusions

Handheld flow meters have higher test accuracy than the COPD Diagnostic Questionnaire for identifying patients with undiagnosed airflow limitation and potentially clinical COPD. Opportunistic invitation of symptomatic ever smokers to undertake screening assessments, using either screening questionnaires or

handheld flow meters, followed by diagnostic assessment in those with a positive screening test, may be more efficient for identifying undiagnosed COPD than directly inviting all ever smokers for diagnostic spirometry. However the quality of the available evidence is limited and there is a need for well conducted RCTs directly comparing the effectiveness of different case finding strategies.

The TargetCOPD model has been developed to help stratify patients in primary care according to their risk of undiagnosed COPD using routine data from electronic health records. External validation of this model has shown that it can discriminate between patients with and without COPD reasonably well and may help primary care services identify patients at high risk who could be targeted for systematic case finding. However it still needs to be validated in other populations before its routine use can be recommended.

The capacity of primary care services to undertake case finding needs to be evaluated, including access to community respiratory services and the education and training needs of healthcare professionals on COPD and diagnostic assessment. Further research is also needed to compare alternative case finding strategies through high quality RCTs, model their cost-effectiveness including potential clinical benefits and harms, and evaluate the management and outcomes of patients who are diagnosed with COPD through case finding.

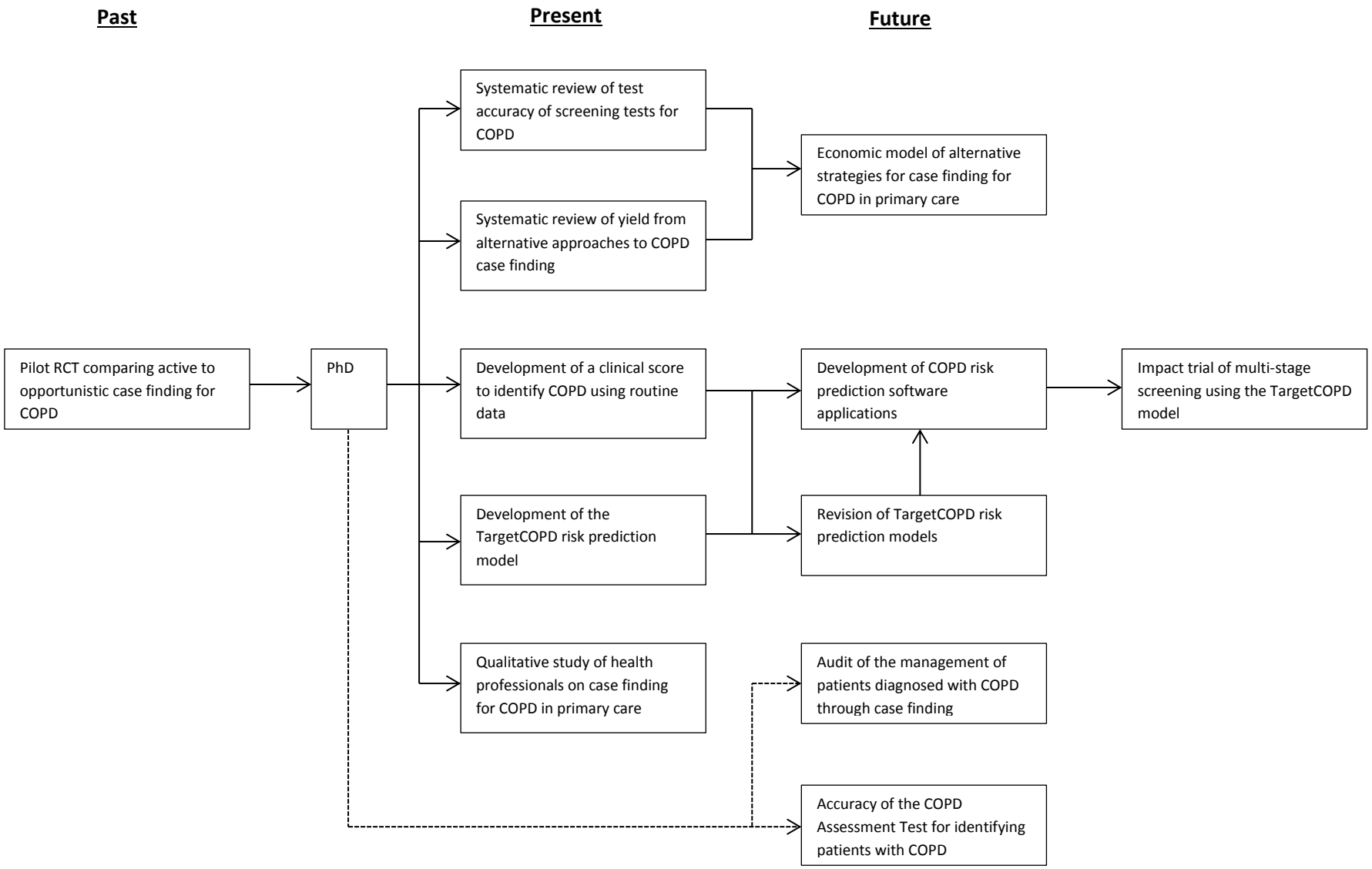

Figure 7.1 My academic journey in COPD epidemiology

7.7 References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
2. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-223.
3. Soriano J, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. Lancet. 2009;374(9691):721 - 32.
4. Jordan R, Lam K-B, Cheng K, Miller M, Marsh J, Ayres J, et al. Case finding for chronic obstructive pulmonary disease: a model for optimizing a targeted approach. Thorax. 2010;65:492 - 8.
5. An outcomes strategy for people with chronic obstructive pulmonary disease (COPD) and asthma in England London: Department of Health; 2011 [cited 2013 29/10/2013]. Available from: https://www.gov.uk/government/publications/an-outcomes-strategy-for-people-with-chronic-obstructive-pulmonary-disease-copd-and-asthma-in-england.
6. Cartwright S. An evaluation of screening for COPD against the National Screening Committee criteria. 2012.
7. Price DB, Tinkelman DG, Halbert RJ, Nordyke RJ, Isonaka S, Nonikov D, et al. Symptom-based questionnaire for identifying COPD in smokers. Respiration. 2006;73(3):285-95.
8. Price DB, Tinkelman DG, Nordyke RJ, Isonaka S, Halbert RJ, Group CQS. Scoring system and clinical application of COPD diagnostic questionnaires. Chest. 2006;129(6):1531-9.
9. Frith P, Crockett A, Beilby J, Marshall D, Attewell R, Ratnanesan A, et al. Simplified COPD screening: validation of the PiKo-6(R) in primary care. Prim Care Respir J. 2011;20(2):190-8, 2 p following 8.
10. Sichletidis L, Spyratos D, Papaioannou M, Chloros D, Tsiotsios A, Tsagaraki V, et al. A combination of the IPAG questionnaire and PiKo-6(R) flow meter is a valuable screening tool for COPD in the primary care setting. Prim Care Respir J. 2011;20(2):184-9, 1 p following 9.
11. Kotz D, Nelemans P, van Schayck CP, Wesseling GJ. External validation of a COPD diagnostic questionnaire. Eur Respir J. 2008;31(2):298-303.
12. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008;336(7659):1475-82.
13. Mapel D, Frost F, Hurly J, Petersen H, Roberts M, Marton J, et al. An algorithm for the identification of undiagnsoed COPD cases using administrative claims data. J Manag Care Pharm. 2006;12(6):458 - 65.
14. Walters JA, Walters EH, Nelson M, Robinson A, Scott J, Turner P, et al. Factors associated with misdiagnosis of COPD in primary care. Prim Care Respir J. 2011;20(4):396-402.
15. Jordan RE, Adab P, Jowett S, Marsh J, Riley R, Enocson A, et al. TargetCOPD: a pragmatic randomised controlled trial of targeted case finding for COPD versus routine practice in primary care: protocol. BMC pulmonary medicine. 2014;14(1):157.
16. Quanjer P, Stanojevic S, Cole T, Baur X, Hall G, Culver B, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40:1324 - 43.
17. Chronic obstructive pulmonary disease : management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Institute for Health and Clinical Excellence; 2010.
18. Lin K, Watkins B, Johnson T, Rodriguez JA, Barton MB, Force USPST. Screening for chronic obstructive pulmonary disease using spirometry: summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;148(7):535-43.
19. Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, managment, and prevention of chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease, 2013.
20. Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin D, et al. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. Lancet. 2009;374(9696):1171 - 8.
21. Jenkins CR, Jones PW, Calverley PM, Celli B, Anderson JA, Ferguson GT, et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respir Res. 2009;10:59.
22. Jones PW, Brusselle G, Dal Negro RW, Ferrer M, Kardos P, Levy ML, et al. Properties of the COPD assessment test in a cross-sectional European study. Eur Respir J. 2011;38(1):29-35.

23. Troosters T, Sciurba F, Battaglia S, Langer D, Valluri SR, Martino L, et al. Physical inactivity in patients with COPD, a controlled multi-center pilot-study. Respiratory medicine. 2010;104(7):1005-11.
24. Mannino DM, Doherty DE, Sonia Buist A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. Respiratory medicine. 2006;100(1):115-22.
25. Maltais F, Dennis N, Chan CK. Rationale for earlier treatment in COPD: a systematic review of published literature in mild-to-moderate COPD. Copd. 2013;10(1):79-103.
26. National Chronic Obstructive Pulmonary Disease (COPD) Audit Programme London: Royal College of Physicians; 2014 [cited 2014 05.12.2014]. Available from: https://www.rcplondon.ac.uk/projects/national-copd-audit-programme-starting-2013.
27. Haroon SM, Adab PA, Jordan RE. Case finding for COPD in primary care: a systematic review. Prim Care Respir J. 2012;21(3):354-7.
28. Haroon S, Adab P, Griffin C, Jordan R. Case finding for chronic obstructive pulmonary disease in primary care: a pilot randomised controlled trial. Brit J Gen Pract. 2013;63(606).
29. Jordan R, Adab P, Jowett S, Marsh J, Riley R, Enocson A, et al. TargetCOPD: a pragmatic randomised controlled trial of targeted case finding for COPD versus routine practice in primary care: protocol. BMC Pulmonary Medicine. 2014;14(1):157.
30. NICE. Chronic obstructive pulmonary disease quality standard. Manchester: National Institute for Health and Care Excellence; 2011.
31. Gupta N, Pinto LM, Morogan A, Bourbeau J. The COPD assessment test: a systematic review. Eur Respir J. 2014;44(4):873-84.
32. Haroon S, Jordan RE, Enocson A, Fitzmaurice D, Adab P. Detecting COPD Amongst Symptomatic Patients In Primary Care: A Comparison Of The COPD Assessment Test And The COPD Diagnostic Questionnaire. B43 COPD: SCREENING AND DIAGNOSTIC TOOLS. American Thoracic Society International Conference Abstracts: American Thoracic Society; 2014. p. A2957-A.

Appendix 1: PRISMA checklist for Chapter 2

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	27
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	27
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	29
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	29
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	30
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	30
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	30
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	30, 31
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	31

Section/topic	#	Checklist item	Reported on page #
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	31
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	31
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	32
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	30
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	32
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	32
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	34, 35
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	34, 36, 37, 52, 56, 60
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	38, 39, 40, 62
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	41, 42, 44, 56, 60
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	41, 43, 44, 46
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	45
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	47
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	49
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	51
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Acknowledgements

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Appendix 2: PRISMA checklist for Chapter 3

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	65
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	65
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	67
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	67
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	69
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	69
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	69
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	30, 31
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	69

Section/topic	#	Checklist item	Reported on page #
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	69
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	69
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	70
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	69, 70
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	70
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	70
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	71
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	72, 81, 93
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	77
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	79, 83, 84, 105, 115, 121
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	85
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	85
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	87
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	89
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	92
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Acknowledgements

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Appendix 3: TRIPOD Checklist for Chapter 3: Prediction Model Development and Validation

Section/Topic	tem		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	126
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	126
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	128
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	128
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	130
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	130
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	130
	5b	D;V	Describe eligibility criteria for participants.	130
	5c	D;V	Give details of treatments received, if relevant.	N/A
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	130
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	7a	D;V	Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured.	130, 131, 132
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A
Sample size	8	D;V	Explain how the study size was arrived at.	131
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	133
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	133
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	133
	10c	V	For validation, describe how the predictions were calculated.	133
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	133
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N/A

Section/Topic	tem		Checklist Item	Page
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	133
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	135
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	135, 137, 138
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	135, 141
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	135
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	137, 138
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	135, 139
	15b	D	Explain how to use the prediction model.	139
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	136
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	N/A
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	149
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	N/A
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	146, 151
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	150
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	N/A
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	Acknowledgements

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V.

Appendix 4: References of published studies on risk factors for COPD

1. Aboussouan LS, Stoller JK. Detection of alpha-1 antitrypsin deficiency: a review. Secondary Detection of alpha-1 antitrypsin deficiency: a review 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19013782.
2. Abusaid GH, Barbagelata A, Tuero E, Mahmood A, Sharma G. Diastolic dysfunction and COPD exacerbation. Secondary Diastolic dysfunction and COPD exacerbation 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19641273.
3. Agarwal R, Hazarika B, Gupta D, Aggarwal AN, Chakrabarti A, Jindal SK. Aspergillus hypersensitivity in patients with chronic obstructive pulmonary disease: COPD as a risk factor for ABPA? Secondary Aspergillus hypersensitivity in patients with chronic obstructive pulmonary disease: COPD as a risk factor for ABPA? 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20370368.
4. Agusti A. Systemic effects of COPD: just the tip of the Iceberg. Secondary Systemic effects of COPD: just the tip of the Iceberg 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18671145.
5. Agusti A, Celli B. Avoiding confusion in COPD: from risk factors to phenotypes to measures of disease characterisation. Secondary Avoiding confusion in COPD: from risk factors to phenotypes to measures of disease characterisation 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21965497.
6. Al Ghobain M, Al-Hajjaj MS, Wali SO. Prevalence of chronic obstructive pulmonary disease among smokers attending primary healthcare clinics in Saudi Arabia. Secondary Prevalence of chronic obstructive pulmonary disease among smokers attending primary healthcare clinics in Saudi Arabia 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21403413.
7. Al Zaabi A, Asad F, Abdou J, et al. Prevalence of COPD in Abu Dhabi, United Arab Emirates. Secondary Prevalence of COPD in Abu Dhabi, United Arab Emirates 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21216136.
8. Alexander RE, Grogan DM. Management of dental patients with obstructive lung diseases. Secondary Management of dental patients with obstructive lung diseases 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18481611.
9. Al-shair K, Kolsum U, Dockry R, Morris J, Singh D, Vestbo J. Biomarkers of systemic inflammation and depression and fatigue in moderate clinically stable COPD. Secondary Biomarkers of systemic inflammation and depression and fatigue in moderate clinically stable COPD 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21208443.
10. Andersen ZJ, Hvidberg M, Jensen SS, et al. Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study. Secondary Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20870755.
11. Andreas S, Anker SD, Scanlon PD, Somers VK. Neurohumoral activation as a link to systemic manifestations of chronic lung disease. Secondary Neurohumoral activation as a link to systemic manifestations of chronic lung disease 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16304321.
12. Andreas S, Hering T, Muhlig S, Nowak D, Raupach T, Worth H. Smoking cessation in chronic obstructive pulmonary disease: an effective medical intervention. Secondary Smoking cessation in chronic obstructive pulmonary disease: an effective medical intervention 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19547629.
13. Aniwidyaningsih W, Varraso R, Cano N, Pison C. Impact of nutritional status on body functioning in chronic obstructive pulmonary disease and how to intervene. Secondary Impact of nutritional status on body functioning in chronic obstructive pulmonary disease and how to intervene 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18542004.
14. Anto JM, Vermeire P, Vestbo J, Sunyer J. Epidemiology of chronic obstructive pulmonary disease. Secondary Epidemiology of chronic obstructive pulmonary disease 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11488336.
15. Aoshiba K, Nagai A. An evolutionary perspective on chronic obstructive pulmonary disease. Secondary An evolutionary perspective on chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19843710.
16. Avino P, De Lisio V, Grassi M, et al. Influence of air pollution on chronic obstructive respiratory diseases: comparison between city (Rome) and hillcountry environments and climates. Secondary Influence of air pollution on chronic obstructive respiratory diseases: comparison between city (Rome) and hillcountry environments and climates 2004.

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15506613.
17. Azarpazhooh A, Leake JL. Systematic review of the association between respiratory diseases and oral health. Secondary Systematic review of the association between respiratory diseases and oral health 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16945022.
18. Bahadori K, FitzGerald JM, Levy RD, Fera T, Swiston J. Risk factors and outcomes associated with chronic obstructive pulmonary disease exacerbations requiring hospitalization. Secondary Risk factors and outcomes associated with chronic obstructive pulmonary disease exacerbations requiring hospitalization 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19707601.
19. Bailey KL, Meza JL, Smith LM, Von Essen SG, Romberger DJ. Agricultural exposures in patients with COPD in health systems serving rural areas. Secondary Agricultural exposures in patients with COPD in health systems serving rural areas 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=19042672.
20. Bakke PS. Factors affecting growth of FEV1. Secondary Factors affecting growth of FEV1 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=14635497.
21. Balkissoon R, Lommatzsch S, Carolan B, Make B. Chronic obstructive pulmonary disease: a concise review. Secondary Chronic obstructive pulmonary disease: a concise review 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22032431.
22. Balmes J, Becklake M, Blanc P, et al. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. Secondary American Thoracic Society Statement: Occupational contribution to the burden of airway disease 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12598220.
23. Balmes JR. Occupational contribution to the burden of chronic obstructive pulmonary disease. Secondary Occupational contribution to the burden of chronic obstructive pulmonary disease 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15706175.
24. Barbee RA. The effects of gender on the development of chronic obstructive pulmonary disease. Secondary The effects of gender on the development of chronic obstructive pulmonary disease 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16679749.
25. Bartal M. COPD and tobacco smoke. Secondary COPD and tobacco smoke 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16454221.
26. Bartolomeo N, Trerotoli P, Serio G. Lung cancer and COPD rates in Apulia: a multilevel multimember model for smoothing disease mapping. Secondary Lung cancer and COPD rates in Apulia: a multilevel multimember model for smoothing disease mapping 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20205714.
27. Baughman P, Marott JL, Lange P, Andrew M, Hnizdo E. Health outcomes associated with lung function decline and respiratory symptoms and disease in a community cohort. Secondary Health outcomes associated with lung function decline and respiratory symptoms and disease in a community cohort 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21495838.
28. Beaumont JL, Victorson D, Su J, et al. Examining web equivalence and risk factor sensitivity of the COPD population screener. Secondary Examining web equivalence and risk factor sensitivity of the COPD population screener 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21669376.
29. Benfield T, Lange P, Vestbo J. COPD stage and risk of hospitalization for infectious disease. Secondary COPD stage and risk of hospitalization for infectious disease 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18403661.
30. Bentham JR, Shaw NJ. Some chronic obstructive pulmonary disease will originate in neonatal intensive care units. Secondary Some chronic obstructive pulmonary disease will originate in neonatal intensive care units 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15698812.
31. Bentley AR, Emrani P, Cassano PA. Genetic variation and gene expression in antioxidant related enzymes and risk of COPD: a systematic review. Secondary Genetic variation and gene expression in antioxidant related enzymes and risk of COPD: a systematic review 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18566111.
32. Biggeri A, Pasetto R, Belli S, et al. Mortality from chronic obstructive pulmonary disease and pleural mesothelioma in an area contaminated by natural fiber (fluoro-edenite). Secondary Mortality from chronic obstructive pulmonary disease and pleural mesothelioma in an area contaminated by natural fiber (fluoro-edenite) 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15250654.
33. Birring SS, Pavord ID. COPD: an autoimmune disease? Secondary COPD: an autoimmune disease? 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21804172.
34. Blanc PD, Eisner MD, Trupin L, Yelin EH, Katz PP, Balmes JR. The association between occupational factors and adverse health outcomes in chronic obstructive pulmonary disease. Secondary The association between occupational factors and adverse health outcomes in chronic obstructive pulmonary disease 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15258271.

35. Blanc PD, Iribarren C, Trupin L, et al. Occupational exposures and the risk of COPD: dusty trades revisited. Secondary Occupational exposures and the risk of COPD: dusty trades revisited 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18678700.
36. Blanc PD, Menezes AMB, Plana E, et al. Occupational exposures and COPD: an ecological analysis of international data. Secondary Occupational exposures and COPD: an ecological analysis of international data 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19010980.
37. Blanc PD, Toren K. Occupation in chronic obstructive pulmonary disease and chronic bronchitis: an update. Secondary Occupation in chronic obstructive pulmonary disease and chronic bronchitis: an update 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17352088.
38. Blecker S, Matsushita K, Fox E, et al. Left ventricular dysfunction as a risk factor for cardiovascular and noncardiovascular hospitalizations in African Americans. Secondary Left ventricular dysfunction as a risk factor for cardiovascular and noncardiovascular hospitalizations in African Americans 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20826258.
39. Blum A, Simsolo C, Sirchan R, Haiek S. "Obesity paradox" in chronic obstructive pulmonary disease. Secondary "Obesity paradox" in chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22279700.
40. Boggia B, Farinaro E, Grieco L, Lucariello A, Carbone U. Burden of smoking and occupational exposure on etiology of chronic obstructive pulmonary disease in workers of Southern Italy. Secondary Burden of smoking and occupational exposure on etiology of chronic obstructive pulmonary disease in workers of Southern Italy 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18332787.
41. Bohadana A, Teculescu D, Martinet Y. Mechanisms of chronic airway obstruction in smokers. Secondary Mechanisms of chronic airway obstruction in smokers 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=14971877.
42. Boots AW, Haenen GRMM, Bast A. Oxidant metabolism in chronic obstructive pulmonary disease. Secondary Oxidant metabolism in chronic obstructive pulmonary disease 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=14621103.
43. Borge CR, Wahl AK, Moum T. Pain and quality of life with chronic obstructive pulmonary disease. Secondary Pain and quality of life with chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21444112.
44. Bowler RP, Canham ME, Ellison MC. Surface enhanced laser desorption/ionization (SELDI) time-of-flight mass spectrometry to identify patients with chronic obstructive pulmonary disease. Secondary Surface enhanced laser desorption/ionization (SELDI) time-of-flight mass spectrometry to identify patients with chronic obstructive pulmonary disease 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17175664.
45. Branden E, Koyi H, Gnarpe J, Gnarpe H, Tornling G. Chronic Chlamydia pneumoniae infection is a risk factor for the development of COPD. Secondary Chronic Chlamydia pneumoniae infection is a risk factor for the development of COPD 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15672844.
46. Brehm JM, Hagiwara K, Tesfaigzi Y, et al. Identification of FGF7 as a novel susceptibility locus for chronic obstructive pulmonary disease. Secondary Identification of FGF7 as a novel susceptibility locus for chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21921092.
47. Bridevaux PO, Gerbase MW, Schindler C, et al. Sex-specific effect of body weight gain on systemic inflammation in subjects with COPD: results from the SAPALDIA cohort study 2. Secondary Sex-specific effect of body weight gain on systemic inflammation in subjects with COPD: results from the SAPALDIA cohort study 2 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19251780.
48. Bruse S, Sood A, Petersen H, et al. New Mexican Hispanic smokers have lower odds of chronic obstructive pulmonary disease and less decline in lung function than non-Hispanic whites. Secondary New Mexican Hispanic smokers have lower odds of chronic obstructive pulmonary disease and less decline in lung function than non-Hispanic whites 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21908412.
49. Bryden C, Bird W, Titley HA, Halpin DMG, Levy ML. Stratification of COPD patients by previous admission for targeting of preventative care. Secondary Stratification of COPD patients by previous admission for targeting of preventative care 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19138504.
50. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. Secondary Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12797497.
51. Budulac SE, Postma DS, Hiemstra PS, et al. Multidrug resistance-associated protein-1 (MRP1) genetic variants,

MRP1 protein levels and severity of COPD. Secondary Multidrug resistance-associated protein-1 (MRP1) genetic variants, MRP1 protein levels and severity of COPD 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20487524.
52. Buist AS, Vollmer WM, McBurnie MA. Worldwide burden of COPD in high- and low-income countries. Part I. The burden of obstructive lung disease (BOLD) initiative. Secondary Worldwide burden of COPD in high- and low-income countries. Part I. The burden of obstructive lung disease (BOLD) initiative 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18544191.
53. Bursi F, Vassallo R, Weston SA, Killian JM, Roger VL. Chronic obstructive pulmonary disease after myocardial infarction in the community. Secondary Chronic obstructive pulmonary disease after myocardial infarction in the community 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20598978.
54. Bush A. Childhood influences on later lung health. Secondary Childhood influences on later lung health 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19029233.
55. Bush A. COPD: a pediatric disease. Secondary COPD: a pediatric disease 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18259975.
56. Butler LM, Koh W-P, Lee H-P, Tseng M, Yu MC, London SJ. On previous findings concerning preserved meat intake and respiratory disease. Secondary On previous findings concerning preserved meat intake and respiratory disease 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17641163.
57. Calverley PMA, Nordyke RJ, Halbert RJ, Isonaka S, Nonikov D. Development of a population-based screening questionnaire for COPD. Secondary Development of a population-based screening questionnaire for COPD 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17136949.
58. Camp PG, O'Donnell DE, Postma DS. Chronic obstructive pulmonary disease in men and women: myths and reality. Secondary Chronic obstructive pulmonary disease in men and women: myths and reality 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19741264.
59. Caramori G, Adcock I. Gene-environment interactions in the development of chronic obstructive pulmonary disease. Secondary Gene-environment interactions in the development of chronic obstructive pulmonary disease 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16954784.
60. Casanova C, de Torres JP, Aguirre-Jaime A, et al. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. Secondary The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21836135.
61. Castagna O, Boussuges A, Nussbaum E, Marqueste L, Brisswalter J. Peripheral arterial disease: an underestimated aetiology of exercise intolerance in chronic obstructive pulmonary disease patients. Secondary Peripheral arterial disease: an underestimated aetiology of exercise intolerance in chronic obstructive pulmonary disease patients 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18446087.
62. Castaldi PJ, Demeo DL, Hersh CP, et al. Impact of non-linear smoking effects on the identification of gene-by-smoking interactions in COPD genetics studies. Secondary Impact of non-linear smoking effects on the identification of gene-by-smoking interactions in COPD genetics studies 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21163806.
63. Cavarra E, Fardin P, Fineschi S, et al. Early response of gene clusters is associated with mouse lung resistance or sensitivity to cigarette smoke. Secondary Early response of gene clusters is associated with mouse lung resistance or sensitivity to cigarette smoke 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19118092.
64. Celik F, Topcu F. Nutritional risk factors for the development of chronic obstructive pulmonary disease (COPD) in male smokers. Secondary Nutritional risk factors for the development of chronic obstructive pulmonary disease (COPD) in male smokers 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16782241.
65. Celli B, Vestbo J, Jenkins CR, et al. Sex differences in mortality and clinical expressions of patients with chronic obstructive pulmonary disease. The TORCH experience. Secondary Sex differences in mortality and clinical expressions of patients with chronic obstructive pulmonary disease. The TORCH experience 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20813884.
66. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. Secondary The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=14999112.
67. Celli BR, Halbert RJ, Nordyke RJ, Schau B. Airway obstruction in never smokers: results from the Third National Health and Nutrition Examination Survey. Secondary Airway obstruction in never smokers: results from the Third National Health and Nutrition Examination Survey 2005.

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16378780.
68. Celli BR, Marin JM, Cote CG, Aguirre A, Macario CC. Prognostic assessment of patients with COPD. Secondary Prognostic assessment of patients with COPD 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19962561.
69. Chan A, Murin S. Up in smoke: the fallacy of the harmless Hookah. Secondary Up in smoke: the fallacy of the harmless Hookah 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21467052.
70. Chan-Yeung M, Ho ASS, Cheung AHK, et al. Determinants of chronic obstructive pulmonary disease in Chinese patients in Hong Kong. Secondary Determinants of chronic obstructive pulmonary disease in Chinese patients in Hong Kong 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17439672.
71. Chapman KR. Chronic obstructive pulmonary disease: are women more susceptible than men? Secondary Chronic obstructive pulmonary disease: are women more susceptible than men? 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15099893.
72. Chapman RS, He X, Blair AE, Lan Q. Improvement in household stoves and risk of chronic obstructive pulmonary disease in Xuanwei, China: retrospective cohort study. Secondary Improvement in household stoves and risk of chronic obstructive pulmonary disease in Xuanwei, China: retrospective cohort study 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16234255.
73. Chappell S, Daly L, Morgan K, et al. Cryptic haplotypes of SERPINA1 confer susceptibility to chronic obstructive pulmonary disease. Secondary Cryptic haplotypes of SERPINA1 confer susceptibility to chronic obstructive pulmonary disease 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16278826.
74. Chappell S, Daly L, Morgan K, et al. Genetic variants of microsomal epoxide hydrolase and glutamate-cysteine ligase in COPD. Secondary Genetic variants of microsomal epoxide hydrolase and glutamate-cysteine ligase in COPD 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18614560.
75. Chen R. Passive smoking exposure and risk of COPD in China. Secondary Passive smoking exposure and risk of COPD in China 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18207011.
76. Chow CK. Consumption of cured meats and risk of chronic obstructive pulmonary disease. Secondary Consumption of cured meats and risk of chronic obstructive pulmonary disease 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19064534.
77. Chung C-W, Wang J-D, Yu C-F, Yang M-C. Lifetime medical expenditure and life expectancy lost attributable to smoking through major smoking related diseases in Taiwan. Secondary Lifetime medical expenditure and life expectancy lost attributable to smoking through major smoking related diseases in Taiwan 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=18048616.
78. Cogo A, Ciaccia A, Legorini C, Grimaldi A, Milani G. Proteinuria in COPD patients with and without respiratory failure. Secondary Proteinuria in COPD patients with and without respiratory failure 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12576398.
79. Coin A, Sergi G, Marin S, et al. Predictors of low bone mineral density in elderly males with chronic obstructive pulmonary disease: the role of body mass index. Secondary Predictors of low bone mineral density in elderly males with chronic obstructive pulmonary disease: the role of body mass index 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20429721.
80. Cordoba-Lanus E, Baz-Davila R, de-Torres JP, et al. TNFA-863 polymorphism is associated with a reduced risk of chronic obstructive pulmonary disease: a replication study. Secondary TNFA-863 polymorphism is associated with a reduced risk of chronic obstructive pulmonary disease: a replication study 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21985478.
81. Cote C, Zilberberg MD, Mody SH, Dordelly LJ, Celli B. Haemoglobin level and its clinical impact in a cohort of patients with COPD. Secondary Haemoglobin level and its clinical impact in a cohort of patients with COPD 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17251227.
82. Cox LAT, Jr. A causal model of chronic obstructive pulmonary disease (COPD) risk. Secondary A causal model of chronic obstructive pulmonary disease (COPD) risk 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20846171.
83. Crothers K. Chronic obstructive pulmonary disease in patients who have HIV infection. Secondary Chronic obstructive pulmonary disease in patients who have HIV infection 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17720045.
84. Crothers K, Butt AA, Gibert CL, et al. Increased COPD among HIV-positive compared to HIV-negative veterans. Secondary Increased COPD among HIV-positive compared to HIV-negative veterans 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17099007.
85. Crothers K, Huang L, Goulet JL, et al. HIV infection and risk for incident pulmonary diseases in the combination

antiretroviral therapy era. Secondary HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20851926.
86. Cui L, Gallagher LG, Ray RM, et al. Unexpected excessive chronic obstructive pulmonary disease mortality among female silk textile workers in Shanghai, China. Secondary Unexpected excessive chronic obstructive pulmonary disease mortality among female silk textile workers in Shanghai, China 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21486992.
87. Curkendall SM, DeLuise C, Jones JK, et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. Secondary Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16039877.
88. Dahl M, Nordestgaard BG. Markers of early disease and prognosis in COPD. Secondary Markers of early disease and prognosis in COPD 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19436688.
89. Dahl M, Tybjaerg-Hansen A, Lange P, Nordestgaard BG. Asthma and COPD in cystic fibrosis intron-8 5T carriers. A population-based study. Secondary Asthma and COPD in cystic fibrosis intron-8 5T carriers. A population-based study 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16212675.
90. Dahl M, Tybjaerg-Hansen A, Vestbo J, Lange P, Nordestgaard BG. Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. Secondary Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11587987.
91. Dam TT, Harrison S, Fink HA, Ramsdell J, Barrett-Connor E, Osteoporotic Fractures in Men Research G. Bone mineral density and fractures in older men with chronic obstructive pulmonary disease or asthma. Secondary Bone mineral density and fractures in older men with chronic obstructive pulmonary disease or asthma 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19816753.
92. Dawkins PA, Dawkins CL, Wood AM, Nightingale PG, Stockley JA, Stockley RA. Rate of progression of lung function impairment in alpha1-antitrypsin deficiency. Secondary Rate of progression of lung function impairment in alpha1-antitrypsin deficiency 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19164359.
93. de la Hoz RE. Occupational asthma and lower airway disease among World Trade Center workers and volunteers. Secondary Occupational asthma and lower airway disease among World Trade Center workers and volunteers 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20424998.
94. de Marco R, Accordini S, Cerveri I, et al. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. Secondary An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=14760151.
95. de Serres FJ, Blanco I, Fernandez-Bustillo E. Estimating the risk for alpha-1 antitrypsin deficiency among COPD patients: evidence supporting targeted screening. Secondary Estimating the risk for alpha-1 antitrypsin deficiency among COPD patients: evidence supporting targeted screening 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17240615.
96. de Torres JP, Campo A, Casanova C, Aguirre-Jaime A, Zulueta J. Gender and chronic obstructive pulmonary disease in high-risk smokers. Secondary Gender and chronic obstructive pulmonary disease in high-risk smokers 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16330871.
97. de Torres JP, Casanova C, Montejo de Garcini A, Aguirre-Jaime A, Celli BR. Gender and respiratory factors associated with dyspnea in chronic obstructive pulmonary disease. Secondary Gender and respiratory factors associated with dyspnea in chronic obstructive pulmonary disease 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17341300.
98. de Vries F, van Staa TP, Bracke MSGM, Cooper C, Leufkens HGM, Lammers JWJ. Severity of obstructive airway disease and risk of osteoporotic fracture. Secondary Severity of obstructive airway disease and risk of osteoporotic fracture 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15863646.
99. Dekhuijzen PNR. The Confronting COPD International Survey: patients hardly know they have COPD. Secondary The Confronting COPD International Survey: patients hardly know they have COPD 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12412664.
100. Dement JM, Welch L, Ringen K, Bingham E, Quinn P. Airways obstruction among older construction and trade workers at Department of Energy nuclear sites. Secondary Airways obstruction among older construction and

trade workers at Department of Energy nuclear sites 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20025074.
101. Demeo DL, Campbell EJ, Barker AF, et al. IL10 polymorphisms are associated with airflow obstruction in severe alpha1-antitrypsin deficiency. Secondary IL10 polymorphisms are associated with airflow obstruction in severe alpha1-antitrypsin deficiency 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=17690329.
102. Deo V, Bhongade ML, Ansari S, Chavan RS. Periodontitis as a potential risk factor for chronic obstructive pulmonary disease: a retrospective study. Secondary Periodontitis as a potential risk factor for chronic obstructive pulmonary disease: a retrospective study 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20139573.
103. Deveci F, Deveci SE, Turkoglu S, et al. The prevalence of chronic obstructive pulmonary disease in Elazig, Eastern Turkey. Secondary The prevalence of chronic obstructive pulmonary disease in Elazig, Eastern Turkey 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21402248.
104. Dhungel S, Paudel B, Shah S. Study of prevalence of hypertension in Chronic Obstructive Pulmonary Disease patients admitted at Nepal Medical College and Teaching Hospital. Secondary Study of prevalence of hypertension in Chronic Obstructive Pulmonary Disease patients admitted at Nepal Medical College and Teaching Hospital 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16519071.
105. Diaz-Guzman E, Mannino DM. Airway obstructive diseases in older adults: from detection to treatment. Secondary Airway obstructive diseases in older adults: from detection to treatment 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20920760.
106. Doehner W, Haeusler KG, Endres M, Anker SD, MacNee W, Lainscak M. Neurological and endocrinological disorders: orphans in chronic obstructive pulmonary disease. Secondary Neurological and endocrinological disorders: orphans in chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22015080.
107. Doehner W, von Haehling S, Anker SD, Lainscak M. Neurohormonal activation and inflammation in chronic cardiopulmonary disease: a brief systematic review. Secondary Neurohormonal activation and inflammation in chronic cardiopulmonary disease: a brief systematic review 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19562289.
108. Duckers JM, Evans BAJ, Fraser WD, Stone MD, Bolton CE, Shale DJ. Low bone mineral density in men with chronic obstructive pulmonary disease. Secondary Low bone mineral density in men with chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21812978.
109. Eagan TM, Damas JK, Ueland T, et al. Neutrophil gelatinase-associated lipocalin: a biomarker in COPD. Secondary Neutrophil gelatinase-associated lipocalin: a biomarker in COPD 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20495108.
110. Eden E. Asthma and COPD in alpha-1 antitrypsin deficiency. Evidence for the Dutch hypothesis. Secondary Asthma and COPD in alpha-1 antitrypsin deficiency. Evidence for the Dutch hypothesis 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20854052.
111. Eduard W, Pearce N, Douwes J. Chronic bronchitis, COPD, and lung function in farmers: the role of biological agents. Secondary Chronic bronchitis, COPD, and lung function in farmers: the role of biological agents 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19318669.
112. Egesten A, Brandt L, Olsson T, et al. Increased prevalence of multiple sclerosis among COPD patients and their first-degree relatives: a population-based study. Secondary Increased prevalence of multiple sclerosis among COPD patients and their first-degree relatives: a population-based study 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18351419.
113. Ehrlich SF, Quesenberry CP, Jr., Van Den Eeden SK, Shan J, Ferrara A. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. Secondary Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19808918.
114. Eisner MD, Anthonisen N, Coultas D, et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. Secondary An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20802169.
115. Eisner MD, Balmes J, Katz PP, Trupin L, Yelin EH, Blanc PD. Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. Secondary Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15890079.

116. Eisner MD, Balmes J, Yelin EH, et al. Directly measured secondhand smoke exposure and COPD health outcomes. Secondary Directly measured secondhand smoke exposure and COPD health outcomes 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16756671.
117. Eisner MD, Iribarren C, Yelin EH, et al. The impact of SHS exposure on health status and exacerbations among patients with COPD. Secondary The impact of SHS exposure on health status and exacerbations among patients with COPD 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19516915.
118. Ekbom A, Brandt L, Granath F, Lofdahl C-G, Egesten A. Increased risk of both ulcerative colitis and Crohn's disease in a population suffering from COPD. Secondary Increased risk of both ulcerative colitis and Crohn's disease in a population suffering from COPD 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18330638.
119. Ekstrom MP, Wagner P, Strom KE. Trends in cause-specific mortality in oxygen-dependent chronic obstructive pulmonary disease. Secondary Trends in cause-specific mortality in oxygen-dependent chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21216882.
120. El Fakir S, Nejjari C, Serhier Z, et al. Alpha 1 antitrypsin phenotypes and obstructive airway disease in subjects over 65 years of age: QUID R cohort. Secondary Alpha 1 antitrypsin phenotypes and obstructive airway disease in subjects over 65 years of age: QUID R cohort 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21791445.
121. Engel RM, Vemulpad S. Progression to chronic obstructive pulmonary disease (COPD): could it be prevented by manual therapy and exercise during the 'at risk' stage (stage 0)? Secondary Progression to chronic obstructive pulmonary disease (COPD): could it be prevented by manual therapy and exercise during the 'at risk' stage (stage 0)? 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19038503.
122. Engstrom G, Segelstorm N, Ekberg-Aronsson M, Nilsson PM, Lindgarde F, Lofdahl CG. Plasma markers of inflammation and incidence of hospitalisations for COPD: results from a population-based cohort study. Secondary Plasma markers of inflammation and incidence of hospitalisations for COPD: results from a population-based cohort study 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18988660.
123. Enright PL, McClelland RL, Buist AS, Lebowitz MD, Cardiovascular Health Study Research G. Correlates of peak expiratory flow lability in elderly persons. Secondary Correlates of peak expiratory flow lability in elderly persons 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11742914.
124. Fabbri LM, Luppi F, Beghe B, Rabe KF. Complex chronic comorbidities of COPD. Secondary Complex chronic comorbidities of COPD 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18166598.
125. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Secondary From COPD to chronic systemic inflammatory syndrome? 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17765529.
126. Falk JA, Kadiev S, Criner GJ, Scharf SM, Minai OA, Diaz P. Cardiac disease in chronic obstructive pulmonary disease. Secondary Cardiac disease in chronic obstructive pulmonary disease 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18453369.
127. Farkas L, Farkas D, Warburton D, et al. Cigarette smoke exposure aggravates air space enlargement and alveolar cell apoptosis in Smad3 knockout mice. Secondary Cigarette smoke exposure aggravates air space enlargement and alveolar cell apoptosis in Smad3 knockout mice 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21743024.
128. Filippone M, Baraldi E. On early life risk factors for COPD. Secondary On early life risk factors for COPD 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21288866.
129. Fimognari FL, Loffredo L, Di Simone S, et al. Hyperhomocysteinaemia and poor vitamin B status in chronic obstructive pulmonary disease. Secondary Hyperhomocysteinaemia and poor vitamin B status in chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19282159.
130. Fimognari FL, Scarlata S, Antonelli-Incalzi R. Why are people with "poor lung function" at increased atherothrombotic risk? A critical review with potential therapeutic indications. Secondary Why are people with "poor lung function" at increased atherothrombotic risk? A critical review with potential therapeutic indications 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19485925.
131. Fischer BM, Pavlisko E, Voynow JA. Pathogenic triad in COPD: oxidative stress, protease-antiprotease imbalance, and inflammation. Secondary Pathogenic triad in COPD: oxidative stress, protease-antiprotease imbalance, and inflammation 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21857781.

132. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. Secondary Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21672193.
133. Fromer L, Barnes T, Garvey C, Ortiz G, Saver DF, Yawn B. Innovations to achieve excellence in COPD diagnosis and treatment in primary care. Secondary Innovations to achieve excellence in COPD diagnosis and treatment in primary care 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20861599.
134. Fujita M, Nakanishi Y. The pathogenesis of COPD: lessons learned from in vivo animal models. Secondary The pathogenesis of COPD: lessons learned from in vivo animal models 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17261992.
135. Fullerton DG, Gordon SB, Calverley PM. Chronic obstructive pulmonary disease in non-smokers. Secondary Chronic obstructive pulmonary disease in non-smokers 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20006126.
136. Fullerton DG, Suseno A, Semple S, et al. Wood smoke exposure, poverty and impaired lung function in Malawian adults. Secondary Wood smoke exposure, poverty and impaired lung function in Malawian adults 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21333109.
137. Funakoshi Y, Omori H, Mihara S, Marubayashi T, Katoh T. Association between airflow obstruction and the metabolic syndrome or its components in Japanese men. Secondary Association between airflow obstruction and the metabolic syndrome or its components in Japanese men 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20930435.
138. Gan WQ, Man SFP, Postma DS, Camp P, Sin DD. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Secondary Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16571126.
139. Gan WQ, Man SFP, Sin DD. The interactions between cigarette smoking and reduced lung function on systemic inflammation. Secondary The interactions between cigarette smoking and reduced lung function on systemic inflammation 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15705996.
140. Garcia RI, Nunn ME, Vokonas PS. Epidemiologic associations between periodontal disease and chronic obstructive pulmonary disease. Secondary Epidemiologic associations between periodontal disease and chronic obstructive pulmonary disease 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11887473.
141. Garcia Rodriguez LA, Ruigomez A, Martin-Merino E, Johansson S, Wallander M-A. Relationship between gastroesophageal reflux disease and COPD in UK primary care. Secondary Relationship between gastroesophageal reflux disease and COPD in UK primary care 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18689591.
142. Garcia Rodriguez LA, Wallander M-A, Tolosa LB, Johansson S. Chronic obstructive pulmonary disease in UK primary care: incidence and risk factors. Secondary Chronic obstructive pulmonary disease in UK primary care: incidence and risk factors 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19863366.
143. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study. Secondary Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17158282.
144. Garcia-Pachon E, Padilla-Navas I, Shum C. Serum uric acid to creatinine ratio in patients with chronic obstructive pulmonary disease. Secondary Serum uric acid to creatinine ratio in patients with chronic obstructive pulmonary disease 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17294336.
145. Giardino ND, Curtis JL, Andrei A-C, et al. Anxiety is associated with diminished exercise performance and quality of life in severe emphysema: a cross-sectional study. Secondary Anxiety is associated with diminished exercise performance and quality of life in severe emphysema: a cross-sectional study 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20214820.
146. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. Secondary Asthma in older adults 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20816547.
147. Gilbert CR, Arum SM, Smith CM. Vitamin D deficiency and chronic lung disease. Secondary Vitamin D deficiency and chronic lung disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19557213.

148. Giltay EJ, Nissinen A, Giampaoli S, Zitman FG, Kromhout D. Low respiratory function increases the risk of depressive symptoms in later life in men. Secondary Low respiratory function increases the risk of depressive symptoms in later life in men 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19933509.
149. Godtfredsen NS, Vestbo J, Osler M, Prescott E. Risk of hospital admission for COPD following smoking cessation and reduction: a Danish population study. Secondary Risk of hospital admission for COPD following smoking cessation and reduction: a Danish population study 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12403880.
150. Goksu E, Oktay C, Kartal M, Oskay A, Sayrac AV. Factors affecting revisit of COPD exacerbated patients presenting to emergency department. Secondary Factors affecting revisit of COPD exacerbated patients presenting to emergency department 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19829119.
151. Gong Y, Fan L, Wan H, et al. Lack of association between the TGF-beta(1) gene and development of COPD in Asians: a case-control study and meta-analysis. Secondary Lack of association between the TGF-beta(1) gene and development of COPD in Asians: a case-control study and meta-analysis 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21556788.
152. Gooneratne NS, Patel NP, Corcoran A. Chronic obstructive pulmonary disease diagnosis and management in older adults. Secondary Chronic obstructive pulmonary disease diagnosis and management in older adults 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20936735.
153. Gouzi F, Prefaut C, Abdellaoui A, et al. Evidence of an early physical activity reduction in chronic obstructive pulmonary disease patients. Secondary Evidence of an early physical activity reduction in chronic obstructive pulmonary disease patients 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21861985.
154. Greene CC, Bradley KA, Bryson CL, et al. The association between alcohol consumption and risk of COPD exacerbation in a veteran population. Secondary The association between alcohol consumption and risk of COPD exacerbation in a veteran population 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18625671.
155. Greene CM, Hassan T, Molloy K, McElvaney NG. The role of proteases, endoplasmic reticulum stress and SERPINA1 heterozygosity in lung disease and alpha-1 anti-trypsin deficiency. Secondary The role of proteases, endoplasmic reticulum stress and SERPINA1 heterozygosity in lung disease and alpha-1 anti-trypsin deficiency 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21702661.
156. Greskevitch M, Kullman G, Bang KM, Mazurek JM. Respiratory disease in agricultural workers: mortality and morbidity statistics. Secondary Respiratory disease in agricultural workers: mortality and morbidity statistics 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=19042666.
157. Groenewegen KH, Postma DS, Hop WCJ, et al. Increased systemic inflammation is a risk factor for COPD exacerbations. Secondary Increased systemic inflammation is a risk factor for COPD exacerbations 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18198263.
158. Grootendorst DC, Rabe KF. Mechanisms of bronchial hyperreactivity in asthma and chronic obstructive pulmonary disease. Secondary Mechanisms of bronchial hyperreactivity in asthma and chronic obstructive pulmonary disease 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16113417.
159. Grzetic-Romcevic T, Devcic B, Sonc S. Spirometric testing on World COPD Day. Secondary Spirometric testing on World COPD Day 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21468166.
160. Guerra S. Overlap of asthma and chronic obstructive pulmonary disease. Secondary Overlap of asthma and chronic obstructive pulmonary disease 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15591882.
161. Guerra S. Asthma and chronic obstructive pulmonary disease. Secondary Asthma and chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19638929.
162. Guinea J, Torres-Narbona M, Gijon P, et al. Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. Secondary Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19906275.
163. Gunen H, Hacievliyagil SS, Yetkin O, Gulbas G, Mutlu LC, Pehlivan E. Prevalence of COPD: first epidemiological study of a large region in Turkey. Secondary Prevalence of COPD: first epidemiological study of a large region in Turkey 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19013377.
164. Hackett T-L, Stefanowicz D, Aminuddin F, et al. Effect of gene environment interactions on lung function and

cardiovascular disease in COPD. Secondary Effect of gene environment interactions on lung function and cardiovascular disease in COPD 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21814463.
165. Hadi HAR, Zubaid M, Al Mahmeed W, et al. Prevalence and prognosis of chronic obstructive pulmonary disease among 8167 Middle Eastern patients with acute coronary syndrome. Secondary Prevalence and prognosis of chronic obstructive pulmonary disease among 8167 Middle Eastern patients with acute coronary syndrome 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20394044.
166. Hallin R, Koivisto-Hursti U-K, Lindberg E, Janson C. Nutritional status, dietary energy intake and the risk of exacerbations in patients with chronic obstructive pulmonary disease (COPD). Secondary Nutritional status, dietary energy intake and the risk of exacerbations in patients with chronic obstructive pulmonary disease (COPD) 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16019198.
167. Halpin DMG, Peterson S, Larsson TP, Calverley PMA. Identifying COPD patients at increased risk of mortality: predictive value of clinical study baseline data. Secondary Identifying COPD patients at increased risk of mortality: predictive value of clinical study baseline data 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18691861.
168. Hanania NA, Mannino DM, Yawn BP, et al. Predicting risk of airflow obstruction in primary care: Validation of the lung function questionnaire (LFQ). Secondary Predicting risk of airflow obstruction in primary care: Validation of the lung function questionnaire (LFQ) 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20226647.
169. Harik-Khan RI, Fleg JL, Wise RA. Body mass index and the risk of COPD. Secondary Body mass index and the risk of COPD 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11834645.
170. Harmsen L, Thomsen SF, Ingebrigtsen T, et al. Chronic mucus hypersecretion: prevalence and risk factors in younger individuals. Secondary Chronic mucus hypersecretion: prevalence and risk factors in younger individuals 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20626952.
171. Hawkins NM, Jhund PS, Simpson CR, et al. Primary care burden and treatment of patients with heart failure and chronic obstructive pulmonary disease in Scotland. Secondary Primary care burden and treatment of patients with heart failure and chronic obstructive pulmonary disease in Scotland 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19951962.
172. Hemminki K, Li X, Sundquist K, Sundquist J. Familial risks for chronic obstructive pulmonary disease among siblings based on hospitalisations in Sweden. Secondary Familial risks for chronic obstructive pulmonary disease among siblings based on hospitalisations in Sweden 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18413451.
173. Hersh CP, Hokanson JE, Lynch DA, et al. Family history is a risk factor for COPD. Secondary Family history is a risk factor for COPD 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21310839.
174. Higenbottam T. Pulmonary hypertension and chronic obstructive pulmonary disease: a case for treatment. Secondary Pulmonary hypertension and chronic obstructive pulmonary disease: a case for treatment 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16113463.
175. Hill K, Goldstein RS, Guyatt GH, et al. Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. Secondary Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20371646.
176. Himes BE, Dai Y, Kohane IS, Weiss ST, Ramoni MF. Prediction of chronic obstructive pulmonary disease (COPD) in asthma patients using electronic medical records. Secondary Prediction of chronic obstructive pulmonary disease (COPD) in asthma patients using electronic medical records 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19261943.
177. Hirayama F, Lee AH, Binns CW, et al. Do vegetables and fruits reduce the risk of chronic obstructive pulmonary disease? A case-control study in Japan. Secondary Do vegetables and fruits reduce the risk of chronic obstructive pulmonary disease? A case-control study in Japan 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19555711.
178. Hirayama F, Lee AH, Oura A, Mori M, Hiramatsu N, Taniguchi H. Dietary intake of six minerals in relation to the risk of chronic obstructive pulmonary disease. Secondary Dietary intake of six minerals in relation to the risk of chronic obstructive pulmonary disease 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21147720.
179. Hirayama F, Lee AH, Terasawa K, Kagawa Y. Folate intake associated with lung function, breathlessness and the prevalence of chronic obstructive pulmonary disease. Secondary Folate intake associated with lung function, breathlessness and the prevalence of chronic obstructive pulmonary disease 2010.

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20199994.
180. Hnizdo E, Vallyathan V. Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. Secondary Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12660371.
181. Hogg JC, Timens W. The pathology of chronic obstructive pulmonary disease. Secondary The pathology of chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18954287.
182. Hokanson JE. COPD and coronary heart disease: challenges in understanding the natural history of common complex chronic diseases. Secondary COPD and coronary heart disease: challenges in understanding the natural history of common complex chronic diseases 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19811368.
183. Holt JB, Zhang X, Presley-Cantrell L, Croft JB. Geographic disparities in chronic obstructive pulmonary disease (COPD) hospitalization among Medicare beneficiaries in the United States. Secondary Geographic disparities in chronic obstructive pulmonary disease (COPD) hospitalization among Medicare beneficiaries in the United States 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21697996.
184. Holt PG, Sly PD. Non-atopic intrinsic asthma and the 'family tree' of chronic respiratory disease syndromes. Secondary Non-atopic intrinsic asthma and the 'family tree' of chronic respiratory disease syndromes 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19400902.
185. Hopkinson NS, Polkey MI. Chronic obstructive pulmonary disease in non-smokers. Secondary Chronic obstructive pulmonary disease in non-smokers 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20006125.
186. Hsieh M-H, Chong I-W, Hwang J-J, et al. Lack of associations between several polymorphisms in cytokine genes and the risk of chronic obstructive pulmonary diseases in Taiwan. Secondary Lack of associations between several polymorphisms in cytokine genes and the risk of chronic obstructive pulmonary diseases in Taiwan 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18364273.
187. Hu Y, Chen B, Yin Z, Jia L, Zhou Y, Jin T. Increased risk of chronic obstructive pulmonary diseases in coke oven workers: interaction between occupational exposure and smoking. Secondary Increased risk of chronic obstructive pulmonary diseases in coke oven workers: interaction between occupational exposure and smoking 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16467069.
188. Hung WW, Wisnivesky JP, Siu AL, Ross JS. Cognitive decline among patients with chronic obstructive pulmonary disease. Secondary Cognitive decline among patients with chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19423714.
189. Hunninghake DB. Cardiovascular disease in chronic obstructive pulmonary disease. Secondary Cardiovascular disease in chronic obstructive pulmonary disease 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16113468.
190. Hurst JR, Donaldson GC, Quint JK, Goldring JJP, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. Secondary Temporal clustering of exacerbations in chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19074596.
191. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. Secondary Susceptibility to exacerbation in chronic obstructive pulmonary disease 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20843247.
192. Hvidsten SC, Storesund L, Wentzel-Larsen T, Gulsvik A, Lehmann S. Prevalence and predictors of undiagnosed chronic obstructive pulmonary disease in a Norwegian adult general population. Secondary Prevalence and predictors of undiagnosed chronic obstructive pulmonary disease in a Norwegian adult general population 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20298413.
193. Hylkema MN, Sterk PJ, de Boer WI, Postma DS. Tobacco use in relation to COPD and asthma. Secondary Tobacco use in relation to COPD and asthma 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17329490.
194. Idolor LF, De Guia TS, Francisco NA, et al. Burden of obstructive lung disease in a rural setting in the Philippines. Secondary Burden of obstructive lung disease in a rural setting in the Philippines 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21801277.
195. Ind PW. COPD disease progression and airway inflammation: uncoupled by smoking cessation. Secondary COPD disease progression and airway inflammation: uncoupled by smoking cessation 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16264034.
196. Isajevs S, Taivans I, Svirina D, Strazda G, Kopeika U. Patterns of inflammatory responses in large and small airways in smokers with and without chronic obstructive pulmonary disease. Secondary Patterns of

inflammatory responses in large and small airways in smokers with and without chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21228544.
197. Ito I, Nagai S, Handa T, et al. Matrix metalloproteinase-9 promoter polymorphism associated with upper lung dominant emphysema. Secondary Matrix metalloproteinase-9 promoter polymorphism associated with upper lung dominant emphysema 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16126934.
198. Izquierdo JL, Martinez A, Guzman E, de Lucas P, Rodriguez JM. Lack of association of ischemic heart disease with COPD when taking into account classical cardiovascular risk factors. Secondary Lack of association of ischemic heart disease with COPD when taking into account classical cardiovascular risk factors 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21103405.
199. Jackson BE, Suzuki S, Lo K, et al. Geographic disparity in COPD hospitalization rates among the Texas population. Secondary Geographic disparity in COPD hospitalization rates among the Texas population 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21255991.
200. Jaen A, Zock JP, Kogevinas M, Ferrer A, Marin A. Occupation, smoking, and chronic obstructive respiratory disorders: a cross sectional study in an industrial area of Catalonia, Spain. Secondary Occupation, smoking, and chronic obstructive respiratory disorders: a cross sectional study in an industrial area of Catalonia, Spain 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16476167.
201. Jiang R, Camargo CA, Jr., Varraso R, Paik DC, Willett WC, Barr RG. Consumption of cured meats and prospective risk of chronic obstructive pulmonary disease in women. Secondary Consumption of cured meats and prospective risk of chronic obstructive pulmonary disease in women 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18400725.
202. Jiang R, Paik DC, Hankinson JL, Barr RG. Cured meat consumption, lung function, and chronic obstructive pulmonary disease among United States adults. Secondary Cured meat consumption, lung function, and chronic obstructive pulmonary disease among United States adults 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17255565.
203. Jimenez-Ruiz C, Miravitlles M, Sobradillo V, et al. Can cumulative tobacco consumption, FTND score, and carbon monoxide concentration in expired air be predictors of chronic obstructive pulmonary disease? Secondary Can cumulative tobacco consumption, FTND score, and carbon monoxide concentration in expired air be predictors of chronic obstructive pulmonary disease? 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15370161.
204. Jindal SK, Aggarwal AN, Chaudhry K, et al. A multicentric study on epidemiology of chronic obstructive pulmonary disease and its relationship with tobacco smoking and environmental tobacco smoke exposure. Secondary A multicentric study on epidemiology of chronic obstructive pulmonary disease and its relationship with tobacco smoking and environmental tobacco smoke exposure 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16482948.
205. Johannessen A, Eagan TML, Omenaas ER, Bakke PS, Gulsvik A. Socioeconomic risk factors for lung function decline in a general population. Secondary Socioeconomic risk factors for lung function decline in a general population 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20150201.
206. Johnson P, Balakrishnan K, Ramaswamy P, et al. Prevalence of chronic obstructive pulmonary disease in rural women of Tamilnadu: implications for refining disease burden assessments attributable to household biomass combustion. Secondary Prevalence of chronic obstructive pulmonary disease in rural women of Tamilnadu: implications for refining disease burden assessments attributable to household biomass combustion 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22065945.
207. Jones A. Causes and effects of chronic obstructive pulmonary disease. Secondary Causes and effects of chronic obstructive pulmonary disease 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11927884.
208. Joo MJ, Au DH, Lee TA. Use of spirometry in the diagnosis of chronic obstructive pulmonary disease and efforts to improve quality of care. Secondary Use of spirometry in the diagnosis of chronic obstructive pulmonary disease and efforts to improve quality of care 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19665686.
209. Joo MJ, Lee TA, Bartle B, van de Graaff WB, Weiss KB. Patterns of healthcare utilization by COPD severity: a pilot study. Secondary Patterns of healthcare utilization by COPD severity: a pilot study 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18463921.
210. Joos L, Pare PD, Sandford AJ. Genetic risk factors of chronic obstructive pulmonary disease. Secondary Genetic risk factors of chronic obstructive pulmonary disease 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11953903.
211. Joost O, Wilk JB, Cupples LA, et al. Genetic loci influencing lung function: a genome-wide scan in the Framingham Study. Secondary Genetic loci influencing lung function: a genome-wide scan in the Framingham Study

2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11897646.
212. Jyrki-Tapani K, Sovijarvi A, Lundback B. Chronic obstructive pulmonary disease in Finland: prevalence and risk factors. Secondary Chronic obstructive pulmonary disease in Finland: prevalence and risk factors 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17146998.
213. Kalucka S. The occurrence of chronic obstructive pulmonary disease (COPD) in cigarette smoking families. Secondary The occurrence of chronic obstructive pulmonary disease (COPD) in cigarette smoking families 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17288170.
214. Kanervisto M, Vasankari T, Laitinen T, Heliovaara M, Jousilahti P, Saarelainen S. Low socioeconomic status is associated with chronic obstructive airway diseases. Secondary Low socioeconomic status is associated with chronic obstructive airway diseases 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21459567.
215. Kaplan Y, Inonu H, Yilmaz A, Ocal S. Restless legs syndrome in patients with chronic obstructive pulmonary disease. Secondary Restless legs syndrome in patients with chronic obstructive pulmonary disease 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18714805.
216. Kasuga I, Hogg JC, Pare PD, et al. Role of genetic susceptibility to latent adenoviral infection and decreased lung function. Secondary Role of genetic susceptibility to latent adenoviral infection and decreased lung function 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19502044.
217. Kauppi P, Kupiainen H, Lindqvist A, et al. Overlap syndrome of asthma and COPD predicts low quality of life. Secondary Overlap syndrome of asthma and COPD predicts low quality of life 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21323613.
218. Kaur-Knudsen D, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. Nicotinic acetylcholine receptor polymorphism, smoking behavior, and tobacco-related cancer and lung and cardiovascular diseases: a cohort study. Secondary Nicotinic acetylcholine receptor polymorphism, smoking behavior, and tobacco-related cancer and lung and cardiovascular diseases: a cohort study 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21646606.
219. Keller CA. Pathophysiology and classification of emphysema. Secondary Pathophysiology and classification of emphysema 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=14682597.
220. Kim DK, Hersh CP, Washko GR, et al. Epidemiology, radiology, and genetics of nicotine dependence in COPD. Secondary Epidemiology, radiology, and genetics of nicotine dependence in COPD 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21232152.
221. Kim DK, Jacobson FL, Washko GR, et al. Clinical and radiographic correlates of hypoxemia and oxygen therapy in the COPDGene study. Secondary Clinical and radiographic correlates of hypoxemia and oxygen therapy in the COPDGene study 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21396809.
222. Kim HC, Mofarrahi M, Hussain SNA. Skeletal muscle dysfunction in patients with chronic obstructive pulmonary disease. Secondary Skeletal muscle dysfunction in patients with chronic obstructive pulmonary disease 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19281080.
223. Kim V, Rogers TJ, Criner GJ. New concepts in the pathobiology of chronic obstructive pulmonary disease. Secondary New concepts in the pathobiology of chronic obstructive pulmonary disease 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18453359.
224. Kinnula VL, Crapo JD. Smoking and COPD-mechanisms and prevention. Secondary Smoking and COPD-mechanisms and prevention 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19811380.
225. Kinnunen T, Saynajakangas O, Tuuponen T, Keistinen T. Impact of comorbidities on the duration of COPD patients' hospital episodes. Secondary Impact of comorbidities on the duration of COPD patients' hospital episodes 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12587964.
226. Kiraz K, Kart L, Demir R, et al. Chronic pulmonary disease in rural women exposed to biomass fumes. Secondary Chronic pulmonary disease in rural women exposed to biomass fumes 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=14596485.
227. Kirkpatrick dP, Dransfield MT. Racial and sex differences in chronic obstructive pulmonary disease susceptibility, diagnosis, and treatment. Secondary Racial and sex differences in chronic obstructive pulmonary disease susceptibility, diagnosis, and treatment 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19532023.
228. Kjensli A, Falch JA, Ryg M, et al. High prevalence of vertebral deformities in COPD patients: relationship to disease severity. Secondary High prevalence of vertebral deformities in COPD patients: relationship to disease severity 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19129288.
229. Kleeberger SR, Peden D. Gene-environment interactions in asthma and other respiratory diseases. Secondary Gene-environment interactions in asthma and other respiratory diseases 2005.

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15660518.
230. Kojima S, Sakakibara H, Motani S, et al. Effects of smoking and age on chronic obstructive pulmonary disease in Japan. Secondary Effects of smoking and age on chronic obstructive pulmonary disease in Japan 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16141629.
231. Kojima S, Sakakibara H, Motani S, et al. Incidence of chronic obstructive pulmonary disease, and the relationship between age and smoking in a Japanese population. Secondary Incidence of chronic obstructive pulmonary disease, and the relationship between age and smoking in a Japanese population 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17420613.
232. Kubo S, Kobayashi M, Masunaga Y, et al. Cytokine and chemokine expression in cigarette smoke-induced lung injury in guinea pigs. Secondary Cytokine and chemokine expression in cigarette smoke-induced lung injury in guinea pigs 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16319327.
233. Kupeli E, Ulubay G, Ulasli SS, Sahin T, Erayman Z, Gursoy A. Metabolic syndrome is associated with increased risk of acute exacerbation of COPD: a preliminary study. Secondary Metabolic syndrome is associated with increased risk of acute exacerbation of COPD: a preliminary study 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20960105.
234. Kurmi OP, Semple S, Simkhada P, Smith WCS, Ayres JG. COPD and chronic bronchitis risk of indoor air pollution from solid fuel: a systematic review and meta-analysis. Secondary COPD and chronic bronchitis risk of indoor air pollution from solid fuel: a systematic review and meta-analysis 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20335290.
235. Lacedonia D, Salerno FG, Sabato R, et al. Airway cell patterns in patients suffering from COPD and OSAS (Overlap Syndrome). Secondary Airway cell patterns in patients suffering from COPD and OSAS (Overlap Syndrome) 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21130635.
236. Lacoma A, Prat C, Andreo F, et al. Value of procalcitonin, C-reactive protein, and neopterin in exacerbations of chronic obstructive pulmonary disease. Secondary Value of procalcitonin, C-reactive protein, and neopterin in exacerbations of chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21468168.
237. Laitinen T, Hodgson U, Kupiainen H, et al. Real-world clinical data identifies gender-related profiles in chronic obstructive pulmonary disease. Secondary Real-world clinical data identifies gender-related profiles in chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19811384.
238. Lakhdar R, Denden S, Knani J, et al. Relationship between glutathione S-transferase P1 polymorphisms and chronic obstructive pulmonary disease in a Tunisian population. Secondary Relationship between glutathione S-transferase P1 polymorphisms and chronic obstructive pulmonary disease in a Tunisian population 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20467983.
239. Lakhdar R, Denden S, Knani J, et al. Combined analysis of EPHX1, GSTP1, GSTM1 and GSTT1 gene polymorphisms in relation to chronic obstructive pulmonary disease risk and lung function impairment. Secondary Combined analysis of EPHX1, GSTP1, GSTM1 and GSTT1 gene polymorphisms in relation to chronic obstructive pulmonary disease risk and lung function impairment 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21734345.
240. Lam HT, Ronmark E, Tu'o'ng NV, Ekerljung L, Chuc NTK, Lundback B. Increase in asthma and a high prevalence of bronchitis: results from a population study among adults in urban and rural Vietnam. Secondary Increase in asthma and a high prevalence of bronchitis: results from a population study among adults in urban and rural Vietnam 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21030231.
241. Lamprecht B, McBurnie MA, Vollmer WM, et al. COPD in never smokers: results from the population-based burden of obstructive lung disease study. Secondary COPD in never smokers: results from the population-based burden of obstructive lung disease study 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20884729.
242. Lange P, Mogelvang R, Marott JL, Vestbo J, Jensen JS. Cardiovascular morbidity in COPD: A study of the general population. Secondary Cardiovascular morbidity in COPD: A study of the general population 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20214458.
243. Lange P, Parner J, Prescott E, Vestbo J. Chronic bronchitis in an elderly population. Secondary Chronic bronchitis in an elderly population 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=14600005.
244. Laniado-Laborin R, Rendon A, Bauerle O. Chronic obstructive pulmonary disease case finding in Mexico in an at-risk population. Secondary Chronic obstructive pulmonary disease case finding in Mexico in an at-risk population 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21575305.

245. Latza U, Baur X. Occupational obstructive airway diseases in Germany: Frequency and causes in an international comparison. Secondary Occupational obstructive airway diseases in Germany: Frequency and causes in an international comparison 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16032736.
246. Laurin C, Labrecque M, Dupuis G, Bacon SL, Cartier A, Lavoie KL. Chronic obstructive pulmonary disease patients with psychiatric disorders are at greater risk of exacerbations. Secondary Chronic obstructive pulmonary disease patients with psychiatric disorders are at greater risk of exacerbations 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19561164.
247. Lee J, Nordestgaard BG, Dahl M. EPHX1 polymorphisms, COPD and asthma in 47,000 individuals and in meta-analysis. Secondary EPHX1 polymorphisms, COPD and asthma in 47,000 individuals and in meta-analysis 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20516053.
248. Leru P. Current aspects in etiopathogenesis and diagnosis of chronic obstructive pulmonary disease. Secondary Current aspects in etiopathogenesis and diagnosis of chronic obstructive pulmonary disease 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15529597.
249. Li L-J, Gao L-B, Lv M-L, et al. Association between SNPs in pre-miRNA and risk of chronic obstructive pulmonary disease. Secondary Association between SNPs in pre-miRNA and risk of chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21565178.
250. Liang W-M, Liu W-P, Kuo H-W. Diurnal temperature range and emergency room admissions for chronic obstructive pulmonary disease in Taiwan. Secondary Diurnal temperature range and emergency room admissions for chronic obstructive pulmonary disease in Taiwan 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18989710.
251. Lieberman D, Ben-Yaakov M, Lazarovich Z, Ohana B, Boldur I. Chlamydia pneumoniae infection in acute exacerbations of chronic obstructive pulmonary disease: analysis of 250 hospitalizations. Secondary Chlamydia pneumoniae infection in acute exacerbations of chronic obstructive pulmonary disease: analysis of 250 hospitalizations 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11757970.
252. Lin H-H, Murray M, Cohen T, Colijn C, Ezzati M. Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time-based, multiple risk factor, modelling study. Secondary Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time-based, multiple risk factor, modelling study 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18835640.
253. Lin J-L, Thomas PS. Current perspectives of oxidative stress and its measurement in chronic obstructive pulmonary disease. Secondary Current perspectives of oxidative stress and its measurement in chronic obstructive pulmonary disease 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20673039.
254. Lindberg A, Bjerg A, Ronmark E, Larsson L-G, Lundback B. Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking Report from the Obstructive Lung Disease in Northern Sweden Studies. Secondary Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking Report from the Obstructive Lung Disease in Northern Sweden Studies 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15975774.
255. Lindberg A, Eriksson B, Larsson L-G, Ronmark E, Sandstrom T, Lundback B. Seven-year cumulative incidence of COPD in an age-stratified general population sample. Secondary Seven-year cumulative incidence of COPD in an age-stratified general population sample 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16608933.
256. Lindberg A, Jonsson A-C, Ronmark E, Lundgren R, Larsson L-G, Lundback B. Prevalence of chronic obstructive pulmonary disease according to BTS, ERS, GOLD and ATS criteria in relation to doctor's diagnosis, symptoms, age, gender, and smoking habits. Secondary Prevalence of chronic obstructive pulmonary disease according to BTS, ERS, GOLD and ATS criteria in relation to doctor's diagnosis, symptoms, age, gender, and smoking habits 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16210885.
257. Lindberg A, Jonsson A-C, Ronmark E, Lundgren R, Larsson L-G, Lundback B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Secondary Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15888826.
258. Lindberg A, Larsson L-G, Ronmark E, Jonsson A-C, Larsson K, Lundback B. Decline in FEV1 in relation to incident chronic obstructive pulmonary disease in a cohort with respiratory symptoms. Secondary Decline in FEV1 in relation to incident chronic obstructive pulmonary disease in a cohort with respiratory symptoms 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17364672.

259. Ling SH, van Eeden SF. Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease. Secondary Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19554194.
260. Littner MR. In the clinic. Chronic obstructive pulmonary disease. Secondary In the clinic. Chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21464346.
261. Liu S, Zhou Y, Wang X, et al. Biomass fuels are the probable risk factor for chronic obstructive pulmonary disease in rural South China. Secondary Biomass fuels are the probable risk factor for chronic obstructive pulmonary disease in rural South China 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17483137.
262. Liu S-F, Wang C-C, Fang W-F, Chen Y-C, Lin M-C. MCP1 -2518 polymorphism and chronic obstructive pulmonary disease in Taiwanese men. Secondary MCP1 -2518 polymorphism and chronic obstructive pulmonary disease in Taiwanese men 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20497022.
263. Liu Y, Liang W-B, Gao L-B, et al. CTLA4 and CD86 gene polymorphisms and susceptibility to chronic obstructive pulmonary disease. Secondary CTLA4 and CD86 gene polymorphisms and susceptibility to chronic obstructive pulmonary disease 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20732370.
264. Lo Coco D, Mattaliano A, Lo Coco A, Randisi B. Increased frequency of restless legs syndrome in chronic obstructive pulmonary disease patients. Secondary Increased frequency of restless legs syndrome in chronic obstructive pulmonary disease patients 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18996743.
265. Lokke A, Lange P, Scharling H, Fabricius P, Vestbo J. Developing COPD: a 25 year follow up study of the general population. Secondary Developing COPD: a 25 year follow up study of the general population 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17071833.
266. Lomas DA. Genetic predisposition to chronic obstructive pulmonary disease: advances in alpha1-antitrypsin deficiency and the serpinopathies. Secondary Genetic predisposition to chronic obstructive pulmonary disease: advances in alpha1-antitrypsin deficiency and the serpinopathies 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17990707.
267. Lomas DA, Silverman EK. The genetics of chronic obstructive pulmonary disease. Secondary The genetics of chronic obstructive pulmonary disease 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11686861.
268. Lu M, Yao W, Zhong N, et al. Chronic obstructive pulmonary disease in the absence of chronic bronchitis in China. Secondary Chronic obstructive pulmonary disease in the absence of chronic bronchitis in China 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20723142.
269. Lu M, Yao W-z, Zhong N-s, et al. Asymptomatic patients of chronic obstructive pulmonary disease in China. Secondary Asymptomatic patients of chronic obstructive pulmonary disease in China 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20819499.
270. Lundback B, Eriksson B, Lindberg A, et al. A 20-year follow-up of a population study-based COPD cohort-report from the obstructive lung disease in Northern Sweden studies. Secondary A 20-year follow-up of a population study-based COPD cohort-report from the obstructive lung disease in Northern Sweden studies 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19811385.
271. Lundback B, Lindberg A, Lindstrom M, et al. Not 15 but 50% of smokers develop COPD?--Report from the Obstructive Lung Disease in Northern Sweden Studies. Secondary Not 15 but 50% of smokers develop COPD?--Report from the Obstructive Lung Disease in Northern Sweden Studies 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12587960.
272. Maclay JD, McAllister DA, Mills NL, et al. Vascular dysfunction in chronic obstructive pulmonary disease. Secondary Vascular dysfunction in chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19542477.
273. Macnee W. Pathogenesis of chronic obstructive pulmonary disease. Secondary Pathogenesis of chronic obstructive pulmonary disease 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17720039.
274. MacNee W, Tuder RM. New paradigms in the pathogenesis of chronic obstructive pulmonary disease I. Secondary New paradigms in the pathogenesis of chronic obstructive pulmonary disease I 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19741262.
275. Maggi S, Siviero P, Gonnelli S, et al. Osteoporosis risk in patients with chronic obstructive pulmonary disease: the EOLO study. Secondary Osteoporosis risk in patients with chronic obstructive pulmonary disease: the EOLO study 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19647671.

276. Mak GK, Gould MK, Kuschner WG. Occupational inhalant exposure and respiratory disorders among never-smokers referred to a hospital pulmonary function laboratory. Secondary Occupational inhalant exposure and respiratory disorders among never-smokers referred to a hospital pulmonary function laboratory 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11570775.
277. Malerba M, Romanelli G. Early cardiovascular involvement in chronic obstructive pulmonary disease. Secondary Early cardiovascular involvement in chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19719036.
278. Man SFP, Connett JE, Anthonisen NR, Wise RA, Tashkin DP, Sin DD. C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. Secondary C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16738034.
279. Mancuso P. Obesity and lung inflammation. Secondary Obesity and lung inflammation 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19875709.
280. Mannino DM. Looking beyond the cigarette in COPD. Secondary Looking beyond the cigarette in COPD 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18252907.
281. Mannino DM. COPD and lung cancer among women: an equal opportunity risk? Secondary COPD and lung cancer among women: an equal opportunity risk? 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19247079.
282. Mannino DM. COPD as a disease of children: hype or hope for better understanding? Secondary COPD as a disease of children: hype or hope for better understanding? 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20029032.
283. Mannino DM. The natural history of chronic obstructive pulmonary disease. Secondary The natural history of chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21351066.
284. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Secondary Global burden of COPD: risk factors, prevalence, and future trends 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17765526.
285. Mannino DM, Davis KJ. Lung function decline and outcomes in an elderly population. Secondary Lung function decline and outcomes in an elderly population 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16517577.
286. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation: data from the Third National Health and Nutrition Examination. Secondary Obstructive and restrictive lung disease and markers of inflammation: data from the Third National Health and Nutrition Examination 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12829203.
287. Mannino DM, Martinez FJ. Lifetime risk of COPD: what will the future bring? Secondary Lifetime risk of COPD: what will the future bring? 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21907847.
288. Mannino DM, Reichert MM, Davis KJ. Lung function decline and outcomes in an adult population. Secondary Lung function decline and outcomes in an adult population 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16439715.
289. Mapel DW, Frost FJ, Hurley JS, et al. An algorithm for the identification of undiagnosed COPD cases using administrative claims data. Secondary An algorithm for the identification of undiagnosed COPD cases using administrative claims data 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16925453.
290. Margretardottir OB, Thorleifsson SJ, Gudmundsson G, et al. Hypertension, systemic inflammation and body weight in relation to lung function impairment-an epidemiological study. Secondary Hypertension, systemic inflammation and body weight in relation to lung function impairment-an epidemiological study 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19811383.
291. Mariani E, Bonati E, Veronesi L, et al. Respiratory function in subjects with chronic obstructive pulmonary disease (COPD) and atmospheric pollution in the city of Parma. Preliminary analysis. Secondary Respiratory function in subjects with chronic obstructive pulmonary disease (COPD) and atmospheric pollution in the city of Parma. Preliminary analysis 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21305875.
292. Martinez-Garcia MA, Soler-Cataluna JJ, Donat Sanz Y, et al. Factors associated with bronchiectasis in patients with COPD. Secondary Factors associated with bronchiectasis in patients with COPD 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21546440.
293. Martins P, Rosado-Pinto J, do Ceu Teixeira M, et al. Under-report and underdiagnosis of chronic respiratory diseases in an African country. Secondary Under-report and underdiagnosis of chronic respiratory diseases in an African country 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19210360.

294. Mastrangelo G, Tartari M, Fedeli U, Fadda E, Saia B. Ascertaining the risk of chronic obstructive pulmonary disease in relation to occupation using a case-control design. Secondary Ascertaining the risk of chronic obstructive pulmonary disease in relation to occupation using a case-control design 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12724550.
295. Masuko H, Sakamoto T, Kaneko Y, et al. Lower FEV1 in non-COPD, nonasthmatic subjects: association with smoking, annual decline in FEV1, total IgE levels, and TSLP genotypes. Secondary Lower FEV1 in non-COPD, nonasthmatic subjects: association with smoking, annual decline in FEV1, total IgE levels, and TSLP genotypes 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21468164.
296. Matheson MC, Benke G, Raven J, et al. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. Secondary Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16061705.
297. Matheson MC, Ellis JA, Raven J, Johns DP, Walters EH, Abramson MJ. Beta2-adrenergic receptor polymorphisms are associated with asthma and COPD in adults. Secondary Beta2-adrenergic receptor polymorphisms are associated with asthma and COPD in adults 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16946993.
298. Matheson MC, Raven J, Walters EH, Abramson MJ, Ellis JA. Microsomal epoxide hydrolase is not associated with COPD in a community-based sample. Secondary Microsomal epoxide hydrolase is not associated with COPD in a community-based sample 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17564249.
299. Matsuoka S, Washko GR, Dransfield MT, et al. Quantitative CT measurement of cross-sectional area of small pulmonary vessel in COPD: correlations with emphysema and airflow limitation. Secondary Quantitative CT measurement of cross-sectional area of small pulmonary vessel in COPD: correlations with emphysema and airflow limitation 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19796970.
300. Mayer AS, Newman LS. Genetic and environmental modulation of chronic obstructive pulmonary disease. Secondary Genetic and environmental modulation of chronic obstructive pulmonary disease 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11535256.
301. McCloskey SC, Patel BD, Hinchliffe SJ, Reid ED, Wareham NJ, Lomas DA. Siblings of patients with severe chronic obstructive pulmonary disease have a significant risk of airflow obstruction. Secondary Siblings of patients with severe chronic obstructive pulmonary disease have a significant risk of airflow obstruction 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11704589.
302. McKeever TM, Lewis SA, Cassano PA, et al. Patterns of dietary intake and relation to respiratory disease, forced expiratory volume in 1 s, and decline in 5-y forced expiratory volume. Secondary Patterns of dietary intake and relation to respiratory disease, forced expiratory volume in 1 s, and decline in 5-y forced expiratory volume 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20554789.
303. McKeever TM, Lewis SA, Smit HA, Burney P, Britton JR, Cassano PA. The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. Secondary The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15735054.
304. Medina-Ramon M, Zanobetti A, Schwartz J. The effect of ozone and PM10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study. Secondary The effect of ozone and PM10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16443803.
305. Mehrotra A, Oluwole AM, Gordon SB. The burden of COPD in Africa: a literature review and prospective survey of the availability of spirometry for COPD diagnosis in Africa. Secondary The burden of COPD in Africa: a literature review and prospective survey of the availability of spirometry for COPD diagnosis in Africa 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19702594.
306. Menezes A, Macedo SC, Gigante DP, et al. Prevalence and risk factors for chronic obstructive pulmonary disease according to symptoms and spirometry. Secondary Prevalence and risk factors for chronic obstructive pulmonary disease according to symptoms and spirometry 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17136985.
307. Menezes AMB, Jardim JR, Perez-Padilla R, et al. Prevalence of chronic obstructive pulmonary disease and associated factors: the PLATINO Study in Sao Paulo, Brazil. Secondary Prevalence of chronic obstructive pulmonary disease and associated factors: the PLATINO Study in Sao Paulo, Brazil 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16158163.
308. Methvin JN, Mannino DM, Casey BR. COPD prevalence in southeastern Kentucky: the burden of lung disease study. Secondary COPD prevalence in southeastern Kentucky: the burden of lung disease study 2009.

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18689574.
309. Mets OM, Buckens CFM, Zanen P, et al. Identification of chronic obstructive pulmonary disease in lung cancer screening computed tomographic scans. Secondary Identification of chronic obstructive pulmonary disease in lung cancer screening computed tomographic scans 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22028353.
310. Milic-Emili J. Does mechanical injury of the peripheral airways play a role in the genesis of COPD in smokers? Secondary Does mechanical injury of the peripheral airways play a role in the genesis of COPD in smokers? 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16997741.
311. Miller BG, MacCalman L. Cause-specific mortality in British coal workers and exposure to respirable dust and quartz. Secondary Cause-specific mortality in British coal workers and exposure to respirable dust and quartz 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19819863.
312. Mills NL, Miller JJ, Anand A, et al. Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. Secondary Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18024535.
313. Minematsu N, Nakamura H, Tateno H, Nakajima T, Yamaguchi K. Genetic polymorphism in matrix metalloproteinase-9 and pulmonary emphysema. Secondary Genetic polymorphism in matrix metalloproteinase-9 and pulmonary emphysema 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11708786.
314. Mintz ML, Yawn BP, Mannino DM, et al. Prevalence of airway obstruction assessed by lung function questionnaire. Secondary Prevalence of airway obstruction assessed by lung function questionnaire 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21531880.
315. Miotto D, Boschetto P, Cavallesco G, et al. Increased neurokinin-2 receptor expression in alveolar macrophages of smokers with COPD. Secondary Increased neurokinin-2 receptor expression in alveolar macrophages of smokers with COPD 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17532769.
316. Miravitlles M. Exacerbations of chronic obstructive pulmonary disease: when are bacteria important? Secondary Exacerbations of chronic obstructive pulmonary disease: when are bacteria important? 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12168752.
317. Miravitlles M. Cough and sputum production as risk factors for poor outcomes in patients with COPD. Secondary Cough and sputum production as risk factors for poor outcomes in patients with COPD 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21353517.
318. Mizuno S, Takiguchi Y, Fujikawa A, et al. Chronic obstructive pulmonary disease and interstitial lung disease in patients with lung cancer. Secondary Chronic obstructive pulmonary disease and interstitial lung disease in patients with lung cancer 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19192220.
319. Moghaddam SJ, Ochoa CE, Sethi S, Dickey BF. Nontypeable Haemophilus influenzae in chronic obstructive pulmonary disease and lung cancer. Secondary Nontypeable Haemophilus influenzae in chronic obstructive pulmonary disease and lung cancer 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21407824.
320. Mohapatra PR, Janmeja AK. Factors associated with hospital admission in patients with acute exacerbation of chronic obstructive pulmonary disease. Secondary Factors associated with hospital admission in patients with acute exacerbation of chronic obstructive pulmonary disease 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21302596.
321. Molfino NA. Genetic predisposition to accelerated decline of lung function in COPD. Secondary Genetic predisposition to accelerated decline of lung function in COPD 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=18044683.
322. Montes de Oca M, Talamo C, Halbert RJ, et al. Health status perception and airflow obstruction in five Latin American cities: the PLATINO study. Secondary Health status perception and airflow obstruction in five Latin American cities: the PLATINO study 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19364640.
323. Morris A, George MP, Crothers K, et al. HIV and chronic obstructive pulmonary disease: is it worse and why? Secondary HIV and chronic obstructive pulmonary disease: is it worse and why? 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21653535.
324. Morris A, Sciurba FC, Lebedeva IP, et al. Association of chronic obstructive pulmonary disease severity and Pneumocystis colonization. Secondary Association of chronic obstructive pulmonary disease severity and Pneumocystis colonization 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15117741.
325. Mortaz E, Adcock IM, Ito K, Kraneveld AD, Nijkamp FP, Folkerts G. Cigarette smoke induces CXCL8 production by human neutrophils via activation of TLR9 receptor. Secondary Cigarette smoke induces CXCL8 production by

human neutrophils via activation of TLR9 receptor 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19840968.
326. Mosharraf-Hossain KM, Islam S, Kalam Azzad A, et al. Detection of chronic obstructive pulmonary disease using spirometric screening. Secondary Detection of chronic obstructive pulmonary disease using spirometric screening 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19377418.
327. Murphy DE, Chaudhry Z, Almoosa KF, Panos RJ. High prevalence of chronic obstructive pulmonary disease among veterans in the urban midwest. Secondary High prevalence of chronic obstructive pulmonary disease among veterans in the urban midwest 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21634301.
328. Murugan V, Peck MJ. Signal transduction pathways linking the activation of alveolar macrophages with the recruitment of neutrophils to lungs in chronic obstructive pulmonary disease. Secondary Signal transduction pathways linking the activation of alveolar macrophages with the recruitment of neutrophils to lungs in chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19842832.
329. Nacul L, Soljak M, Samarasundera E, et al. COPD in England: a comparison of expected, model-based prevalence and observed prevalence from general practice data. Secondary COPD in England: a comparison of expected, model-based prevalence and observed prevalence from general practice data 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20522452.
330. Nazir SA, Al-Hamed MM, Erbland ML. Chronic obstructive pulmonary disease in the older patient. Secondary Chronic obstructive pulmonary disease in the older patient 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17967289.
331. Nielsen R, Johannessen A, Bakke PS, Askildsen JE, Omenaas ER, Gulsvik A. Aspects of healthcare utilisation in self-reported obstructive lung disease. Secondary Aspects of healthcare utilisation in self-reported obstructive lung disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20298370.
332. Nielsen R, Johannessen A, Omenaas ER, Bakke PS, Askildsen JE, Gulsvik A. Excessive costs of COPD in ever-smokers. A longitudinal community study. Secondary Excessive costs of COPD in ever-smokers. A longitudinal community study 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21030232.
333. Nihlen U, Montnemery P, Andersson M, et al. Specific nasal symptoms and symptom-provoking factors may predict increased risk of developing COPD. Secondary Specific nasal symptoms and symptom-provoking factors may predict increased risk of developing COPD 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18331572.
334. Nussbaumer-Ochsner Y, Rabe KF. Systemic manifestations of COPD. Secondary Systemic manifestations of COPD 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21208876.
335. Nuti R, Siviero P, Maggi S, et al. Vertebral fractures in patients with chronic obstructive pulmonary disease: the EOLO Study. Secondary Vertebral fractures in patients with chronic obstructive pulmonary disease: the EOLO Study 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18931817.
336. Oberley-Deegan RE, Regan EA, Kinnula VL, Crapo JD. Extracellular superoxide dismutase and risk of COPD. Secondary Extracellular superoxide dismutase and risk of COPD 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19811392.
337. O'Donoghue FJ, Catcheside PG, Ellis EE, et al. Sleep hypoventilation in hypercapnic chronic obstructive pulmonary disease: prevalence and associated factors. Secondary Sleep hypoventilation in hypercapnic chronic obstructive pulmonary disease: prevalence and associated factors 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12797491.
338. Ohar JA, Sadeghnejad A, Meyers DA, Donohue JF, Bleecker ER. Do symptoms predict COPD in smokers? Secondary Do symptoms predict COPD in smokers? 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20363841.
339. Ohara T, Hirai T, Muro S, et al. Relationship between pulmonary emphysema and osteoporosis assessed by CT in patients with COPD. Secondary Relationship between pulmonary emphysema and osteoporosis assessed by CT in patients with COPD 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18641115.
340. Orozco-Levi M, Garcia-Aymerich J, Villar J, Ramirez-Sarmiento A, Anto JM, Gea J. Wood smoke exposure and risk of chronic obstructive pulmonary disease. Secondary Wood smoke exposure and risk of chronic obstructive pulmonary disease 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16507854.
341. Ottenheim NR, Giltay EJ, Zitman FG, van der Mast RC, de Craen AJM. Risk of depressive symptoms in the oldest

old subjects with chronic obstructive pulmonary disease: the Leiden 85-plus study. Secondary Risk of depressive symptoms in the oldest old subjects with chronic obstructive pulmonary disease: the Leiden 85-plus study 2010.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20220575.
342. Pabst S, Yenice V, Lennarz M, et al. Toll-like receptor 2 gene polymorphisms Arg677Trp and Arg753Gln in chronic obstructive pulmonary disease. Secondary Toll-like receptor 2 gene polymorphisms Arg677Trp and Arg753Gln in chronic obstructive pulmonary disease 2009.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19381722.
343. Paek Y-J, Jung K-S, Hwang Y-I, Lee K-S, Lee DR, Lee J-U. Association between low pulmonary function and metabolic risk factors in Korean adults: the Korean National Health and Nutrition Survey. Secondary Association between low pulmonary function and metabolic risk factors in Korean adults: the Korean National Health and Nutrition Survey 2010.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20045536.
344. Panetta NL, Krachman S, Chatila WM. Chronic obstructive pulmonary disease and its comorbidities. Secondary Chronic obstructive pulmonary disease and its comorbidities 2009.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19776712.
345. Papatheodorou A, Makrythanasis P, Kaliakatsos M, et al. Development of novel microarray methodology for the study of mutations in the SERPINA1 and ADRB2 genes--their association with Obstructive Pulmonary Disease and Disseminated Bronchiectasis in Greek patients. Secondary Development of novel microarray methodology for the study of mutations in the SERPINA1 and ADRB2 genes--their association with Obstructive Pulmonary Disease and Disseminated Bronchiectasis in Greek patients 2010.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19747908.
346. Park JY, Chen L, Wadhwa N, Tockman MS. Polymorphisms for microsomal epoxide hydrolase and genetic susceptibility to COPD. Secondary Polymorphisms for microsomal epoxide hydrolase and genetic susceptibility to COPD 2005.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15702235.
347. Parr DG, White AJ, Bayley DL, Guest PJ, Stockley RA. Inflammation in sputum relates to progression of disease in subjects with COPD: a prospective descriptive study. Secondary Inflammation in sputum relates to progression of disease in subjects with COPD: a prospective descriptive study 2006.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17112387.
348. Patankar AM, Trivedi PL. Monetary burden of health impacts of air pollution in Mumbai, India: implications for public health policy. Secondary Monetary burden of health impacts of air pollution in Mumbai, India: implications for public health policy 2011.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21334032.
349. Patel ARC, Hurst JR. Extrapulmonary comorbidities in chronic obstructive pulmonary disease: state of the art. Secondary Extrapulmonary comorbidities in chronic obstructive pulmonary disease: state of the art 2011.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21955235.
350. Patel BD, Luben RN, Welch AA, et al. Childhood smoking is an independent risk factor for obstructive airways disease in women. Secondary Childhood smoking is an independent risk factor for obstructive airways disease in women 2004.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15282389.
351. Paudel B, Dhungel S, Paudel K, Pandru K, Paudel R. When left ventricular failure complicates chronic obstructive pulmonary disease: hypoxia plays the major role. Secondary When left ventricular failure complicates chronic obstructive pulmonary disease: hypoxia plays the major role 2008.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18604113.
352. Pavord ID, Yousaf N, Birring SS. Chronic obstructive pulmonary disease in non-smokers. Secondary Chronic obstructive pulmonary disease in non-smokers 2009.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20006127.
353. Peabody JW, Schau B, Lopez-Vidriero M, Vestbo J, Wade S, Iqbal A. COPD: a prevalence estimation model. Secondary COPD: a prevalence estimation model 2005.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16268912.
354. Pelkonen M. Smoking: relationship to chronic bronchitis, chronic obstructive pulmonary disease and mortality. Secondary Smoking: relationship to chronic bronchitis, chronic obstructive pulmonary disease and mortality 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18303418.
355. Penyige A, Poliska S, Csanky E, et al. Analyses of association between PPAR gamma and EPHX1 polymorphisms and susceptibility to COPD in a Hungarian cohort, a case-control study. Secondary Analyses of association between PPAR gamma and EPHX1 polymorphisms and susceptibility to COPD in a Hungarian cohort, a case-control study 2010.
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21044285.
356. Phulpoto MA, Qayyum S, Rizvi N, Khuhawar SM. Proportion of gastroesophageal reflux symptoms in patients with

chronic obstructive pulmonary disease. Secondary Proportion of gastroesophageal reflux symptoms in patients with chronic obstructive pulmonary disease 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16108509.
357. Pillai SG, Ge D, Zhu G, et al. A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. Secondary A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19300482.
358. Pistelli R, Lange P, Miller DL. Determinants of prognosis of COPD in the elderly: mucus hypersecretion, infections, cardiovascular comorbidity. Secondary Determinants of prognosis of COPD in the elderly: mucus hypersecretion, infections, cardiovascular comorbidity 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12762568.
359. Polkey MI, Rabe KF. Chicken or egg: physical activity in COPD revisited. Secondary Chicken or egg: physical activity in COPD revisited 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19181910.
360. Postma DS, Kerkhof M, Boezen HM, Koppelman GH. Asthma and chronic obstructive pulmonary disease: common genes, common environments? Secondary Asthma and chronic obstructive pulmonary disease: common genes, common environments? 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21297068.
361. Poulain M, Doucet M, Drapeau V, et al. Metabolic and inflammatory profile in obese patients with chronic obstructive pulmonary disease. Secondary Metabolic and inflammatory profile in obese patients with chronic obstructive pulmonary disease 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18303100.
362. Price DB, Tinkelman DG, Nordyke RJ, Isonaka S, Halbert RJ, Group CQS. Scoring system and clinical application of COPD diagnostic questionnaires. Secondary Scoring system and clinical application of COPD diagnostic questionnaires 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16778271.
363. Pujades-Rodriguez M, McKeever T, Lewis S, Whyatt D, Britton J, Venn A. Effect of traffic pollution on respiratory and allergic disease in adults: cross-sectional and longitudinal analyses. Secondary Effect of traffic pollution on respiratory and allergic disease in adults: cross-sectional and longitudinal analyses 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19703291.
364. Purdue MP, Gold L, Jarvholm B, Alavanja MCR, Ward MH, Vermeulen R. Impaired lung function and lung cancer incidence in a cohort of Swedish construction workers. Secondary Impaired lung function and lung cancer incidence in a cohort of Swedish construction workers 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16928722.
365. Rahmanian SD, Diaz PT, Wewers ME. Tobacco use and cessation among women: research and treatment-related issues. Secondary Tobacco use and cessation among women: research and treatment-related issues 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21375414.
366. Rammaert B, Verdier N, Cavestri B, Nseir S. Procalcitonin as a prognostic factor in severe acute exacerbation of chronic obstructive pulmonary disease. Secondary Procalcitonin as a prognostic factor in severe acute exacerbation of chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19659517.
367. Ramsey SD, Hobbs FDR. Chronic obstructive pulmonary disease, risk factors, and outcome trials: comparisons with cardiovascular disease. Secondary Chronic obstructive pulmonary disease, risk factors, and outcome trials: comparisons with cardiovascular disease 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16963547.
368. Raynaud C, Roche N, Chouaid C. Interactions between HIV infection and chronic obstructive pulmonary disease: Clinical and epidemiological aspects. Secondary Interactions between HIV infection and chronic obstructive pulmonary disease: Clinical and epidemiological aspects 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21884608.
369. Reed RM, Iacono A, DeFilippis A, Eberlein M, Girgis RE, Jones S. Advanced chronic obstructive pulmonary disease is associated with high levels of high-density lipoprotein cholesterol. Secondary Advanced chronic obstructive pulmonary disease is associated with high levels of high-density lipoprotein cholesterol 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21306919.
370. Regan E. COPD and bone loss. Secondary COPD and bone loss 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18972273.
371. Reilly KH, Gu D, Duan X, et al. Risk factors for chronic obstructive pulmonary disease mortality in Chinese adults. Secondary Risk factors for chronic obstructive pulmonary disease mortality in Chinese adults 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18256446.
372. Rennard SI. Overview of causes of COPD. New understanding of pathogenesis and mechanisms can guide future therapy. Secondary Overview of causes of COPD. New understanding of pathogenesis and mechanisms can

guide future therapy 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12082919.
373. Rich MW. An association between prinzmetal's angina pectoris and obstructive lung disease. Secondary An association between prinzmetal's angina pectoris and obstructive lung disease 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16310452.
374. Richmond RJ, Zellner KM. Alpha1-antitrypsin deficiency: incidence and implications. Secondary Alpha1-antitrypsin deficiency: incidence and implications 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16327507.
375. Rizkallah J, Man SFP, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. Secondary Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18812453.
376. Roche N, Gaillat J, Garre M, Meunier J-P, Lemaire N, Bendjenana H. Acute respiratory illness as a trigger for detecting chronic bronchitis in adults at risk of COPD: a primary care survey. Secondary Acute respiratory illness as a trigger for detecting chronic bronchitis in adults at risk of COPD: a primary care survey 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20842324.
377. Rodriguez E, Ferrer J, Marti S, Zock J-P, Plana E, Morell F. Impact of occupational exposure on severity of COPD. Secondary Impact of occupational exposure on severity of COPD 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18689596.
378. Rodriguez J, Jiang R, Johnson WC, MacKenzie BA, Smith LJ, Barr RG. The association of pipe and cigar use with cotinine levels, lung function, and airflow obstruction: a cross-sectional study. Secondary The association of pipe and cigar use with cotinine levels, lung function, and airflow obstruction: a cross-sectional study 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20157134.
379. Rodriguez LAG, Wallander M-A, Martin-Merino E, Johansson S. Heart failure, myocardial infarction, lung cancer and death in COPD patients: a UK primary care study. Secondary Heart failure, myocardial infarction, lung cancer and death in COPD patients: a UK primary care study 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20483577.
380. Rogha M, Behravesh B, Pourmoghaddas Z. Association of gastroesophageal reflux disease symptoms with exacerbations of chronic obstructive pulmonary disease. Secondary Association of gastroesophageal reflux disease symptoms with exacerbations of chronic obstructive pulmonary disease 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20922187.
381. Rohde G, Borg I, Arinir U, et al. Relevance of human metapneumovirus in exacerbations of COPD. Secondary Relevance of human metapneumovirus in exacerbations of COPD 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16371156.
382. Roig M, Eng JJ, Road JD, Reid WD. Falls in patients with chronic obstructive pulmonary disease: a call for further research. Secondary Falls in patients with chronic obstructive pulmonary disease: a call for further research 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19419852.
383. Ronmark E, Bjerg A, Hedman L, Perzanowski M, Sundberg S, Lundback B. The Obstructive Lung Disease in Northern Sweden (OLIN) longitudinal paediatric study I--the first 10 years. Secondary The Obstructive Lung Disease in Northern Sweden (OLIN) longitudinal paediatric study I--the first 10 years 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20298347.
384. Rubinstein AL, Irazola VE, Bazzano LA, et al. Detection and follow-up of chronic obstructive pulmonary disease (COPD) and risk factors in the Southern Cone of Latin America: the pulmonary risk in South America (PRISA) study. Secondary Detection and follow-up of chronic obstructive pulmonary disease (COPD) and risk factors in the Southern Cone of Latin America: the pulmonary risk in South America (PRISA) study 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21627849.
385. Rushton L. Chronic obstructive pulmonary disease and occupational exposure to silica. Secondary Chronic obstructive pulmonary disease and occupational exposure to silica 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=18351226.
386. Ryu YJ, Chun E-M, Lee JH, Chang JH. Prevalence of depression and anxiety in outpatients with chronic airway lung disease. Secondary Prevalence of depression and anxiety in outpatients with chronic airway lung disease 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20195403.
387. Sabit R, Bolton CE, Edwards PH, et al. Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. Secondary Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17363772.
388. Sadeghnejad A, Ohar JA, Zheng SL, et al. Adam33 polymorphisms are associated with COPD and lung function in long-term tobacco smokers. Secondary Adam33 polymorphisms are associated with COPD and lung function in long-term tobacco smokers 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19284602.
389. Salvi S, Barnes PJ. Is exposure to biomass smoke the biggest risk factor for COPD globally? Secondary Is

exposure to biomass smoke the biggest risk factor for COPD globally? 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20605806.
390. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Secondary Chronic obstructive pulmonary disease in non-smokers 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19716966.
391. Samarakoon P, Soubani AO. Invasive pulmonary aspergillosis in patients with COPD: a report of five cases and systematic review of the literature. Secondary Invasive pulmonary aspergillosis in patients with COPD: a report of five cases and systematic review of the literature 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18303098.
392. Sampsonas F, Antonacopoulou A, Spathas D, et al. Positive association between two polymorphic sites (+134 insA/delA and G198T) of the endothelin-1 gene and chronic obstructive pulmonary disease. A case-control study. Secondary Positive association between two polymorphic sites (+134 insA/delA and G198T) of the endothelin-1 gene and chronic obstructive pulmonary disease. A case-control study 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19640695.
393. Sampsonas F, Karkoulias K, Kaparianos A, Spiropoulos K. Genetics of chronic obstructive pulmonary disease, beyond a1-antitrypsin deficiency. Secondary Genetics of chronic obstructive pulmonary disease, beyond a1-antitrypsin deficiency 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17073633.
394. Sandelowsky H, Stallberg B, Nager A, Hasselstrom J. The prevalence of undiagnosed chronic obstructive pulmonary disease in a primary care population with respiratory tract infections - a case finding study. Secondary The prevalence of undiagnosed chronic obstructive pulmonary disease in a primary care population with respiratory tract infections - a case finding study 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22047519.
395. Sandford AJ, Joos L, Pare PD. Genetic risk factors for chronic obstructive pulmonary disease. Secondary Genetic risk factors for chronic obstructive pulmonary disease 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11845002.
396. Sandhaus RA. Alpha-1 antitrypsin deficiency: whom to test, whom to treat? Secondary Alpha-1 antitrypsin deficiency: whom to test, whom to treat? 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20496303.
397. Santo Tomas LH. Emphysema and chronic obstructive pulmonary disease in coal miners. Secondary Emphysema and chronic obstructive pulmonary disease in coal miners 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21178627.
398. Santus P, Casanova F, Biondi ML, Blasi F, Di Marco F, Centanni S. Stromelysin-1 polymorphism as a new potential risk factor in progression of chronic obstructive pulmonary disease. Secondary Stromelysin-1 polymorphism as a new potential risk factor in progression of chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19522160.
399. Scarduelli C, Ambrosino N, Confalonieri M, et al. Prevalence and prognostic role of cardiovascular complications in patients with exacerbation of chronic obstructive pulmonary disease admitted to Italian respiratory intensive care units. Secondary Prevalence and prognostic role of cardiovascular complications in patients with exacerbation of chronic obstructive pulmonary disease admitted to Italian respiratory intensive care units 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15706999.
400. Schane RE, Walter LC, Dinno A, Covinsky KE, Woodruff PG. Prevalence and risk factors for depressive symptoms in persons with chronic obstructive pulmonary disease. Secondary Prevalence and risk factors for depressive symptoms in persons with chronic obstructive pulmonary disease 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18690488.
401. Schikowski T, Ranft U, Sugiri D, et al. Decline in air pollution and change in prevalence in respiratory symptoms and chronic obstructive pulmonary disease in elderly women. Secondary Decline in air pollution and change in prevalence in respiratory symptoms and chronic obstructive pulmonary disease in elderly women 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20727210.
402. Schikowski T, Sugiri D, Ranft U, et al. Long-term air pollution exposure and living close to busy roads are associated with COPD in women. Secondary Long-term air pollution exposure and living close to busy roads are associated with COPD in women 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16372913.
403. Schikowski T, Sugiri D, Reimann V, Pesch B, Ranft U, Kramer U. Contribution of smoking and air pollution exposure in urban areas to social differences in respiratory health. Secondary Contribution of smoking and air pollution exposure in urban areas to social differences in respiratory health 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18505547.
404. Seo T, Pahwa P, McDuffie HH, et al. Association between cytochrome P450 3A5 polymorphism and the lung function in Saskatchewan grain workers. Secondary Association between cytochrome P450 3A5 polymorphism and the lung function in Saskatchewan grain workers 2008.

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18496128.
405. Sethi S. Infection as a comorbidity of COPD. Secondary Infection as a comorbidity of COPD 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20513910.
406. Sharma B, Feinsilver S, Owens RL, Malhotra A, McSharry D, Karbowitz S. Obstructive airway disease and obstructive sleep apnea: effect of pulmonary function. Secondary Obstructive airway disease and obstructive sleep apnea: effect of pulmonary function 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21132554.
407. Shen M, Vermeulen R, Chapman RS, et al. A report of cytokine polymorphisms and COPD risk in Xuan Wei, China. Secondary A report of cytokine polymorphisms and COPD risk in Xuan Wei, China 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=17681858.
408. Shetty R, Seddighzadeh A, Piazza G, Goldhaber SZ. Chronic obstructive pulmonary disease and deep vein thrombosis: a prevalent combination. Secondary Chronic obstructive pulmonary disease and deep vein thrombosis: a prevalent combination 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=17940729.
409. Siafakas NM, Tzortzaki EG. Few smokers develop COPD. Why? Secondary Few smokers develop COPD. Why? 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12195843.
410. Siedlinski M, Boezen HM, Boer JMA, Smit HA, Postma DS. ABCC1 polymorphisms contribute to level and decline of lung function in two population-based cohorts. Secondary ABCC1 polymorphisms contribute to level and decline of lung function in two population-based cohorts 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19687781.
411. Siedlinski M, Postma DS, Boer JMA, et al. Level and course of FEV1 in relation to polymorphisms in NFE2L2 and KEAP1 in the general population. Secondary Level and course of FEV1 in relation to polymorphisms in NFE2L2 and KEAP1 in the general population 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19671143.
412. Siedlinski M, van Diemen CC, Postma DS, Vonk JM, Boezen HM. Superoxide dismutases, lung function and bronchial responsiveness in a general population. Secondary Superoxide dismutases, lung function and bronchial responsiveness in a general population 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19213780.
413. Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. Secondary Asthma as a risk factor for COPD in a longitudinal study 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15249443.
414. Silverman EK. Genetic Epidemiology of COPD. Secondary Genetic Epidemiology of COPD 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11893649.
415. Silverman EK. Progress in chronic obstructive pulmonary disease genetics. Secondary Progress in chronic obstructive pulmonary disease genetics 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16799082.
416. Silverman M, Kuehni CE. Early lung development and COPD. Secondary Early lung development and COPD 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17765505.
417. Simon-Tuval T, Scharf SM, Maimon N, Bernhard-Scharf BJ, Reuveni H, Tarasiuk A. Determinants of elevated healthcare utilization in patients with COPD. Secondary Determinants of elevated healthcare utilization in patients with COPD 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21232087.
418. Sin DD, Man SFP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Secondary Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12654609.
419. Sin DD, Man SFP. Impact of cancers and cardiovascular diseases in chronic obstructive pulmonary disease. Secondary Impact of cancers and cardiovascular diseases in chronic obstructive pulmonary disease 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18303420.
420. Singh D, Edwards L, Tal-Singer R, Rennard S. Sputum neutrophils as a biomarker in COPD: findings from the ECLIPSE study. Secondary Sputum neutrophils as a biomarker in COPD: findings from the ECLIPSE study 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20550701.
421. Sinvhal R, Tosiello L, Cable G. Confounding issues in COPD risk study? Secondary Confounding issues in COPD risk study? 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12527640.
422. Slebos DJ, van der Toorn M, Bakker SJL, Kauffman HF. Mitochondrial dysfunction in COPD patients with low body mass index. Secondary Mitochondrial dysfunction in COPD patients with low body mass index 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17766639.
423. Slinde F, Gronberg A, Engstrom C-P, Rossander-Hulthen L, Larsson S. Body composition by bioelectrical

impedance predicts mortality in chronic obstructive pulmonary disease patients. Secondary Body composition by bioelectrical impedance predicts mortality in chronic obstructive pulmonary disease patients 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15950141.
424. Slowik N, Ma S, He J, et al. The effect of secondhand smoke exposure on markers of elastin degradation. Secondary The effect of secondhand smoke exposure on markers of elastin degradation 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21415130.
425. Smith DD. Failure to prove asbestos exposure produces obstructive lung disease. Secondary Failure to prove asbestos exposure produces obstructive lung disease 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15364787.
426. Snoeck-Stroband JB, Postma DS, Lapperre TS, et al. Airway inflammation contributes to health status in COPD: a cross-sectional study. Secondary Airway inflammation contributes to health status in COPD: a cross-sectional study 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17137518.
427. Soares S, Costa I, Neves AL, Couto L. Characterisation of a population at increased risk of COPD. Secondary Characterisation of a population at increased risk of COPD 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20437002.
428. Soler JJ, Sanchez L, Roman P, Martinez MA, Perpina M. Risk factors of emergency care and admissions in COPD patients with high consumption of health resources. Secondary Risk factors of emergency care and admissions in COPD patients with high consumption of health resources 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15072172.
429. Song G, Chen G, Jiang L, et al. Diurnal temperature range as a novel risk factor for COPD death. Secondary Diurnal temperature range as a novel risk factor for COPD death 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18922144.
430. Sood A. Obesity, adipokines, and lung disease. Secondary Obesity, adipokines, and lung disease 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19926824.
431. Sood A, Petersen H, Blanchette CM, et al. Wood smoke exposure and gene promoter methylation are associated with increased risk for COPD in smokers. Secondary Wood smoke exposure and gene promoter methylation are associated with increased risk for COPD in smokers 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20595226.
432. Sorheim IC, Gulsvik A. Genetics of chronic obstructive pulmonary disease: a case-control study in Bergen, Norway. Secondary Genetics of chronic obstructive pulmonary disease: a case-control study in Bergen, Norway 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20298363.
433. Sorheim I-C, Bakke P, Gulsvik A, et al. alpha1-Antitrypsin protease inhibitor MZ heterozygosity is associated with airflow obstruction in two large cohorts. Secondary alpha1-Antitrypsin protease inhibitor MZ heterozygosity is associated with airflow obstruction in two large cohorts 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20595457.
434. Sorheim I-C, Johannessen A, Grydeland TB, Omenaas ER, Gulsvik A, Bakke PS. Case-control studies on risk factors for chronic obstructive pulmonary disease: how does the sampling of the cases and controls affect the results? Secondary Case-control studies on risk factors for chronic obstructive pulmonary disease: how does the sampling of the cases and controls affect the results? 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20565482.
435. Sorheim I-C, Johannessen A, Gulsvik A, Bakke PS, Silverman EK, DeMeo DL. Gender differences in COPD: are women more susceptible to smoking effects than men? Secondary Gender differences in COPD: are women more susceptible to smoking effects than men? 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20522842.
436. Soriano JB, Miravitlles M. Your racing horses will help you to quit: a lesson for COPD and alpha1-antitrypsin deficiency research. Secondary Your racing horses will help you to quit: a lesson for COPD and alpha1-antitrypsin deficiency research 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19483042.
437. Soriano JB, Rodriguez-Roisin R. Chronic obstructive pulmonary disease overview: epidemiology, risk factors, and clinical presentation. Secondary Chronic obstructive pulmonary disease overview: epidemiology, risk factors, and clinical presentation 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21816993.
438. Soriano JB, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. Secondary Screening for and early detection of chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19716965.
439. Sorino C, Sherrill D. Frequent exacerbators in COPD: who are they? Secondary Frequent exacerbators in COPD: who are they? 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19633159.

440. Sousa CAd, Cesar CLG, Barros MBdA, Carandina L, Goldbaum M, Pereira JCR. Prevalence of chronic obstructive pulmonary disease and risk factors in Sao Paulo, Brazil, 2008-2009. Secondary Prevalence of chronic obstructive pulmonary disease and risk factors in Sao Paulo, Brazil, 2008-2009 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21808830.
441. Speletas M, Merentiti V, Kostikas K, et al. Association of TLR4-T399I polymorphism with chronic obstructive pulmonary disease in smokers. Secondary Association of TLR4-T399I polymorphism with chronic obstructive pulmonary disease in smokers 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20169003.
442. Stanciu S, Marinescu R, Iordache M, Dumitrescu S, Muresan M, Bogdan MA. Are systemic inflammatory profiles different in patients with COPD and metabolic syndrome as compared to those with COPD alone? Secondary Are systemic inflammatory profiles different in patients with COPD and metabolic syndrome as compared to those with COPD alone? 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21179920.
443. Stanescu D. Identifying smokers at risk of COPD and GOLD. Secondary Identifying smokers at risk of COPD and GOLD 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12912735.
444. Stankovic M, Nikolic A, Divac A, et al. The CFTR M470V gene variant as a potential modifier of COPD severity: study of Serbian population. Secondary The CFTR M470V gene variant as a potential modifier of COPD severity: study of Serbian population 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18652532.
445. Steer J, Gibson GJ, Bourke SC. Predicting outcomes following hospitalization for acute exacerbations of COPD. Secondary Predicting outcomes following hospitalization for acute exacerbations of COPD 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20660633.
446. Stockley RA, Mannino D, Barnes PJ. Burden and pathogenesis of chronic obstructive pulmonary disease. Secondary Burden and pathogenesis of chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19741261.
447. Sunyer J. Urban air pollution and chronic obstructive pulmonary disease: a review. Secondary Urban air pollution and chronic obstructive pulmonary disease: a review 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11488305.
448. Svanes C. What has the ECRHS told us about the childhood risks of asthma, allergy and lung function? Secondary What has the ECRHS told us about the childhood risks of asthma, allergy and lung function? 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20298348.
449. Svartengren M, Engstrom G, Anderson M, et al. Twins studies as a model for studies on the interaction between smoking and genetic factors in the development of chronic bronchitis. Secondary Twins studies as a model for studies on the interaction between smoking and genetic factors in the development of chronic bronchitis 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19614600.
450. Szymanski P, Mosiewicz J, Myslinski W, Dzida G, Rymarz E. The influence of chronic obstructive pulmonary disease on the occurrence rate and intensification of osteoporosis. Secondary The influence of chronic obstructive pulmonary disease on the occurrence rate and intensification of osteoporosis 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12898923.
451. Takada K, Matsumoto S, Kojima E, et al. Prospective evaluation of the relationship between acute exacerbations of COPD and gastroesophageal reflux disease diagnosed by questionnaire. Secondary Prospective evaluation of the relationship between acute exacerbations of COPD and gastroesophageal reflux disease diagnosed by questionnaire 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21454063.
452. Tamagawa E, van Eeden SF. Impaired lung function and risk for stroke: role of the systemic inflammation response? Secondary Impaired lung function and risk for stroke: role of the systemic inflammation response? 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17166971.
453. Tan SL, Wood AM. Chronic obstructive pulmonary disease and comorbidity: a review and consideration of pathophysiology. Secondary Chronic obstructive pulmonary disease and comorbidity: a review and consideration of pathophysiology 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19776710.
454. Tan WC. Trends in chronic obstructive pulmonary disease in the Asia-Pacific regions. Secondary Trends in chronic obstructive pulmonary disease in the Asia-Pacific regions 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21178626.
455. Tashkin DP. Does smoking marijuana increase the risk of chronic obstructive pulmonary disease? Secondary Does smoking marijuana increase the risk of chronic obstructive pulmonary disease? 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19364782.
456. Taylor JD. COPD and the response of the lung to tobacco smoke exposure. Secondary COPD and the response of the lung to tobacco smoke exposure 2010.

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20382250.
457. Terada K, Muro S, Sato S, et al. Impact of gastro-oesophageal reflux disease symptoms on COPD exacerbation. Secondary Impact of gastro-oesophageal reflux disease symptoms on COPD exacerbation 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18535116.
458. Teramoto S. 1. COPD pathogenesis from the viewpoint of risk factors. Secondary 1. COPD pathogenesis from the viewpoint of risk factors 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17220602.
459. Teramoto S, Ishii T, Yamamoto H, Yamaguchi Y, Matsuse T. Xenobiotic enzymes and genetics of COPD. Secondary Xenobiotic enzymes and genetics of COPD 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15654009.
460. Teramoto S, Kume H, Ouchi Y. Altered Swallowing Physiology and Aspiration in COPD. Secondary Altered Swallowing Physiology and Aspiration in COPD 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12226067.
461. Terpenning MS. The relationship between infections and chronic respiratory diseases: an overview. Secondary The relationship between infections and chronic respiratory diseases: an overview 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11887472.
462. Terzano C, Conti V, Di Stefano F, et al. Comorbidity, hospitalization, and mortality in COPD: results from a longitudinal study. Secondary Comorbidity, hospitalization, and mortality in COPD: results from a longitudinal study 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20066539.
463. Tesfaigzi Y, Myers OB, Stidley CA, et al. Genotypes in matrix metalloproteinase 9 are risk factors for chronic obstructive pulmonary disease. Secondary Genotypes in matrix metalloproteinase 9 are risk factors for chronic obstructive pulmonary disease 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16395864.
464. Tesfaigzi Y, Myers OB, Stidley CA, et al. Genotypes in matrix metalloproteinase 9 are a risk factor for COPD. Secondary Genotypes in matrix metalloproteinase 9 are a risk factor for COPD 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=18046864.
465. Thakur H, Gupta L, Sobti RC, Janmeja AK, Seth A, Singh SK. Association of GSTM1T1 genes with COPD and prostate cancer in north Indian population. Secondary Association of GSTM1T1 genes with COPD and prostate cancer in north Indian population 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20842440.
466. Thakur N, Blanc PD, Julian LJ, et al. COPD and cognitive impairment: the role of hypoxemia and oxygen therapy. Secondary COPD and cognitive impairment: the role of hypoxemia and oxygen therapy 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20856825.
467. Thompson WH, St-Hilaire S. Prevalence of chronic obstructive pulmonary disease and tobacco use in veterans at Boise Veterans Affairs Medical Center. Secondary Prevalence of chronic obstructive pulmonary disease and tobacco use in veterans at Boise Veterans Affairs Medical Center 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20420725.
468. Thorn J, Bjorkelund C, Bengtsson C, Guo X, Lissner L, Sundh V. Low socio-economic status, smoking, mental stress and obesity predict obstructive symptoms in women, but only smoking also predicts subsequent experience of poor health. Secondary Low socio-economic status, smoking, mental stress and obesity predict obstructive symptoms in women, but only smoking also predicts subsequent experience of poor health 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17211495.
469. Tkac J, Man SFP, Sin DD. Systemic consequences of COPD. Secondary Systemic consequences of COPD 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=19124347.
470. Tkacova R, Salagovic J, Ceripkova M, Tkac I, Stubna J, Kalina I. Glutathione S-transferase M1 gene polymorphism is related to COPD in patients with non-small-cell lung cancer. Secondary Glutathione S-transferase M1 gene polymorphism is related to COPD in patients with non-small-cell lung cancer 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15038404.
471. Torres SH, Montes de Oca M, Loeb E, Mata A, Hernandez N. Gender and skeletal muscle characteristics in subjects with chronic obstructive pulmonary disease. Secondary Gender and skeletal muscle characteristics in subjects with chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20580542.
472. Tsiligianni IG, van der Molen T. A systematic review of the role of vitamin insufficiencies and supplementation in COPD. Secondary A systematic review of the role of vitamin insufficiencies and supplementation in COPD 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21134250.
473. Tsuda Y, Noguchi T, Mochizuki H, et al. Patients with mild-to-moderate asthma may develop clinically significant chronic obstructive pulmonary disease. Secondary Patients with mild-to-moderate asthma may develop clinically significant chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19645870.

474. Tukek T, Yildiz P, Akkaya V, et al. Factors associated with the development of atrial fibrillation in COPD patients: the role of P-wave dispersion. Secondary Factors associated with the development of atrial fibrillation in COPD patients: the role of P-wave dispersion 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12167183.
475. Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. Secondary Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17478615.
476. Tverdal A, Bjartveit K. Health consequences of reduced daily cigarette consumption. Secondary Health consequences of reduced daily cigarette consumption 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17130377.
477. Udwadia ZF. The burden of undiagnosed airflow obstruction in India. Secondary The burden of undiagnosed airflow obstruction in India 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=18019793.
478. van Diemen CC, Postma DS, Aulchenko YS, et al. Novel strategy to identify genetic risk factors for COPD severity: a genetic isolate. Secondary Novel strategy to identify genetic risk factors for COPD severity: a genetic isolate 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19797132.
479. van Diemen CC, Postma DS, Siedlinski M, Blokstra A, Smit HA, Boezen HM. Genetic variation in TIMP1 but not MMPs predict excess FEV1 decline in two general population-based cohorts. Secondary Genetic variation in TIMP1 but not MMPs predict excess FEV1 decline in two general population-based cohorts 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21524282.
480. Van Durme YMTA, Eijgelsheim M, Joos GF, et al. Hedgehog-interacting protein is a COPD susceptibility gene: the Rotterdam Study. Secondary Hedgehog-interacting protein is a COPD susceptibility gene: the Rotterdam Study 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19996190.
481. van Durme YMTA, Verhamme KMC, Aarnoudse A-JLHJ, et al. C-reactive protein levels, haplotypes, and the risk of incident chronic obstructive pulmonary disease. Secondary C-reactive protein levels, haplotypes, and the risk of incident chronic obstructive pulmonary disease 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19096002.
482. van Eeden SF, Hogg JC. Chronic obstructive pulmonary disease: do regional differences in tissue inflammation matter? Secondary Chronic obstructive pulmonary disease: do regional differences in tissue inflammation matter? 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21335946.
483. van Eeden SF, Yeung A, Quinlam K, Hogg JC. Systemic response to ambient particulate matter: relevance to chronic obstructive pulmonary disease. Secondary Systemic response to ambient particulate matter: relevance to chronic obstructive pulmonary disease 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16113470.
484. van Gestel YRBM, Flu W-J, van Kuijk J-P, et al. Association of COPD with carotid wall intima-media thickness in vascular surgery patients. Secondary Association of COPD with carotid wall intima-media thickness in vascular surgery patients 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19942421.
485. van Haren-Willems J, Heijdra Y. Increasing evidence for gender differences in chronic obstructive pulmonary disease. Secondary Increasing evidence for gender differences in chronic obstructive pulmonary disease 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20597622.
486. van Manen JG, Bindels PJE, Dekker FW, Ijzermans CJ, van der Zee JS, Schade E. Risk of depression in patients with chronic obstructive pulmonary disease and its determinants. Secondary Risk of depression in patients with chronic obstructive pulmonary disease and its determinants 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11978917.
487. Van Schayck CP, Kaper J, Wagena EJ, Wouters EFM, Severens JL. The cost-effectiveness of antidepressants for smoking cessation in chronic obstructive pulmonary disease (COPD) patients. Secondary The cost-effectiveness of antidepressants for smoking cessation in chronic obstructive pulmonary disease (COPD) patients 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19922576.
488. Van Schayck CP, Loozen JMC, Wagena E, Akkermans RP, Wesseling GJ. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. Secondary Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12052807.
489. Vardavas CI, Flouris AD, Tsatsakis A, Kafatos AG, Saris WHM. Does adherence to the Mediterranean diet have a protective effect against active and passive smoking? Secondary Does adherence to the Mediterranean diet

have a protective effect against active and passive smoking? 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21276993.
490. Varkey AB. Chronic obstructive pulmonary disease in women: exploring gender differences. Secondary Chronic obstructive pulmonary disease in women: exploring gender differences 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15021178.
491. Varraso R, Fung TT, Hu FB, Willett W, Camargo CA. Prospective study of dietary patterns and chronic obstructive pulmonary disease among US men. Secondary Prospective study of dietary patterns and chronic obstructive pulmonary disease among US men 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17504819.
492. Varraso R, Jiang R, Barr RG, Willett WC, Camargo CA, Jr. Prospective study of cured meats consumption and risk of chronic obstructive pulmonary disease in men. Secondary Prospective study of cured meats consumption and risk of chronic obstructive pulmonary disease in men 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17785711.
493. Vasankari T, Jousilahti P, Knekt P, et al. Serum cotinine predicts bronchial obstruction regardless of self-reported smoking history. Secondary Serum cotinine predicts bronchial obstruction regardless of self-reported smoking history 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21406476.
494. Vecchio D, Arezzini B, Pecorelli A, Valacchi G, Martorana PA, Gardi C. Reactivity of mouse alveolar macrophages to cigarette smoke is strain dependent. Secondary Reactivity of mouse alveolar macrophages to cigarette smoke is strain dependent 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20154225.
495. Vestbo J, Lange P. Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? Secondary Can GOLD Stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12153965.
496. Viegi G, Di Pede C. Chronic obstructive lung diseases and occupational exposure. Secondary Chronic obstructive lung diseases and occupational exposure 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11964759.
497. Viegi G, Maio S, Pistelli F, Baldacci S, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease: health effects of air pollution. Secondary Epidemiology of chronic obstructive pulmonary disease: health effects of air pollution 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16916323.
498. Viegi G, Pistelli F, Sherrill DL, Maio S, Baldacci S, Carrozzi L. Definition, epidemiology and natural history of COPD. Secondary Definition, epidemiology and natural history of COPD 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17978157.
499. Vonk JM, Jongepier H, Panhuysen CIM, Schouten JP, Bleecker ER, Postma DS. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. Secondary Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12668795.
500. Walker PP, Burnett A, Flavahan PW, Calverley PMA. Lower limb activity and its determinants in COPD. Secondary Lower limb activity and its determinants in COPD 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18487318.
501. Walter RE, Beiser A, Givelber RJ, O'Connor GT, Gottlieb DJ. Association between glycemic state and lung function: the Framingham Heart Study. Secondary Association between glycemic state and lung function: the Framingham Heart Study 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12623860.
502. Wan ES, Cho MH, Boutaoui N, et al. Genome-wide association analysis of body mass in chronic obstructive pulmonary disease. Secondary Genome-wide association analysis of body mass in chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21037115.
503. Wan ES, DeMeo DL, Hersh CP, et al. Clinical predictors of frequent exacerbations in subjects with severe chronic obstructive pulmonary disease (COPD). Secondary Clinical predictors of frequent exacerbations in subjects with severe chronic obstructive pulmonary disease (COPD) 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21145719.
504. Wan ES, Silverman EK. Genetics of COPD and emphysema. Secondary Genetics of COPD and emphysema 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19736190.
505. Wang Y-C, Lin J-M, Li C-Y, Lee L-T, Guo Y-L, Sung F-C. Prevalence and risks of chronic airway obstruction: a population cohort study in taiwan. Secondary Prevalence and risks of chronic airway obstruction: a population cohort study in taiwan 2007.

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17356083.
506. Watson L, Margetts B, Howarth P, Dorward M, Thompson R, Little P. The association between diet and chronic obstructive pulmonary disease in subjects selected from general practice. Secondary The association between diet and chronic obstructive pulmonary disease in subjects selected from general practice 2002. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12212961.
507. Watson L, Vonk JM, Lofdahl CG, et al. Predictors of lung function and its decline in mild to moderate COPD in association with gender: results from the Euroscop study. Secondary Predictors of lung function and its decline in mild to moderate COPD in association with gender: results from the Euroscop study 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16199147.
508. Watz H, Waschki B, Meyer T, et al. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. Secondary Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20190002.
509. Wauters E, Smeets D, Coolen J, et al. The TERT-CLPTM1L locus for lung cancer predisposes to bronchial obstruction and emphysema. Secondary The TERT-CLPTM1L locus for lung cancer predisposes to bronchial obstruction and emphysema 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21622582.
510. Wedzicha JA. Airway infection accelerates decline of lung function in chronic obstructive pulmonary disease. Secondary Airway infection accelerates decline of lung function in chronic obstructive pulmonary disease 2001. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11734418.
511. Weill D, Weill H. Diagnosis and initial management of nonmalignant diseases related to asbestos. Secondary Diagnosis and initial management of nonmalignant diseases related to asbestos 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15722420.
512. Weitzenblum E, Chaouat A, Kessler R, Canuet M. Overlap syndrome: obstructive sleep apnea in patients with chronic obstructive pulmonary disease. Secondary Overlap syndrome: obstructive sleep apnea in patients with chronic obstructive pulmonary disease 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18250217.
513. White CS, Jerome S. Coronary calcium scoring on nongated chest CT: is it ready for prime time? Secondary Coronary calcium scoring on nongated chest CT: is it ready for prime time? 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21477788.
514. Willemse BWM, ten Hacken NHT, Rutgers B, Lesman-Leegte IGAT, Postma DS, Timens W. Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers. Secondary Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16264044.
515. Willemse BWM, ten Hacken NHT, Rutgers B, Postma DS, Timens W. Association of current smoking with airway inflammation in chronic obstructive pulmonary disease and asymptomatic smokers. Secondary Association of current smoking with airway inflammation in chronic obstructive pulmonary disease and asymptomatic smokers 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15850494.
516. Wilson D, Adams R, Appleton S, Ruffin R. Difficulties identifying and targeting COPD and population-attributable risk of smoking for COPD: a population study. Secondary Difficulties identifying and targeting COPD and population-attributable risk of smoking for COPD: a population study 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16236852.
517. Wong SYS, Woo J, Lynn HSH, Leung J, Tang YN, Leung PC. Risk of depression in patients with chronic respiratory diseases: results from two large cohort studies in Chinese elderly from Hong Kong. Secondary Risk of depression in patients with chronic respiratory diseases: results from two large cohort studies in Chinese elderly from Hong Kong 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=16440404.
518. Wood AM. Re-evaluating COPD risk: just a matter of definition. Secondary Re-evaluating COPD risk: just a matter of definition 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21474423.
519. Wood AM, Stockley RA. The genetics of chronic obstructive pulmonary disease. Secondary The genetics of chronic obstructive pulmonary disease 2006. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17054776.
520. Wu J, Sin DD. Improved patient outcome with smoking cessation: when is it too late? Secondary Improved patient outcome with smoking cessation: when is it too late? 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21814462.
521. Wu T-L, Chang P-Y, Tsao K-C, Sun C-F, Wu LL, Wu JT. A panel of multiple markers associated with chronic systemic inflammation and the risk of atherogenesis is detectable in asthma and chronic obstructive pulmonary disease. Secondary A panel of multiple markers associated with chronic systemic inflammation and the risk of

atherogenesis is detectable in asthma and chronic obstructive pulmonary disease 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=18041101.
522. Xu F, Yin X, Shen H, Xu Y, Ware RS, Owen N. Better understanding the influence of cigarette smoking and indoor air pollution on chronic obstructive pulmonary disease: a case-control study in Mainland China. Secondary Better understanding the influence of cigarette smoking and indoor air pollution on chronic obstructive pulmonary disease: a case-control study in Mainland China 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17986120.
523. Xu W, Collet J-P, Shapiro S, et al. Independent effect of depression and anxiety on chronic obstructive pulmonary disease exacerbations and hospitalizations. Secondary Independent effect of depression and anxiety on chronic obstructive pulmonary disease exacerbations and hospitalizations 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18755925.
524. Yamane T, Hattori N, Kitahara Y, et al. Productive cough is an independent risk factor for the development of COPD in former smokers. Secondary Productive cough is an independent risk factor for the development of COPD in former smokers 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20070589.
525. Yan F, Chen C, Jing J, Li W, Shen H, Wang X. Association between polymorphism of glutathione S-transferase P1 and chronic obstructive pulmonary disease: a meta-analysis. Secondary Association between polymorphism of glutathione S-transferase P1 and chronic obstructive pulmonary disease: a meta-analysis 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20117922.
526. Yang C-Y, Chen C-J. Air pollution and hospital admissions for chronic obstructive pulmonary disease in a subtropical city: Taipei, Taiwan. Secondary Air pollution and hospital admissions for chronic obstructive pulmonary disease in a subtropical city: Taipei, Taiwan 2007. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=17573635.
527. Yang P, Sun Z, Krowka MJ, et al. Alpha1-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk. Secondary Alpha1-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18504338.
528. Yawn BP, Kaplan A. Co-morbidities in people with COPD: a result of multiple diseases, or multiple manifestations of smoking and reactive inflammation? Secondary Co-morbidities in people with COPD: a result of multiple diseases, or multiple manifestations of smoking and reactive inflammation? 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18338090.
529. Yentes JM, Sayles H, Meza J, Mannino DM, Rennard SI, Stergiou N. Walking abnormalities are associated with COPD: An investigation of the NHANES III dataset. Secondary Walking abnormalities are associated with COPD: An investigation of the NHANES III dataset 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20615681.
530. Yohannes AM. Depression and COPD in older people: a review and discussion. Secondary Depression and COPD in older people: a review and discussion 2005. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15750501.
531. Yoon HI, Sin DD. Confronting the colossal crisis of COPD in China. Secondary Confronting the colossal crisis of COPD in China 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21467051.
532. Young R, Hopkins R. Lung function predicts lung cancer. Secondary Lung function predicts lung cancer 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20513918.
533. Young R, Hopkins R, Etzel C, El-Zein R. Genetics of lung cancer susceptibility and COPD. Secondary Genetics of lung cancer susceptibility and COPD 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21708349.
534. Young RP, Hopkins RJ. How the genetics of lung cancer may overlap with COPD. Secondary How the genetics of lung cancer may overlap with COPD 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=21749550.
535. Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Secondary COPD prevalence is increased in lung cancer, independent of age, sex and smoking history 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19196816.
536. Zaher C, Halbert R, Dubois R, George D, Nonikov D. Smoking-related diseases: the importance of COPD. Secondary Smoking-related diseases: the importance of COPD 2004. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=15636487.
537. Zaman M, Mahmood S, Altayeh A. Low inspiratory capacity to total lung capacity ratio is a risk factor for chronic obstructive pulmonary disease exacerbation. Secondary Low inspiratory capacity to total lung capacity ratio is a risk factor for chronic obstructive pulmonary disease exacerbation 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20375693.

538. Zamarron C, Garcia Paz V, Morete E, del Campo Matias F. Association of chronic obstructive pulmonary disease and obstructive sleep apnea consequences. Secondary Association of chronic obstructive pulmonary disease and obstructive sleep apnea consequences 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19281082.
539. Zeki AA, Schivo M, Chan AL, et al. Geoepidemiology of COPD and idiopathic pulmonary fibrosis. Secondary Geoepidemiology of COPD and idiopathic pulmonary fibrosis 2010. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20018478.
540. Zhan P, Wang J, Wei S-Z, et al. TNF-308 gene polymorphism is associated with COPD risk among Asians: meta-analysis of data for 6,118 subjects. Secondary TNF-308 gene polymorphism is associated with COPD risk among Asians: meta-analysis of data for 6,118 subjects 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20364405.
541. Zhang H, Cai B. The impact of tobacco on lung health in China. Secondary The impact of tobacco on lung health in China 2003. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12856737.
542. Zhou H, Alexis NE, Almond M, et al. Influence of C-159T SNP of the CD14 gene promoter on lung function in smokers. Secondary Influence of C-159T SNP of the CD14 gene promoter on lung function in smokers 2009. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=19361972.
543. Zhou X, Wang Z, Song Y, Zhang J, Wang C. Periodontal health and quality of life in patients with chronic obstructive pulmonary disease. Secondary Periodontal health and quality of life in patients with chronic obstructive pulmonary disease 2011. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=20630736.
544. Zidzik J, Slaba E, Joppa P, et al. Glutathione S-transferase and microsomal epoxide hydrolase gene polymorphisms and risk of chronic obstructive pulmonary disease in Slovak population. Secondary Glutathione S-transferase and microsomal epoxide hydrolase gene polymorphisms and risk of chronic obstructive pulmonary disease in Slovak population 2008. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=18461673.

Appendix 5: TRIPOD Checklist for Chapter 5: Prediction Model Development and Validation

Section/Topic	tem		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	157
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	157
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	159
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	159, 160
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	161
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	161
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	161
	5b	D;V	Describe eligibility criteria for participants.	161
	5c	D;V	Give details of treatments received, if relevant.	N/A
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	162
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	7a	D;V	Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured.	163, 164
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A
Sample size	8	D;V	Explain how the study size was arrived at.	163
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	164
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	164
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	164
	10c	V	For validation, describe how the predictions were calculated.	165
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	165
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N/A

Section/Topic	tem		Checklist Item	Page
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	165
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	165
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	167, 168
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	168, 170, 171, 172
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	173, 177
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	168, 173
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	176
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	176
	15b	D	Explain how to use the prediction model.	176
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	174
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	N/A
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	182
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	179
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	179, 183
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	173
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	N/A
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	Acknowledgements

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V.

Appendix 6: TargetCOPD screening questionnaire

TargetCOPD POSTAL QUESTIONNAIRE TO PATIENTS

PATIENT ID_____

Thank you for taking the time to fill in this questionnaire. Your input is very valuable so please complete as many questions as you are able and return in the reply-paid envelope. Alternatively you may complete this form online at

https://www.pc-crtu.bham.ac.uk/Target

Please try to answer every question with the closest answer possible by ticking the appropriate box.

SECTION 1: YOUR LUNG HEALTH

1. (a) Do you usually have a cough (either during the day, or night, or first thing in the morning)?

   Yes ☐

   No ☐ **(If No, go to Q2)**

   (b) Do you usually cough like this on most days for 3 consecutive months or more during the year?

   Yes ☐ → If yes, for how many years have you had this cough? .....years

   No ☐

   (c) Does the weather affect your cough? Yes ☐ No ☐

2. (a) Do you ever cough up phlegm from your chest when you don't have a cold

   Yes ☐

   No ☐ **(If No, go to Q3)**

   (b) Do you usually bring up phlegm from your chest (either during the day, or night, or first thing in the morning)? Yes ☐ No ☐

(c) Do you bring up phlegm on most days for 3 consecutive months or more during the year?

Yes ☐ → If yes, for how many years have you had trouble with phlegm? ..... years

No ☐

3. Have you had wheezing or whistling in the chest in the past 12 months?

Yes ☐ → If yes, how frequently do you wheeze?

Occasionally ☐ More often ☐

No ☐

4. Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?

Yes ☐ No ☐

5. Do you get short of breath walking with other people of your own age on level ground or have to stop for breath after about 15 minutes when walking at your own pace?

Yes ☐ No ☐

6. Do you have to stop for breath after walking about 100m or after a few minutes on level ground?

Yes ☐ No ☐

7. Are you too breathless to leave the house, or breathless while dressing or undressing?

Yes ☐ No☐

8. Can you lie flat at night?

Yes ☐

No ☐ → If no, how many pillows do you need **in total**?.....

9. Do you have or have you had any allergies?

Yes ☐

No ☐ **(If No, go to Q11)**

10. If yes, what type of allergies? (tick any that apply)

Hay fever ☐ Eczema ☐ Skin allergies ☐ Allergic rhinitis (nose/eye symptoms) ☐

Food allergies ☐ Other ☐ (please specify)…….....…….

11. Do you usually have a blocked or running nose? Yes ☐ No ☐

12. Over the last year has your breathing kept you from doing as much as you used to? Yes ☐ No ☐

SECTION 2: YOUR GENERAL HEALTH AND CIRCUMSTANCES

13. How would you describe your health in general?

Very good ☐ Good ☐ Fair ☐ Bad ☐ Very bad ☐

14. Has a doctor ever said you have (please tick any that apply):

Asthma	☐	High blood pressure	☐
COPD	☐	Diabetes	☐
Chronic bronchitis	☐	Stroke	☐
Emphysema	☐	Lung cancer	☐
Heart disease	☐	Tuberculosis	☐
Heart failure	☐	Depression	☐

Other medical condition (please specify)

……

15. Have you ever had a paid job?

Yes ☐ Please state the occupation you have been employed in most of your life

…….....

.....

.....

Please describe what you do/did in this job

…….....

.....……

……

……

……

No ☐

16. Have you ever worked in a job which exposed you to vapours, gas, dust or fumes?

Yes ☐

No ☐ **(If No, go to Q18)**

17. If yes, for how many years have you been exposed?

.....

18. (a) Have you ever smoked as much as one cigarette a day (or one cigar a week or an ounce of tobacco a month) for as long as one year? ☐ Yes

No ☐ **(If No, go to Q19)**

(b) (b) How much do/did you smoke a day?

.....cigarettes/day .....cigars/week.....oz or .....g tobacco/week

(c) How old were you when you started smoking?.....

(d) Do you still smoke?

Yes ☐ **(If Yes, go to Q19)**

No ☐

(e) How old were you when you finally stopped smoking?.....

19. In most weeks, how many hours per week are you exposed to other people's tobacco smoke? .....

20. What is your current height without shoes? …… metres **or** ……feet..…inches

21. What is your current weight without shoes? …….kg **or**……stone…..pounds

22. Please indicate your date of birth: ……..

23. Sex: Male ☐ Female ☐

24. How would you class your ethnic group? (Please tick one)

White

English/Welsh/Scottish/Northern Irish/British ☐
Irish ☐
Gypsy/Irish Traveller ☐
Any other white background ☐

Mixed / multiple ethnic groups

White & Black Caribbean ☐
White & Black African ☐
White & Asian ☐
Other mixed ☐

Asian / Asian British

Indian ☐
Pakistani ☐

Bangladeshi ☐
Chinese ☐
Any other Asian background ☐

Black / African / Caribbean / Black British

African ☐
Caribbean ☐
Any other Black / African / Caribbean background ☐

Other ethnic group

Arab ☐
Other ☐
Prefer not to say ☐

SECTION 3: CONTACT INFORMATION

25. Title……. First name…….....……

Surname

……..……..……...

26. Address……

……

……

……

….....

27. Postcode…….....……

……

28. Telephone number

Home:…….....……

Mobile:…….....……

……

29. Email address……...……

…

30. You may be invited for further assessment; to help us schedule these appropriately please indicate your preferred appointment times (tick any when you are available)

Monday	morning	☐	afternoon	☐	evening	☐
Tuesday	morning	☐	afternoon	☐	evening	☐
Wednesday	morning	☐	afternoon	☐	evening	☐
Thursday	morning	☐	afternoon	☐	evening	☐
Friday	morning	☐	afternoon	☐	evening	☐
Saturday	morning	☐	afternoon	☐	evening	☐

THANK YOU FOR TAKING THE TIME TO FILL OUT THIS QUESTIONNAIRE!

PLEASE RETURN AS INDICATED USING EITHER THE REPLY-PAID ENVELOPE OR ONLINE AT

https://www.pc-crtu.bham.ac.uk/Target

Appendix 7: Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

No	Item	Guide questions/description	Page
Domain 1: Research team and reflexivity			
Personal Characteristics			
1.	Interviewer/facilitator	Which author/s conducted the interview or focus group?	193
2.	Credentials	What were the researcher's credentials? *E.g. PhD, MD*	N/A
3.	Occupation	What was their occupation at the time of the study?	N/A
4.	Gender	Was the researcher male or female?	N/A
5.	Experience and training	What experience or training did the researcher have?	N/A
Relationship with participants			
6.	Relationship established	Was a relationship established prior to study commencement?	193
7.	Participant knowledge of the interviewer	What did the participants know about the researcher? e.*g. personal goals, reasons for doing the research*	N/A
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. *Bias, assumptions, reasons and interests in the research topic*	206
Domain 2: study design			
Theoretical framework			
9.	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis*	194
Participant selection			
10.	Sampling	How were participants selected? *e.g. purposive, convenience, consecutive, snowball*	193
11.	Method of approach	How were participants approached? e.*g. face-to-face, telephone, mail, email*	193
12.	Sample size	How many participants were in the study?	195
13.	Non-participation	How many people refused to participate or dropped out? Reasons?	195
Setting			
14.	Setting of data collection	Where was the data collected? e.*g. home, clinic, workplace*	195
15.	Presence of non-participants	Was anyone else present besides the participants and researchers?	193
16.	Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*	195
Data collection			
17.	Interview guide	Were questions, prompts, guides provided by	194

		the authors? Was it pilot tested?	
18.	Repeat interviews	Were repeat interviews carried out? If yes, how many?	193
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?	193
20.	Field notes	Were field notes made during and/or after the interview or focus group?	193
21.	Duration	What was the duration of the interviews or focus group?	193
22.	Data saturation	Was data saturation discussed?	193
23.	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	193
Domain 3: analysis and findings			
Data analysis			
24.	Number of data coders	How many data coders coded the data?	194
25.	Description of the coding tree	Did authors provide a description of the coding tree?	N/A
26.	Derivation of themes	Were themes identified in advance or derived from the data?	194
27.	Software	What software, if applicable, was used to manage the data?	194
28.	Participant checking	Did participants provide feedback on the findings?	N/A
Reporting			
29.	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.*g. participant number*	195-202
30.	Data and findings consistent	Was there consistency between the data presented and the findings?	195-202
31.	Clarity of major themes	Were major themes clearly presented in the findings?	205
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	185-202