EVALUATING STRATEGIES FOR THE EARLY DETECTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

by

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease that often goes undiagnosed. Reducing the burden of undiagnosed COPD requires well designed early detection programs that have been formally evaluated.

Objectives: The objective of this thesis was to determine whether there are subgroups of COPD patients in which case detection, followed by evidence-based disease management, would be cost-effective compared with the status quo (no case detection). To answer this question, I 1) identified factors that distinguish patients with undiagnosed from those with diagnosed COPD, 2) assessed heterogeneity in the presence of respiratory symptoms, 3) analysed healthcare encounters prior to COPD diagnosis to identify opportunities for case detection, and 4) evaluated the cost-effectiveness of early detection strategies.

Methods: I performed a systematic review to generate pooled odds ratios for factors associated with a COPD diagnosis. I used data from a population-based Canadian study to assess heterogeneity between individuals in the occurrence of respiratory symptoms. I characterised healthcare encounters before COPD diagnosis using health administrative data from British Columbia. I combined evidence from Objectives 1-3 in a whole disease model of COPD to assess the cost-effectiveness of case detection strategies implemented during routine primary care visits.

Results: Patients with diagnosed COPD were less likely to have mild disease (OR 0.30, 95%CI 0.24–0.37) and more likely to report respiratory symptoms (OR 11.45 95%CI 7.20–18.21) than patients with undiagnosed COPD. However, individual-specific probabilities for the occurrence of symptoms indicated substantial heterogeneity between patients. COPD patients frequently

visited primary care physicians before diagnosis (mean 10.29, IQR 4–13 visits/year). In the two years prior to diagnosis, 72.1% of COPD patients had a respiratory-related primary care visit that did not result in a diagnosis. In the preferred case detection strategy, all patients ≥40 years received a screening questionnaire during their routine visits to a primary care physician. This strategy had an Incremental Cost-Effectiveness Ratio of $18,791/QALY compared to no case detection.

Conclusions: Patients with undiagnosed COPD have identifiable characteristics, they frequently encounter the healthcare system, and strategies for improving their **e**arly detection are cost-effective when combined with guideline-recommended treatment.

Lay Summary

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease that affects over 2.6 million Canadians. Despite its prevalence, 70% of patients with COPD in Canada have not been diagnosed and are not receiving treatment. The objective of this thesis was to characterise undiagnosed COPD patients, assess their interactions with the healthcare system, and evaluate strategies for improving their diagnosis. I found that patients with undiagnosed COPD tend to have mild disease and few respiratory symptoms. Although current guidelines recommend restricting testing for COPD to patients with symptoms, I found that the presence of symptoms was highly variable between patients. Nearly all COPD patients encountered the healthcare system in the five years before they were diagnosed. Regular use of a questionnaire to assess the risk of COPD, implemented during the routine primary care visits of patients over 40 years, is a cost-effective strategy for improving early detection of COPD.

Preface

This thesis is composed of three original studies and one systematic review addressing the burden of undiagnosed COPD and evaluating policies for improving its early detection. I was responsible for developing the research questions, conducting the statistical analyses, developing the decision model, and writing the chapters. My supervisors, Drs. Mohsen Sadatsafavi and Stirling Bryan, and my PhD committee members, Drs. Mark Harrison, Corey Nislow, Larry Lynd, and Don Sin, provided feedback on the research design and interpretation of results.

The following manuscripts resulted from this thesis:

1) Kate M. Johnson, Stirling Bryan, Shahzad Ghanbarian, Don D. Sin, and Mohsen Sadatsafavi. Characterizing Undiagnosed Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. 2018. Respiratory Research 19:26. (published, Chapter 2)

   MS, SB, and KJ formulated the study idea and designed the study. KJ and SG performed all data analyses and MS, SB and DS contributed to interpretation of findings. KJ wrote the first draft of the manuscript. All authors critically commented on the manuscript and approved the final version. My total contribution to this research was >90%.

2) Kate M. Johnson, Abdollah Safari, Wan C. Tan, Jean Bourbeau, J. Mark FitzGerald, and Mohsen Sadatsafavi. Heterogeneity in the Respiratory Symptoms of Patients with Mild-to-Moderate COPD. 2018. International Journal of Chronic Obstructive Pulmonary Disease 2018:13 pg. 3983-3995. (published, Chapter 3)

WT and JB are co-Principal Investigators of the CanCOLD study, which was the source of data for this analysis. MS and KJ formulated the current study idea. KJ performed all data analyses and wrote the first draft of the manuscript. AS provided guidance on the statistical analysis. All authors contributed to the interpretation of findings, critically commented on the manuscript, and approved the final version. My total contribution to this research was >90%.

3) Kate M. Johnson, Amir Khakban, Stirling Bryan, Don D. Sin, and Mohsen Sadatsafavi. Healthcare system encounters before COPD diagnosis: a registry-based longitudinal cohort study. 2020. Thorax 75:108-115. (published, Chapter 4)
MS, SB and KJ formulated the study idea. AK prepared the data. KJ performed all data analyses and wrote the first draft of the manuscript. All authors contributed to interpretation of findings, critically commented on the manuscript and approved the final version. My total contribution to this research was >85%.

Ethics approval was required for data related to this thesis:

1) Ethics approval for the CanCOLD study was obtained by the respective university and institutional ethical review boards from each study site: UBC/PHC Research Ethics Board, P05-006 (Vancouver); Biomedical-C Research Ethics Board, BMC-06-002 (Montreal); UHN REB, 06-0421-B (Toronto); Capital Health Research Ethics Board, CDHA-RS/ 2007-255 (Halifax); Conjoint Health Research Ethics Board, ID21258 (Calgary); DMED-1240-09 (Kingston); 2009519-01H (Ottawa); Bio-REB09-162 (Saskatoon); CER20459 (Quebec City). Written informed consent was obtained from all

participants prior to study entry. CanCOLD was carried out in accordance with the principles of the Declaration of Helsinki.

2) Ethics approval for obtaining and analysing data from the administrative health databases of British Columbia (BC) Ministry of Health was obtained from Population Data BC (H13-00684).

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AECOPD, Acute Exacerbations of COPD

BC, British Columbia

BMI, Body Mass Index

BOLD, Burden of Obstructive Lung Disease

CanCOLD, Canadian Cohort of Obstructive Lung Disease Study

CAT, COPD Assessment Test

CHEERS, Consolidated Health Economic Evaluation Reporting Standards

CI, Confidence Interval

COPD, Chronic Obstructive Pulmonary Disease

CDQ, COPD Diagnostic Questionnaire

DIN, Drug Identification Number

EPIC, Evaluation Platform in COPD

EPI-SCAN, Epidemiologic Study of COPD in Spain

FEV_1, Forced Expiratory Volume in 1 second

FVC, Forced Vital Capacity

GOLD, Global Initiative for chronic Obstructive Lung Disease

ICER, Incremental Cost-Effectiveness Ratio

INMB, Incremental Net Monetary Benefit

ICS, Inhaled Corticosteroids

IQR, Interquartile Range

LAMA, Long-Acting Muscarinic Antagonists

LABA, Long-Acting Beta-Agonists

LLN, Lower Limit of Normal

MD, Mean Difference

MPR, Medication Possession Ratio

MRC, Medical Research Council dyspnea scale

mMRC, modified Medical Research Council dyspnea scale

NRT, Nicotine Replacement Therapy

OR, Odds Ratio

PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease

PREPOCOL, Prevalence study of COPD in Colombia

QALY, Quality Adjusted Life Year

RR, Rate Ratio

SABA, Short-Acting Beta-Agonists

SAMA, Short-Acting Muscarinic Agents

SES, Socioeconomic Status

SD, Standard Deviation

WTP, Willingness to Pay

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I thank my supervisors, Drs. Mohsen Sadatsafavi and Stirling Bryan, for their time and encouragement in helping to produce this work. I will always be grateful for their mentorship, and their genuine and unwavering support for my success. May every PhD student be as fortunate as I have been.

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For Alex

My partner on the road to Ithaka

Chapter 1: Introduction

Early detection is an important component of high-quality care for many diseases. Programs to detect patients with undiagnosed disease have been developed to meet this objective. Two widespread examples of this approach are screening for cervical cancer among adult women[1], and screening for hypertension in older adults[2], which have both been associated with reduced morbidity and mortality from disease[3,4]. The goal of early detection programs is to diagnose disease while it is early in its progression. However, in order for early detection to be of value, a diagnosis must be associated with altered disease progression in patients[5]. It might be this criterion that that has, thus far, prevented widespread implementation of early detection programs for chronic obstructive pulmonary disease (COPD). Many authors argue that early detection of COPD will uncover mostly asymptomatic patients with mild disease, for whom there are limited treatment options and ability to alter the disease progression[6,7]. On the other hand, objective evaluations of these policies are rare, and respiratory researchers have been accused of nihilism with regards to the value of early detection[8]. This is in contrast to the key role economic evaluations have played in informing policies related to early intervention for diabetes[9], cancer[10], and cardiovascular disease[11], which have ultimately helped reduce the burden of these diseases[3,4,12]. A formal evaluation of 'value for money' is required before any early detection program is adopted. This evidence is currently lacking for COPD, and although controversial, an earlier diagnosis could have substantial public health benefits[13].

The overarching themes of this thesis are evidence generation on patterns of care for COPD and the natural history of disease, followed by decision modelling to evaluate policies for the early detection of COPD. Chronic obstructive pulmonary disease is an extremely

heterogeneous disease, and a policy for improving its diagnosis should account for differences in patient characteristics and disease trajectories. I applied the lens of precision medicine to incorporate heterogeneity between individuals when assessing components of the natural history of COPD. Evidence on heterogeneity between individuals can serve as a foundation for individualised prediction tools and enable more precise risk factor and disease management[14]. This evidence was also synthesised in the disease model that was used to assess the value of early detection for COPD.

In this chapter, I will provide an overview of the epidemiology, burden, and treatment of COPD, and current practices for its diagnosis. I discuss existing evidence on the value of early detection of COPD, and knowledge gaps in these evaluations. I place the specific objectives of this thesis in the context of my research themes: evidence generation for precision medicine, followed by whole disease modelling to evaluate policy. I conclude with background information on the whole disease model that was used to evaluate early detection strategies.

1.1 COPD epidemiology

Chronic obstructive pulmonary disease is a disease of the airways that is associated with irreversible airflow obstruction and progressive lung function decline[15]. Patients with COPD typically experience symptoms such as shortness of breath, cough, sputum production, and periods of intensified disease activity referred to as exacerbations[16]. Although 80% of the burden of COPD has been attributed to cigarette smoking[17], aging, environmental and occupational exposures are also important risk factors[18]. Because COPD is often caused by chronic and repeated lung injury; patients with COPD tend to be over 40 years old[19]. Disease progression is characterised by increasing airflow limitation, as measured by forced expiratory volume in 1

second (FEV_1). Exacerbations are a major cause of morbidity, mortality and economic burden[16], and are the leading cause of hospital admissions among chronic diseases in Canada[20]. A third, often underappreciated component of the burden of COPD is the high incidence of extra-pulmonary comorbidities, including cardiovascular disease, diabetes mellitus[21], and depression[22]. In particular, cardiovascular disease is 2.5 times more prevalent in patients with COPD than in the general population[23], and it is the leading cause of mortality in patients with COPD[24]. This may be due to the underlying role of systemic inflammation, or to shared risk factors. Comorbidities complicate the management of disease[25], contribute to disease progression, and increase its burden[24].

An important aspect of COPD is that it is very heterogeneous. The extent and rate of lung function decline tends to vary substantially between individuals[26–28]. In the landmark Lung Health Study, which followed early stage COPD patients for up to 11 years[29], patients had an annual rate of change in lung function that ranged from rapidly declining to modestly increasing (interval for the rate of change in FEV_1 containing 95% of patients: -83 mL/yr to 15 mL/yr)[28]. Easily measured clinical characteristics including age, sex and smoking history, explained 88% of this variation in lung function decline[28]. The rate and severity of exacerbations is also heterogeneous between patients with COPD[30,31]. In the Azithromycin for Prevention of Exacerbations of COPD (MACRO) clinical trial, 95% of COPD patients had model-based exacerbation rate between 0.47 and 4.22 exacerbations per year[32]. Heterogeneity in respiratory symptoms, a third major component of the natural history of COPD, has not been well quantified.

1.2 Burden of COPD

Chronic obstructive pulmonary disease is a highly prevalent disease. In 2014, there were 94,647 cases of diagnosed COPD in British Columbia (BC) and 804,043 cases in Canada[33]. In BC, the prevalence of COPD is estimated at 19% in adults ≥40 years[34]. Globally, the number of COPD cases is approximately 400 million[35]. COPD is also associated with a large economic burden. In BC, the total direct medical costs of COPD were $5,452 (2010 CAD) per patient per year from 2001 to 2010. 57% of these costs were due to hospital admissions[36]. In Canada, expenditures related to COPD were estimated to cost the healthcare system $4.25 billion in 2011 alone[37].

The aging population is expected to result in a 150% increase in the prevalence of COPD by 2030, and a 220% increase in prevalence in the population 75 years of age or older[38]. This is despite a 43% decrease in the prevalence of smoking in BC between 1999 and 2013[39]. Similarly, hospitalisations due to COPD are projected to increase by 182% between 2010 and 2030[38]. The economic burden of COPD is predicted to increase in conjunction with its prevalence. It is critical to develop disease management strategies to alleviate the increasing economic and public health burden of COPD.

1.3 Definition of COPD

The Global Initiative for chronic Obstructive Lung Disease (GOLD) recommends considering a diagnosis of COPD in patients with recurring respiratory symptoms such as dyspnea, cough, or sputum, and a history of exposure to risk factors[15]. Spirometry, a lung function test that measures airflow limitation, is used to diagnose COPD. Spirometry is a simple and safe diagnostic procedure that is highly reliable if performed correctly[8]. GOLD defines COPD as the ratio of FEV_1 to forced vital capacity (FVC) of less than 0.7 after the administration of a bronchodilator.

An alternative definition of COPD is FEV_1/FVC below the lower limit of normal (LLN), which is the lower fifth percentile of an age and gender-stratified healthy reference population[40]. The severity of COPD is divided into four stages based on the ratio of FEV_1 to its predicted reference value for a healthy individual[41] (Table 1-1).

Table 1-1 Global Initiative for chronic Obstructive Lung Disease (GOLD) classification of COPD severity.

COPD Severity		
GOLD 1 (mild COPD)	$FEV_1 \geq 80\%$ predicted	$FEV_1/FVC < 0.70$
GOLD 2 (moderate COPD)	$50\% \leq FEV_1 < 80\%$ predicted	
GOLD 3 (severe COPD)	$30\% \leq FEV_1 < 50\%$ predicted	
GOLD 4 (very severe COPD)	$FEV_1 < 30\%$ predicted	

1.4 Diagnosis of COPD

Patients with COPD generally seek medical attention that results in a diagnosis because they are experiencing respiratory symptoms, most frequently chronic and progressive dyspnea[15]. However, the presence and severity of symptoms varies between patients, and also within patients over time[42]. In some cases, respiratory symptoms may precede airflow limitation, and conversely, symptoms may not be present in patients with early stage COPD[15]. As a result, and because adults rarely use the full capacity of their lungs[43], progressive airflow limitation is often undetected in its early stages. In many cases, patients do not receive a diagnosis of COPD until after being hospitalised due to a severe exacerbation[44].

The Canadian Cohort of Obstructive Lung Disease (CanCOLD) is a prospective, population-based, longitudinal cohort study. Individuals with COPD were selected from the general population for long-term follow-up in CanCOLD, along with a matched cohort of at-risk subjects and healthy controls[45]. 70% of subjects with COPD in CanCOLD had not previously

received a physician diagnosis of COPD[46]. Global estimates of the burden of undiagnosed COPD are even higher. Lamprecht et al.[47] reported an average underdiagnosis rate of 81% in a prevalence study that included 30,874 participants across 44 countries. The undiagnosed patients in this study tended to be younger, male, never smokers, with fewer respiratory symptoms, and less severe COPD.

1.5 Treatment of COPD

The mainstays of treatment for COPD are interventions for smoking cessation and inhaled therapies. Smoking is the only major risk factor for COPD that is modifiable, and aside from oxygen therapy in patients with severe disease[15], smoking cessation is the only intervention that can slow the progression of lung function decline[29]. Interventions for smoking cessation increase the likelihood of sustained quitting and reduce the rate of FEV_1 decline[29,48,49]. Pulmonary rehabilitation, which aims to improve functional ability through exercise and behavioural modification, is a second effective therapy, although it is most commonly used in patients with severe COPD[50]. A recent review of randomised controlled trials found that pulmonary rehabilitation led to clinically important improvements in lung function, health-related quality of life and functional ability[50].

In addition to lifestyle interventions, inhaled pharmacotherapies can reduce symptoms, the risk and severity of exacerbations, and improve quality of life in patients with COPD[15]. Maintenance pharmacotherapy is generally used in patients with moderate to very severe disease, with the most important medications being short and long-acting bronchodilators (beta-agonists and anticholinergics), and inhaled corticosteroids (ICS)[15]. ICS has also been found to reduce the risk of lung cancer in patients with COPD[51].

In 2011, GOLD refined its assessment to include the burden of symptoms and risk of exacerbations as part of its criteria for guiding management decisions. The resulting 'ABCD' groups determine the recommended treatment for COPD patients after assessing airflow limitation (Table 1-2)[15]. Patients with few symptoms and a low risk of exacerbations ('group A') are treated with a short-acting bronchodilator (SABA), and stepped up to a long-acting muscarinic antagonist (LAMA) if symptoms increase ('group B'). Patients with few symptoms but a high risk of exacerbations ('group C') are treated with combination long-acting beta-agonist and muscarinic antagonist (LAMA/LABA). This is increased to triple combination therapy with LAMA, LABA, and ICS if symptoms are also high ('group D')[15].

Table 1-2 Global Initiative for chronic Obstructive Lung Disease (GOLD) assessment tool to guide therapeutic decisions in COPD.

Exacerbation history		
≥2 moderate exacerbations* or 1 hospitalisation due to exacerbation in the previous year	**C** *Few symptoms, High exacerbation risk*	**D** *Many symptoms, High exacerbation risk*
≤1 moderate exacerbation in the previous year	**A** *Few symptoms, Low exacerbation risk*	**B** *Many symptoms, Low exacerbation risk*
	mMRC† 0-1 or CAT‡ score <10	mMRC ≥2 or CAT score ≥10
	Symptoms	

* Moderate exacerbations are defined as those requiring treatment with antibiotics or oral corticosteroids[15]

† modified Medical Research Council dyspnea scale[52]

‡ COPD Assessment Test[53]

1.6 Potential benefits of an early diagnosis

A late diagnosis of COPD can be a missed opportunity to modify the course of disease through evidence-informed risk factor management and treatment[54]. In most cases, undiagnosed patients have mild or early stage COPD. The goals of treatment are similar in these patients: modify risk factors and reduce both symptoms and the risk of exacerbations. To accomplish this, guidelines recommend administering short or long-acting bronchodilators and smoking cessation (if applicable)[15]. Receiving a COPD diagnosis might itself lead to smoking cessation if the extent of lung obstruction is conveyed to the patient in easily understood terms (e.g., the 'lung age')[55]. Although smoking cessation is the only intervention with a direct disease-modifying effect in patients with mild disease, inhaled therapies may indirectly slow the rate of disease progression by reducing the rate of exacerbations, which are in turn associated with accelerated lung function decline[56]. In a prospective cohort study, moderate exacerbations were associated with an additional 23 mL/year decline in FEV_1 among patients with mild COPD, which was greater than was observed in moderate or severe COPD[57]. Emerging evidence suggests that early administration of long-acting bronchodilators can also have a disease-modifying effect in patients with mild COPD[58], and ICS might reduce the risk of lung cancer[51]. However, the conventional wisdom is that pharmacotherapy does not directly reduce the rate of lung function decline at any disease stage[15]. Therefore, modifying risk factors such as smoking and hazardous exposures while the disease is early in its progression is the most important component of treatment[59].

1.7 Case detection for COPD

Given the high rate of underdiagnosis in COPD, many authors have called for screening or case detection programs to diagnose patients with COPD earlier[8,60–62]. Screening and case detection are interventions applied in addition to routine diagnosis that increase the likelihood of detecting patients with undiagnosed COPD. Screening involves actively seeking out asymptomatic individuals in the general population to test for COPD. In contrast, case detection is opportunistic[8]. For example, a case detection strategy could involve testing individuals as they encounter the healthcare system for reasons related to cardiovascular disease. The definitions of case detection, screening, and routine diagnosis used in this thesis are summarised in Table 1-3.

Table 1-3 Definitions of key methods for increasing the probability of a COPD diagnosis.

	Definition
Case detection	An intervention that increases the likelihood of detecting individuals with undiagnosed COPD through opportunistic testing of patients who encounter the healthcare system for any reason.
Screening	An intervention that increases the likelihood of detecting individuals with undiagnosed COPD by systematically seeking out and testing individuals from the general population.
Routine diagnosis	A physician determining whether a patient has COPD based on the degree of airflow limitation, respiratory symptoms, and risk factors for the disease.

Despite the success of some programs, most guidelines do not recommend screening for airflow limitation in healthy adults with no respiratory symptoms[6,63]. These guidelines suggest that the high rate of false positives and questionable benefits of treating asymptomatic patients are not worth the economic costs to society. These costs can include subsequent diagnostic spirometry, and repeat follow-up visits with comprehensive pulmonary function tests and lung imaging[64].

The U.S. Preventive Services Task Force determined that 883 asymptomatic smokers would need to be screened to prevent one exacerbation in the next 6-36 months. They concluded that this would not be an efficient use of resources[65]. However, this was a simplified analysis that did not assess the impact of population characteristics, healthcare setting, or diagnostic modality on the number needed to screen. Targeted testing of patients with a high risk of undiagnosed COPD is possible through case detection, and many authors have suggested that this has the potential to improve health outcomes through earlier detection and intervention[8,60–62].

Existing case detection modalities are composed of screening spirometry or questionnaire-based methods[8]. Handheld flow meters measure airflow limitation using the ratio of FEV_1 to forced expiratory volume in 6 seconds (FEV_6). They are often used in case detection because they are cheaper and quicker to administer than diagnostic spirometry[66]. Patients with evidence of airflow limitation using a handheld flow meter are referred for high-quality diagnostic spirometry to confirm a diagnosis. In five studies in which patients were opportunistically recruited from general practices (irrespective of respiratory symptoms) and screened with handheld flow meters, the yield of new COPD cases per subject screened was between 6 and 20%[59], suggesting that the efficiency of these programs is variable.

Questionnaire-based case detection methods typically use one of two validated questionnaires: the COPD diagnostic questionnaire (CDQ)[67,68], or the lung function questionnaire[69]. The CDQ is most extensively used and has been externally validated four times[59,70]. It assesses risk factors and respiratory symptoms to determine whether a patient should undergo diagnostic spirometry. Different thresholds for referral have been used[66]; typically, a total score $\geq$19.5 indicates a high risk of COPD, and a score between 16.5 and 19.5 indicates medium risk[68] (Table 1-4).

Table 1-4 COPD diagnostic questionnaire (CDQ).

Questions	CDQ Score
Age (years)	
40-49	0
50-59	4
60-69	8
≥70	10
BMI	
<25.4	5
25.4-29.7	1
>29.7	0
Pack-years of smoking	
0-14	0
15-24	2
25-49	3
≥50	7
Does the weather affect your cough?	
Yes	3
No/No cough	0
Do you ever cough up phlegm (sputum) from your chest when you don't have a cold?	
Yes	3
No	0
Do you usually cough up phlegm (sputum) from your chest first thing in the morning?	
Yes	0
No	3
How frequently do you wheeze?	
Occasionally or more often	4
Never	0
Do you have or have you ever had allergies?	
Yes	0
No	3

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1.8 Current knowledge gaps

A major challenge for improving the early detection of COPD is that it is not clear which individuals are most likely to have undiagnosed COPD. Identifying subgroups of patients with a high prevalence of underdiagnosis can facilitate targeted case detection, which would increase the value of any early detection strategy. To date, there have been several studies comparing the clinical characteristics and risk factors of patients with a previous diagnosis to those who are undiagnosed[46,47,71]. However, the data collection and analysis standards of these studies are variable, and a formal meta-analysis to generate pooled estimates has not been performed. I hypothesise that there are easily identifiable patient characteristics that can predict the likelihood of a patient having undiagnosed COPD.

Respiratory symptoms are increasingly recognised as an important component of the burden of COPD on patients and healthcare systems[72]. However, in contrast to other components of the natural history of COPD such as lung function[28] and exacerbations[30,32], heterogeneity in symptoms has not been well studied. Patients with COPD generally seek medical attention when they experience respiratory symptoms, and evaluating the natural history of symptoms in undiagnosed patients can inform opportunities for case detection. The traditional paradigm is that respiratory symptoms increase linearly in conjunction with lung function decline[73]. However, more recent evidence suggests that symptoms are only weakly correlated with objective measures of airflow obstruction[74]. There is a need to characterise heterogeneity in the presence of respiratory symptoms among patients with COPD, and to quantify the extent to which lung function and other easily measured clinical characteristics can explain this heterogeneity.

Case detection strategies rely on encounters between undiagnosed COPD patients and the healthcare system. Understanding patterns of healthcare services use among patients with

undiagnosed COPD can provide critical information for developing case detection strategies. Previous studies have reported an increase in healthcare utilisation two[75] and five[76] years prior to an initial diagnosis of COPD. Jones et al.[76] found a missed opportunity for an earlier diagnosis in 85% of COPD patients. However, these studies did not assess the type of healthcare encounters that occur most frequently, and in comparison to a control cohort. In order to devise more efficient case detection strategies, the types of visits that offer high value opportunities for case detection should be determined.

Finally, despite information on the performance of existing case detection modalities[59], there is very little evidence on which of many proposed case detection techniques will provide the best value for money in different patient subgroups and healthcare settings. The lack of formal evaluations of the cost-effectiveness of case detection strategies is in stark contrast to other disease areas, where economic evaluations have played a major role in the adoption and implementation of screening and case finding programs[9–11]. It is increasingly accepted that evidence on cost-effectiveness is required before implementation of any early detection strategy[77].

1.9 Objectives

Given these knowledge gaps, my objectives are as follows: 1) evaluate existing evidence on the relationship between patient characteristics and the presence of undiagnosed COPD; 2) assess heterogeneity in the respiratory symptoms of patients with COPD and the extent to which easily measured patient and disease factors can explain this heterogeneity; 3) characterise the routine healthcare encounters of COPD patients before diagnosis; 4) evaluate the cost-effectiveness of

case detection strategies for COPD, including initial criteria for selecting patients, case detection method, and disease management strategies for newly diagnosed patients.

1.10 Thesis themes

The overarching themes of my work are evidence generation to understand patterns of care for COPD and the natural history of disease, followed by whole disease modelling to evaluate policy.

1.10.1 Evidence generation

To evaluate case detection strategies, I generated evidence on the characteristics of undiagnosed COPD patients, heterogeneity in respiratory symptoms, and patterns of care that give rise to opportunities for an earlier diagnosis. In addition to addressing stand-alone research questions related to undiagnosed COPD, each chapter was also used as an input in the disease model that was used to evaluate the cost-effectiveness of case detection (Figure 1-1).

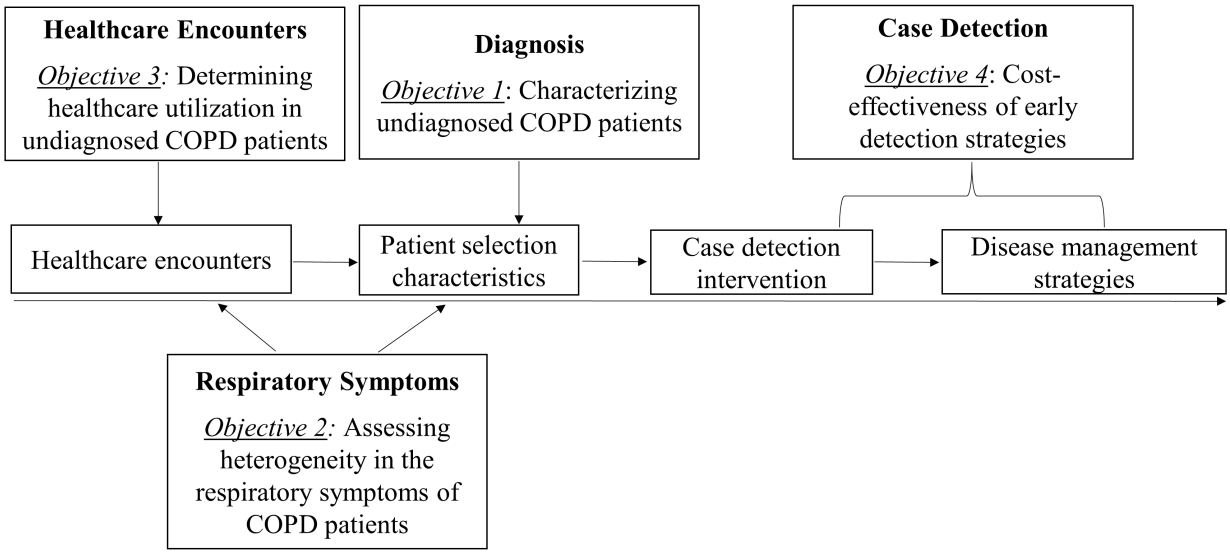


Figure 1-1 Diagram of the simulated case detection pathway and sources of evidence.

My first objective (Chapter 2) was to summarise existing evidence on the characteristics of undiagnosed COPD patients. Identifying these patients can increase our understanding of current practices around diagnosis of COPD in the community, and help identify subgroups of the population that should be targeted for case detection. This evidence was also used to identify components of disease that should be included in the whole disease model in order to simulate routine diagnosis of COPD. This was necessary to evaluate early detection strategies in Chapter 5.

My second objective (Chapter 3) was to quantify heterogeneity between individuals in the occurrence of respiratory symptoms. The results of Chapter 2 indicated that symptoms were highly influential in determining whether a patient with COPD had received a diagnosis. Therefore, the respiratory symptoms of COPD patients needed to be simulated in the whole disease model. Symptoms are also a core component of the natural history of COPD, and the highly anticipated paradigm shift from population-level to individual-level decision making in healthcare requires robust evidence on heterogeneity in disease outcomes[78]. In many cases, sufficient evidence to enable this paradigm shift does not exist. Information on heterogeneity between individuals in the natural history of disease is fundamental to developments in precision medicine, such as identifying COPD phenotypes to characterise disease trajectory and guide treatment decisions. By explicitly incorporating heterogeneity between simulated individuals in disease characteristics, the disease model can also be used as a platform to evaluate policies in precision medicine.

My third objective (Chapter 4) was to assess the type and frequency of encounters between undiagnosed COPD patients and the healthcare system. Case detection strategies rely on opportunistic encounters, and identifying patterns of care among undiagnosed COPD patients is therefore critical to their effectiveness. In addition to informing the feasibility of case detection, I used the results of this chapter to identify the type of healthcare visits to simulate in the disease model. These visits were opportunities for simulated individuals to receive case detection.

My final objective (Chapter 5) was to evaluate the cost-effectiveness of case detection for COPD. Case detection strategies were composed of eligibility characteristics to receive case detection, the case detection modality (questionnaire- or spirometry-based case detection methods), and the frequency at which case detection was administered (3- or 5-year intervals). I assessed the total costs and quality adjusted life years (QALYs) of patients receiving case detection, compared to the status quo scenario with no case detection. I determined the cost-effectiveness of each case detection strategy, identified a preferred strategy, and assessed the influence of various aspects of treatment on the value of early detection. The whole disease model that was used to evaluate case detection strategies is discussed in the next section.

1.10.2 Whole disease modelling

An objective assessment of case detection strategies requires a decision-analytic model that is capable of translating the performance of combinations of selection characteristics and case detection method into the long-term economic and health consequences of early detection. In this context, the overarching goals of decision-analytic modelling are threefold: 1) to incorporate evidence from diverse sources on the performance of case detection methods among various subgroups of patients; 2) to generate predictions over a long-time frame that may exceed the

assessment periods of empirical studies; and, 3) to translate the available evidence from intermediate outcomes (e.g., FEV_1) into final outcome measures of interest (e.g., costs and quality of life). Decision modelling can provide objective and evidence-informed comparisons of the value of different case detection strategies in terms of their overall costs and benefits.

Any strategy for improving a diagnosis of COPD needs to be combined with disease management to be impactful. Therefore, the efficiency of case detection is closely linked to the effectiveness of treatment for diagnosed patients. An improvement in treatment would greatly increase the value of early detection. In order to account for this potential feedback, both diagnosis and treatment need to be modelled simultaneously. A class of models, referred to as 'whole disease models', are particularly well suited to these types of interactions between model components[79].

Whole disease models simulate the entire trajectory of disease from biological inception until death. This is critical for policy design, as it allows a fuller exploration of the decision space created by a multitude of patient- and disease-related factors. Whole disease models can be used to evaluate interventions at any point along the care pathway. They can account for the downstream impacts of decisions, and the potential for changes that occur later in the care pathway to feed back into the decision point of interest[79]. I expanded a whole disease model of COPD, referred to as Evaluation Platform in COPD (EPIC)[80], by using the evidence generated in Chapters 2-4 to add diagnosis, symptoms, and primary care visits to the model. This allowed me to simulate case detection strategies in EPIC and evaluate their cost-effectiveness.

1.10.2.1 Evaluation Platform in COPD (EPIC)

EPIC simulates the demographics, risk factors, development, and progression of COPD in the entire Canadian population over 40 years of age from 2015 onwards. The core function of EPIC is to simulate individuals who experience events, such as the occurrence of COPD, at probabilities that are quantified through risk equations. These risk equations are developed using empirical data and serve as inputs to the model. Each component of EPIC has been checked for internal validity, meaning the model produces results that match the patterns observed in the input dataset. A second and more rigorous test of model validity is external validity, which tests whether the model correctly predicts data that was not used in its development. The core functions and structure of EPIC are depicted in Figure 1-2.

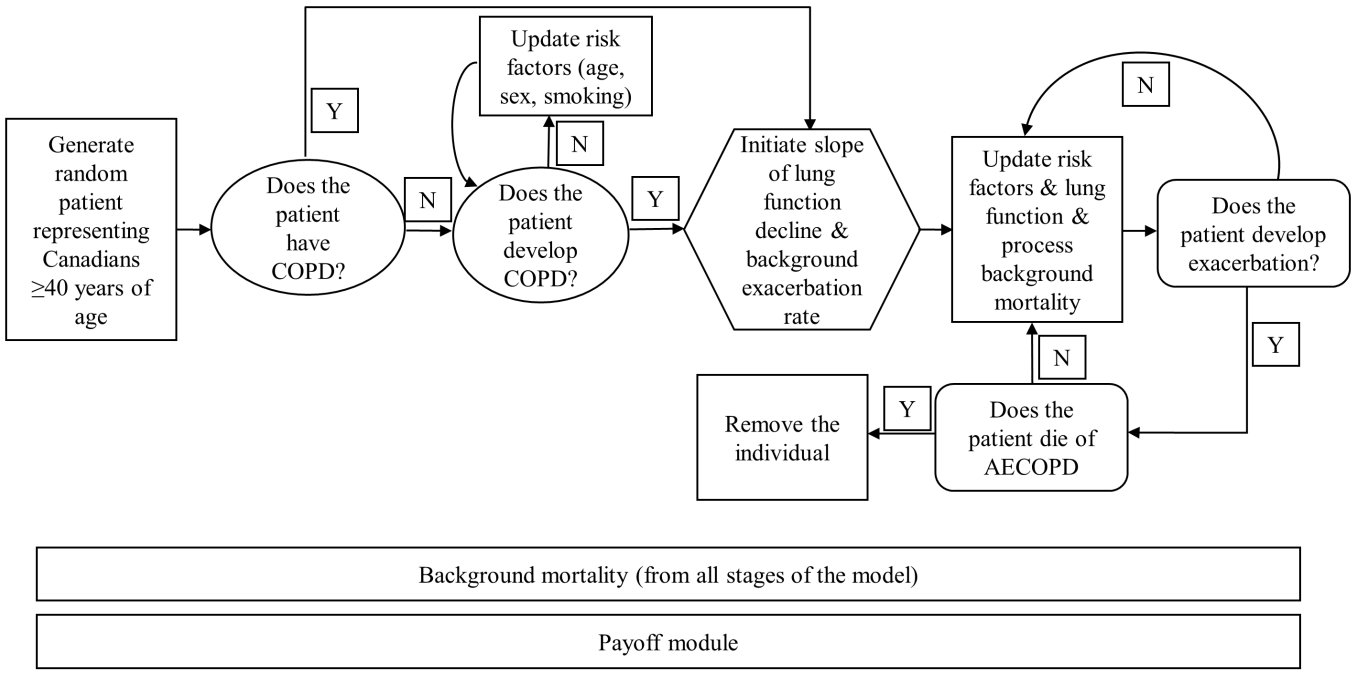


Figure 1-2 Flow diagram of Evaluation Platform in COPD model structure.

This figure is adapted from Sadatsafavi et al.[80].

EPIC models a dynamic (open) population using discrete event simulation[79]. Individuals are simulated and followed through time as they die, emigrate, or the time horizon is reached. There are five core components to the model. Their development and validation is detailed in a previous study[80] and summarised here. (1) In the demographic module, the entire Canadian population ≥40 years of age in 2015 is created. Each simulated individual is assigned an age, sex, and baseline smoking history. The resulting demographic trends were validated against Statistics Canada projections[81]. (2) The smoking module assesses the smoking behaviour of individuals over time. Individuals can initiate or quit smoking at rates predicted by the Canadian Community Health Survey and CanCOLD[45]. This module was validated against overall trends in smoking prevalence in Canada, including a 4% annual decline in current smokers[39]. (3) The COPD module simulates prevalent and incident COPD. The proportion of individuals with COPD at the start of the model time horizon was validated with the Canadian COPD prevalence study (COLD)[45]. (4) When COPD occurs, the lung function module assigns a baseline FEV_1 using regression equations developed from COLD. The progression of FEV_1 over time is determined from previously published equations that were developed using data from the Lung Health Study and have been extensively externally validated[28]. (5) Simulated individuals could experience exacerbations at rates and severities that were validated with a meta-analysis[82] and the MACRO clinical trial[83]. There was also a probability of mortality associated with severe exacerbations. (5) Finally, the payoff module assigns background costs[84] and utilities[84–86] stratified by GOLD grade. A cost[87,88] and disutility[84] is also associated with exacerbations. Overall mortality, and the

rate and severity of exacerbations generated by EPIC were validated against two external cohort studies (TORCH and UPLIFT) with robust results[80].

1.11 Thesis summary

In this thesis, I identified patient and disease characteristics associated with a diagnosis of COPD, quantified heterogeneity in the respiratory symptoms of COPD patients, which are a key component of the natural history of disease, and assessed healthcare encounters among undiagnosed COPD patients. The results of each chapter informed the simulation of case detection in EPIC, which was used to evaluate the cost-effectiveness of early detection strategies for COPD.

In Chapter 2, I performed a systematic review and meta-analysis to compare patient and disease characteristics between individuals with undiagnosed persistent airflow limitation and those with diagnosed COPD. I extracted and pooled summary data on the proportion or mean of each risk factor among diagnosed and undiagnosed patients, and coefficients for the adjusted association between risk factors and diagnosis status. This analysis was used to determine which aspects of the natural history of COPD needed to be added to EPIC in order to simulate current practices around COPD diagnosis.

In Chapter 3, I used a longitudinal cohort study of the general Canadian population with persistent airflow limitation to assess overall heterogeneity in the occurrence of symptoms. I determined the proportion of heterogeneity in the burden of symptoms that could be explained by lung function versus all other measured clinical characteristics of participants. The risk equations developed in this chapter were used to simulate respiratory symptoms in EPIC.

In Chapter 4, I used administrative health data for the province of British Columbia to create a retrospective cohort of COPD patients before diagnosis. I assessed the rate of visits to pharmacists, primary care physicians, and specialist physicians in the 5 years prior to an initial diagnosis of COPD. I compared this to non-COPD subjects matched on age, sex, and socioeconomic status. The results of this chapter were used to identify routine healthcare encounters that could be used as opportunities for case detection of undiagnosed patients.

In Chapter 5, I used EPIC to assess the cost-effectiveness of 16 case detection scenarios. Individuals meeting selection criteria based on age, smoking history, or symptoms, received the CDQ or screening spirometry (using a handheld flow meter) during their routine visits to a primary care physician. I determined the case detection strategy with the highest value, and provided evidence on whether early detection of COPD is a worthwhile investment of resources.

In Chapter 6, I conclude by summarizing my findings on the value of early detection for COPD, and suggest specific policies that should be targeted for implementation. I identify key messages for improving existing practices around the diagnosis of COPD in the community, and suggest changes to current guidelines that reflect this. Finally, I critique my research in terms of its strengths and limitations, and discuss future work to facilitate policy development and adoption.

The results of this thesis can help identify undiagnosed COPD patients, improve our understanding of disease heterogeneity, inform opportunities for diagnosis, and provide an objective evaluation of the value for money of early detection strategies for COPD. Evidence on the impact of an early diagnosis on the long-term health outcomes of patients with COPD, and the cost-effectiveness of strategies for improving detection, can help reduce the large burden of COPD on patients and the healthcare system.

Chapter 2: Characterising Undiagnosed Chronic Obstructive Pulmonary Disease: a Systematic Review and Meta-Analysis

2.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a lung disorder that is characterised by persistent airflow limitation[15] and associated with symptoms of shortness of breath, cough, and sputum production[16]. Patients with COPD generally seek medical attention when they experience respiratory symptoms, most notably dyspnea that is persistent and progressive[15]. However, owing to under-utilisation of lung function measurements and non-specific nature of the symptoms, COPD is often not recognised until late in the disease process. Indeed, many patients do not receive a diagnosis of COPD until after being hospitalised due to a severe exacerbation[44].

Lamprecht et al.[47] reported an average underdiagnosis rate of 81% in a prevalence study that included 30,874 participants across 44 countries. Reducing risk factors such as smoking and occupational risk factors while the disease is early in its progression is an important component of treatment for COPD[59]. As such, late diagnosis of COPD represents a missed opportunity to modify the course of the disease through evidence-informed risk factor management and treatment[54,61]. The extent of this missed opportunity is a function of the number of COPD patients who are undiagnosed, and the burden of disease (e.g., symptom burden, lung function status) in this population.

Quantifying the true burden of undiagnosed COPD and the benefit of screening and case detection can be informed by a comparative assessment of patient and disease factors between diagnosed and undiagnosed patients. Numerous studies have compared the characteristics of

patients with undiagnosed and diagnosed COPD, but to the best of my knowledge, these studies have never been systematically compiled and pooled. The objective of this review was to synthesise existing evidence on patient and disease factors in patients with undiagnosed persistent airflow limitation compared to those with diagnosed COPD. I hypothesised that the characteristics of patients, their risk factors, respiratory symptoms, and disease stage influence the likelihood of receiving a diagnosis of COPD.

2.2 Methods

2.2.1 Search strategy and selection criteria

The protocol for this study is registered on the PROSPERO register of systematic reviews (CRD42017058235)[89]. I conducted a systematic review and meta-analysis to compare patient characteristics, risk factors, and symptoms in diagnosed and undiagnosed patients. I searched MEDLINE and EMBASE using the Ovid interface for eligible articles. The search strategy (Appendix A.1) was developed in MEDLINE and adapted to EMBASE using appropriate vocabulary terms. I included longitudinal or cross-sectional studies published in English between 1980 and April 11, 2017 that were based on original analysis of individual data. I did not assess grey literature but conference abstracts were eligible if they provided all the required information. I extracted summary data from the eligible articles and contacted the authors to obtain additional information when required (one author group provided us with additional information). Title and abstract screening were initially performed, followed by full-text analysis to determine article eligibility. I extracted data using a customised Excel spreadsheet after the eligible articles had been compiled. I initially performed the selection procedure, and a second reviewer independently repeated each step on a subset (10%) of articles. Discrepancies were

resolved through a discussion with the second reviewer. Duplicate articles found in both MEDLINE and EMBASE were identified using a reference manager and manually removed. I used the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies developed by the National Institutes of Health[90] to assign an overall quality rating (good, fair, or poor) to each study. I extracted relevant data and assessed the quality of the included studies, and the second reviewer replicated the assessment on 10% of articles. Both reviewers determined the overall quality of each article by assigning 'yes', 'no', or 'other' (cannot determine, not applicable, or not reported) to 14 questions relating to external validity, bias in the measurements of the risk factors or outcomes, and confounders present in the study. The results of this assessment were interpreted qualitatively.

The population of interest in this review was adult patients (≥18 years old) with persistent airflow limitation at the time of assessment. Persistent airflow limitation was defined when the study subjects demonstrated a ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) < 0.7 (fixed ratio definition)[15] or FEV_1 to FVC lower than the lower limit of normal (LLN definition)[40] after the administration of a bronchodilator during spirometry. Study subjects who had airflow limitation and also a prior diagnosis of COPD or an obstructive lung disease (emphysema, chronic bronchitis, asthma) from a healthcare professional were considered to have ‘diagnosed’ COPD, whereas those with persistent airflow limitation but without a prior health professional diagnosis of COPD were considered to be ‘undiagnosed’. Studies in which COPD was not the primary disease of interest were excluded. I included studies that used either population-based (random sampling of the general population) or convenience (e.g., recruiting patients from a healthcare setting) sampling.

Given the exploratory nature of the observational studies included in this review, I used a broad definition of risk factors that included any observable factor that could be associated with the probability of having received a diagnosis of COPD. Risk factors included patient-reported respiratory symptoms (cough, wheeze, phlegm, dyspnea), sex, age, current smoking status, smoking history (pack-years), and disease severity classified using the Global Initiative for chronic Obstructive Lung Disease (GOLD) grades. The relationship of interest was the association between these risk factors and the probability of having 'diagnosed' COPD among patients with persistent airflow limitation.

I extracted summary data from each eligible article, which included study characteristics, the definition of persistent airflow limitation that was employed in each of the studies, the method of COPD diagnosis, sampling methodology, and sample size. I also extracted the proportion or mean of risk factors between the diagnosed and undiagnosed groups, as well as the odds ratios (ORs) and their confidence intervals in studies that used regression modelling to assess the independent impact of the risk factors on diagnosis status. Studies reporting the characteristics of diagnosed and undiagnosed patients using means or proportions in contingency tables were pooled in an 'unadjusted analysis.' Studies that reported associations using multivariable regression modelling were pooled in a separate 'adjusted analysis.'

2.2.2 Data analysis

I used data extracted from articles measuring categorical data to generate ORs and standard errors for the association between risk factors and the probability of having received a diagnosis of COPD. In articles assessing continuous data, I calculated the mean difference (MD) in risk factors and their standard errors among diagnosed and undiagnosed patients. I pooled the ORs or

MDs from individual studies using the inverse variance method implemented with the 'meta' package[91] in R Statistical Software[92] (version 3.3.3). I used fixed-effects models when estimates from only two studies were being pooled, or if the null hypothesis that all studies evaluated the same effect was not rejected (at 0.05 significance level) using Cochran's Q statistic[93]. Otherwise, I used random-effects models. I quantified heterogeneity between studies using the I^2 statistic[94]. I did not pool together studies that used alternate definitions of persistent airflow limitation (fixed ratio and LLN) given the demonstrated differences in patients meeting these criteria[95]. When separate studies used subsets of the same dataset (i.e., the Latin American Project for the Investigation of Obstructive Lung Disease [PLATINO] dataset[47,96–98]), I used the estimate from the study with the largest sample size. I conducted a sensitivity analysis to determine the association between risk factors and COPD diagnosis only among population-based studies (as opposed to convenience sampling).

2.3 Results

The search resulted in 1,857 references after excluding duplicates. 1,788 references were excluded by screening their titles and abstracts, and 69 remained for full-text review to determine eligibility. A total of 18 articles met the inclusion criteria following the screening process, but only 16 articles were included in the quantitative synthesis (Figure 2-1). Two eligible articles were excluded from the meta-analysis because they were missing the necessary information[99], or did not measure any risk factors in common with other studies[100]. The overall agreement between reviewers was high (90%).

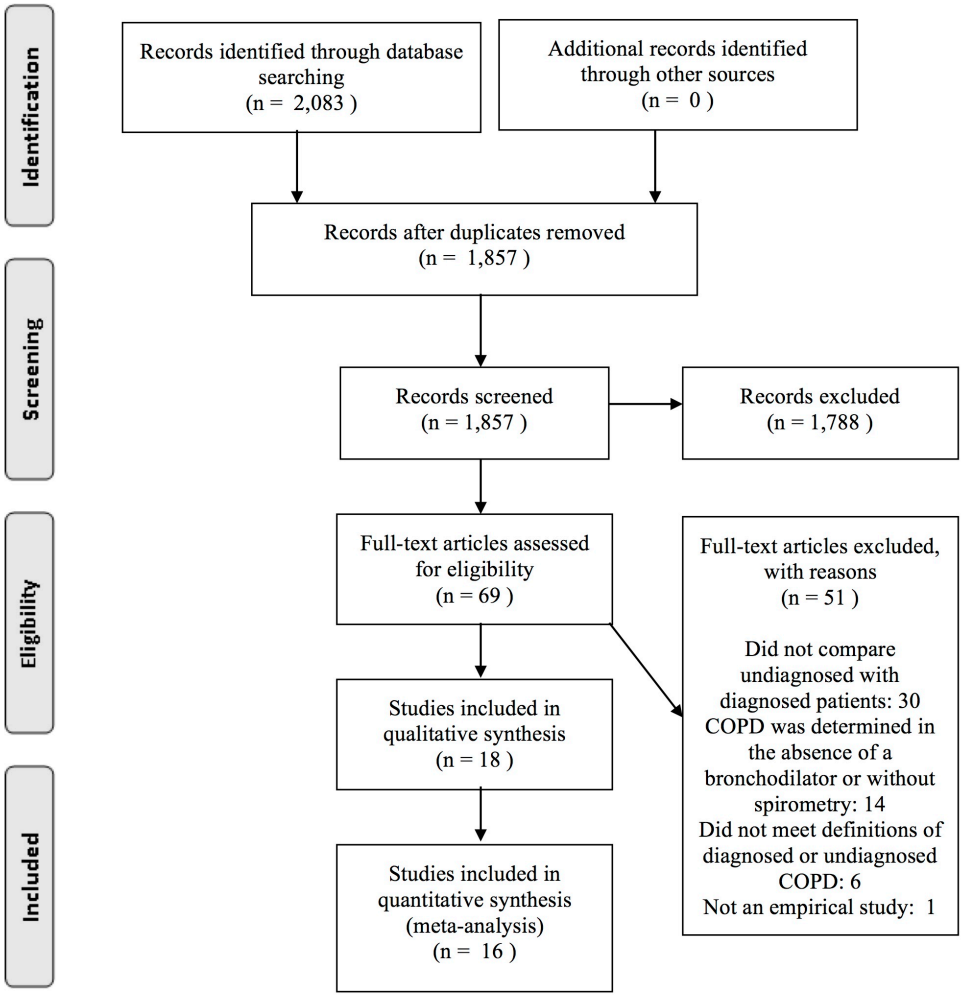


Figure 2-1 Preferred reporting items for systematic reviews and meta-analyses flow diagram.

A summary of the 16 eligible articles is presented in Table 2-1. The majority of the 16 eligible articles were cross-sectional (n=14), and population-based (n=9). Other studies sampled patients from primary care clinics (n=4), or among hospitalised patients (n=3). Studies originated from Europe (n=6), Latin America (n=5), Canada (n=2), and Asia (n=1). Data from the Epidemiologic Study of COPD in Spain (EPI-SCAN)[47,101,102], PLATINO, and the Burden of Obstructive Lung Disease (BOLD)[47,103], were used in three, four, and two different studies,

respectively, but only one study from each dataset was included in pooled analyses. The definition of persistent airflow limitation varied between articles; 13 studies defined it as the fixed ratio, two studies used the LLN definition, and one study reported results using both definitions. Only one of the eligible articles[71] included asthma as a risk factor for assessing a previous diagnosis. The percentage of patients with undiagnosed persistent airflow limitation was greater than 50% in all but two studies (which sampled from healthcare settings).

The quality of the 16 eligible articles was variable. Nine studies were assigned a quality rating of 'good', six studies were assigned a rating of 'fair', and one was deemed poor in quality. Studies that were not assigned a 'good' quality rating generally had a primary study focus that was not my question of interest. The use of regression modelling to examine the independent impact of risk factors on the likelihood of receiving a COPD diagnosis was performed in seven studies, but the risk factors that were adjusted for varied substantially across studies.

Table 2-1 Characteristics of selected studies.

	Country	Study type	Population	Definition of COPD	Definition of undiagnosed COPD	Participants with COPD	Percentage undiagnosed	Quality rating
Ancochea et al. (2013)[101]	Spain	Cross-sectional *(EPI-SCAN*)*	General Population, random sample	Post-bronchodilator $FEV_1/FVC<0.7$	Spirometric obstruction and no previous diagnosis of COPD (self-reported)	386	73%	Good
Balcells et al. (2015)[44]	Spain	Prospective cohort study	Hospitalised patients, all eligible patients were invited	Post-bronchodilator $FEV_1/FVC<0.7$, 3 months after discharge	Spirometric obstruction and no diagnosis of respiratory disease or regular use of pharmacological respiratory treatment (self-reported)	342	34%	Good
Herrera et al. (2016)[104]	Argentina, Colombia, Venezuela, Uruguay	Cross-sectional	Primary care clinics, convenience sample	Post-bronchodilator $FEV_1/FVC<0.7$ and LLN	Spirometric obstruction and no previous diagnosis of chronic bronchitis, emphysema, or COPD (self-reported)	309	77%	Fair
Hill et al. (2010)[105]	Canada	Cross-sectional	Primary care clinics, convenience sample	Post-bronchodilator FEV1/FVC<0.7 and FEV1<80% predicted	Spirometric obstruction and no previous diagnosis of COPD based on medical chart review over the previous 12-months	107	46%	Good
Hvidsten et al. (2010)[71]	Norway	Cross-sectional	General Population, random sample	Post-bronchodilator $FEV_1/FVC<0.7$	Spriometric obstruction and being treated by a physician or admitted to hospital for a diagnosis of obstructive lung disease (asthma, chronic bronchitis, emphysema, or COPD) in the previous 12-months (self-reported)	303	66%	Good
Labonté et al. (2016)[46]	Canada	Prospective cohort study	General Population, random sample	Post-bronchodilator $FEV_1/FVC<0.7$	Spirometric obstruction and no previous diagnosis of chronic bronchitis, emphysema, or COPD (self-reported)	505	70%	Fair
Lamprecht et al. (2015)[47]	Global	Cross-sectional *(BOLD†, PLATINO‡,*	General Population, random sample	Post-bronchodilator $FEV_1/FVC<LLN$	Spirometric obstruction and no previous diagnosis of chronic bronchitis, emphysema, or COPD (self-reported)	2992	81%	Good

	Country	Study type	Population	Definition of COPD	Definition of undiagnosed COPD	Participants with COPD	Percentage undiagnosed	Quality rating
		EPI-SCAN, PREPOCOL§)						
Llordes et al. (2015)[106]	Spain	Cross-sectional	Primary care clinic, all eligible patients were invited	Post-bronchodilator $FEV_1/FVC<0.7$ in 2 tests 4 weeks apart (the 2nd after 4 weeks of pharmacological treatment)	Spirometric obstruction and no previous diagnosis of COPD in medical reports	422	57%	Fair
Mahishale et al. (2015)[107]	Not reported	Cross-sectional	Hospitalised patients, convenience sample	Post-bronchodilator $FEV_1/FVC<0.7$	Spirometric obstruction and no previous diagnosis of COPD (self-reported)	404	56%	Poor
Miravitlles et al. (2009)[102]	Spain	Cross-sectional *(EPI-SCAN)*	General Population, random sample	Post-bronchodilator $FEV_1/FVC<0.7$	Spirometric obstruction and no previous diagnosis of chronic bronchitis, emphysema, or COPD (self-reported)	408	73%	Good
Moreira et al. (2013)[96]	Brazil	Cross-sectional *(PLATINO)*	General Population, random sample	Post-bronchodilator $FEV_1/FVC<0.7$	Spirometric obstruction and no previous diagnosis of chronic bronchitis, emphysema, or COPD (self-reported)	53	62%	Fair
Nascimento et al. (2007)[97]	Brazil	Cross-sectional *(PLATINO)*	General Population, random sample	Post-bronchodilator $FEV_1/FVC<0.7$	Spirometric obstruction and no previous diagnosis of chronic bronchitis, emphysema, or COPD (self-reported)	144	88%	Fair
Queiroz et al. (2012)[108]	Brazil	Cross-sectional	Primary care clinics, convenience sample	Post-bronchodilator $FEV_1/FVC<0.7$	Spirometric obstruction and no previous diagnosis of chronic bronchitis, emphysema, or COPD (self-reported)	63	71%	Good
Schirnhofer et al. (2011)[103]	Austria	Cross-sectional *(BOLD)*	General Population, random sample	Post-bronchodilator $FEV_1/FVC<LLN$	Spirometric obstruction and no previous diagnosis of chronic bronchitis, emphysema, or COPD (self-reported)	199	86%	Good

	Country	Study type	Population	Definition of COPD	Definition of undiagnosed COPD	Participants with COPD	Percentage undiagnosed	Quality rating
Talamo et al. (2007)[98]	Brazil, Chile, Mexico, Uruguay, Venezuela	Cross-sectional *(PLATINO*	General Population, random sample	Post-bronchodilator $FEV_1/FVC<0.7$	Spirometric obstruction and no previous diagnosis of chronic bronchitis, emphysema, or COPD (self-reported)	758	89%	Good
Zhang et al. (2013)[109]	China	Cross-sectional	Hospitalised patients, all eligible patients were invited	Post-bronchodilator $FEV_1/FVC<0.7$	Spirometric obstruction and COPD not recorded as a discharge diagnosis in medical records	705	93%	Fair

* Epidemiologic Study of COPD in Spain (EPI-SCAN)

† Burden of Obstructive Lung Disease (BOLD)

‡ Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO)

§ Prevalence study of COPD in Colombia (PREPOCOL)

2.3.1 Unadjusted analysis

The characteristics of diagnosed and undiagnosed patients meeting the fixed ratio definition of airflow limitation were compared using contingency tables ('unadjusted analysis') in 12 studies. The pooled results are shown in Figure 2-2. Patients with 'diagnosed' COPD were more likely to be experiencing respiratory symptoms such as wheezing (OR 3.51, 95% CI 2.19-5.63, 3 studies), phlegm (OR 2.16, 95% CI 1.38-3.38, 3 studies), dyspnea (OR 4.67, 95% CI 2.62-8.35, 3 studies), or any respiratory symptoms (OR 11.45 95% CI 7.20-18.21, 3 studies). They were much less likely to have mild (GOLD grade I) COPD than moderate to very severe COPD (grade II-IV) as measured by GOLD grades (OR 0.30 95% CI 0.24-0.37, 7 studies). The heterogeneity between studies was relatively low (I^2<35.0% for all symptoms and COPD severity). Patient sex, current smoking status, and smoking history were not associated with a COPD diagnosis. Having a cough was also not significantly associated with diagnosis status; however, variability between the three studies measuring this risk factor was particularly high (I^2 77.9%).

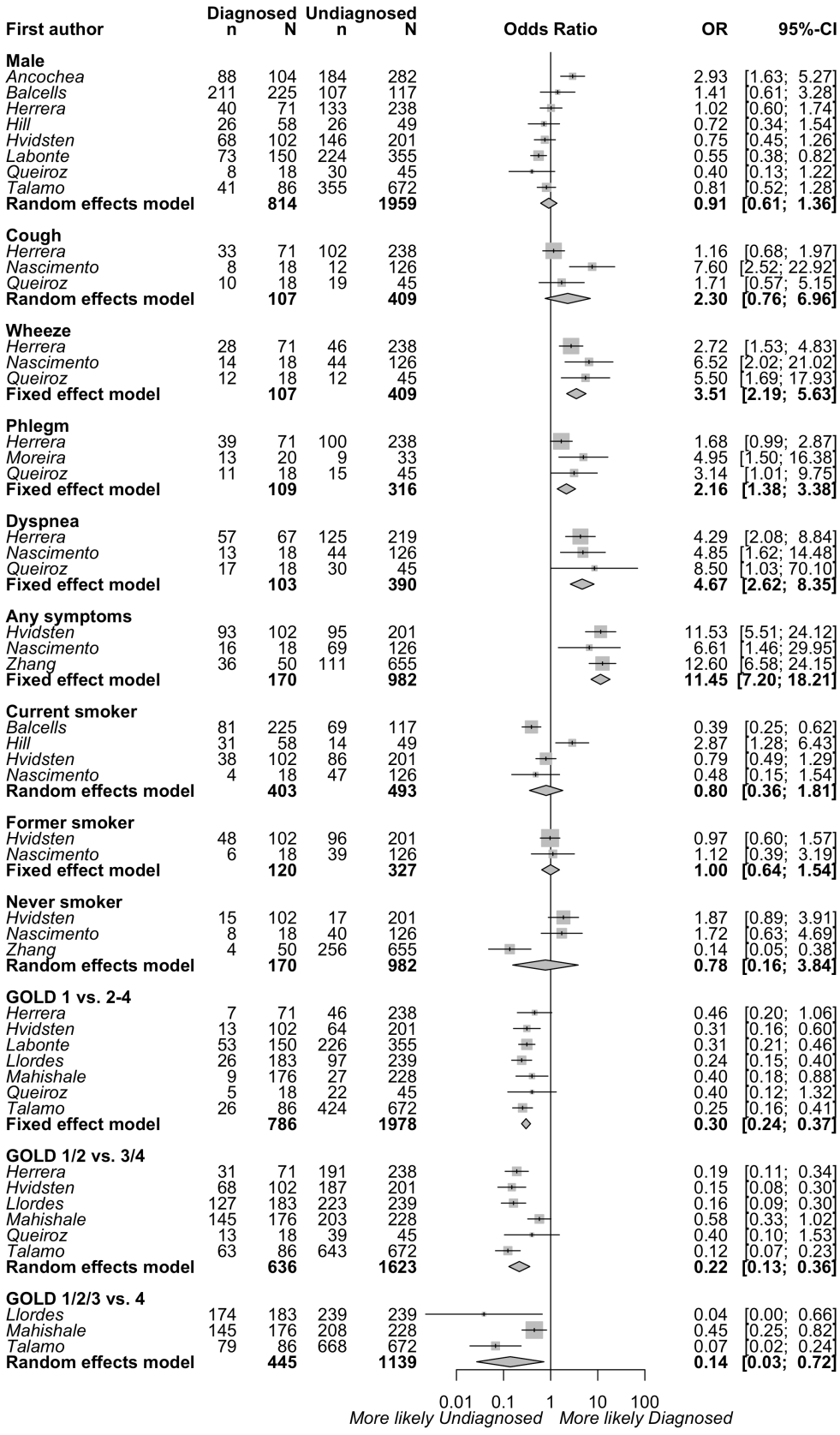

First author
Diagnosed n N
Undiagnosed n N
Odds Ratio
OR 95%-CI
Male
Ancochea 88 104 184 282 2.93 [1.63; 5.27]
Balcells 211 225 107 117 1.41 [0.61; 3.28]
Herrera 40 71 133 238 1.02 [0.60; 1.74]
Hill 26 58 26 49 0.72 [0.34; 1.54]
Hvidsten 68 102 146 201 0.75 [0.45; 1.26]
Labonte 73 150 224 355 0.55 [0.38; 0.82]
Queiroz 8 18 30 45 0.40 [0.13; 1.22]
Talamo 41 86 355 672 0.81 [0.52; 1.28]
Random effects model 814 1959 0.91 [0.61; 1.36]
Cough
Herrera 33 71 102 238 1.16 [0.68; 1.97]
Nascimento 8 18 12 126 7.60 [2.52; 22.92]
Queiroz 10 18 19 45 1.71 [0.57; 5.15]
Random effects model 107 409 2.30 [0.76; 6.96]
Wheeze
Herrera 28 71 46 238 2.72 [1.53; 4.83]
Nascimento 14 18 44 126 6.52 [2.02; 21.02]
Queiroz 12 18 12 45 5.50 [1.69; 17.93]
Fixed effect model 107 409 3.51 [2.19; 5.63]
Phlegm
Herrera 39 71 100 238 1.68 [0.99; 2.87]
Moreira 13 20 9 33 4.95 [1.50; 16.38]
Queiroz 11 18 15 45 3.14 [1.01; 9.75]
Fixed effect model 109 316 2.16 [1.38; 3.38]
Dyspnea
Herrera 57 67 125 219 4.29 [2.08; 8.84]
Nascimento 13 18 44 126 4.85 [1.62; 14.48]
Queiroz 17 18 30 45 8.50 [1.03; 70.10]
Fixed effect model 103 390 4.67 [2.62; 8.35]
Any symptoms
Hvidsten 93 102 95 201 11.53 [5.51; 24.12]
Nascimento 16 18 69 126 6.61 [1.46; 29.95]
Zhang 36 50 111 655 12.60 [6.58; 24.15]
Fixed effect model 170 982 11.45 [7.20; 18.21]
Current smoker
Balcells 81 225 69 117 0.39 [0.25; 0.62]
Hill 31 58 14 49 2.87 [1.28; 6.43]
Hvidsten 38 102 86 201 0.79 [0.49; 1.29]
Nascimento 4 18 47 126 0.48 [0.15; 1.54]
Random effects model 403 493 0.80 [0.36; 1.81]
Former smoker
Hvidsten 48 102 96 201 0.97 [0.60; 1.57]
Nascimento 6 18 39 126 1.12 [0.39; 3.19]
Fixed effect model 120 327 1.00 [0.64; 1.54]
Never smoker
Hvidsten 15 102 17 201 1.87 [0.89; 3.91]
Nascimento 8 18 40 126 1.72 [0.63; 4.69]
Zhang 4 50 256 655 0.14 [0.05; 0.38]
Random effects model 170 982 0.78 [0.16; 3.84]
GOLD 1 vs. 2-4
Herrera 7 71 46 238 0.46 [0.20; 1.06]
Hvidsten 13 102 64 201 0.31 [0.16; 0.60]
Labonte 53 150 226 355 0.31 [0.21; 0.46]
Llordes 26 183 97 239 0.24 [0.15; 0.40]
Mahishale 9 176 27 228 0.40 [0.18; 0.88]
Queiroz 5 18 22 45 0.40 [0.12; 1.32]
Talamo 26 86 424 672 0.25 [0.16; 0.41]
Fixed effect model 786 1978 0.30 [0.24; 0.37]
GOLD 1/2 vs. 3/4
Herrera 31 71 191 238 0.19 [0.11; 0.34]
Hvidsten 68 102 187 201 0.15 [0.08; 0.30]
Llordes 127 183 223 239 0.16 [0.09; 0.30]
Mahishale 145 176 203 228 0.58 [0.33; 1.02]
Queiroz 13 18 39 45 0.40 [0.10; 1.53]
Talamo 63 86 643 672 0.12 [0.07; 0.23]
Random effects model 636 1623 0.22 [0.13; 0.36]
GOLD 1/2/3 vs. 4
Llordes 174 183 239 239 0.04 [0.00; 0.66]
Mahishale 145 176 208 228 0.45 [0.25; 0.82]
Talamo 79 86 668 672 0.07 [0.02; 0.24]
Random effects model 445 1139 0.14 [0.03; 0.72]
0.01 0.1 1 10 100
More likely Undiagnosed
More likely Diagnosed

Figure 2-2 Associations between diagnosed (v. 'undiagnosed') COPD and sex, the presence of cough, wheeze, phlegm, dyspnea, any respiratory symptoms, smoking status, smoking history, and COPD severity based on contingency tables ('unadjusted analysis').

Persistent airflow limitation was defined as post-bronchodilator $FEV_1/FVC<0.7$. Squares represent individual study estimates with the size of the square corresponding to their weight in the pooled estimate (represented with diamonds).

Sensitivity analysis of only the population-based studies (excluding those that used convenience sampling) revealed very similar results (n=5 studies, Appendix A.2). Pooled analysis of two studies[103,104] using the LLN definition of airflow limitation was consistent with the findings based on fixed ratio results (Appendix A.3); however, cough was marginally associated with diagnosis status in this analysis (OR 1.65, 95% CI 1.02-2.66).

Similarly, patients with 'diagnosed' COPD (fixed ratio definition) were more impaired by dyspnea (modified Medical Research Council [mMRC] dyspnea scale[52] MD 0.52, 95% CI 0.40-0.64, 3 studies) and had greater airflow obstruction (percent predicted FEV_1 MD -12.85%, 95% CI -15.26% to -10.44%, 4 studies) than undiagnosed patients (Figure 2-3). Patients with 'diagnosed' COPD also had a slightly greater smoking history (pack-years MD 8.39, 95% CI 0.68-16.44, 4 studies); however, there was high variability between the study means (I^2 84.2%). There was no difference in mean age between diagnosed and undiagnosed patients.

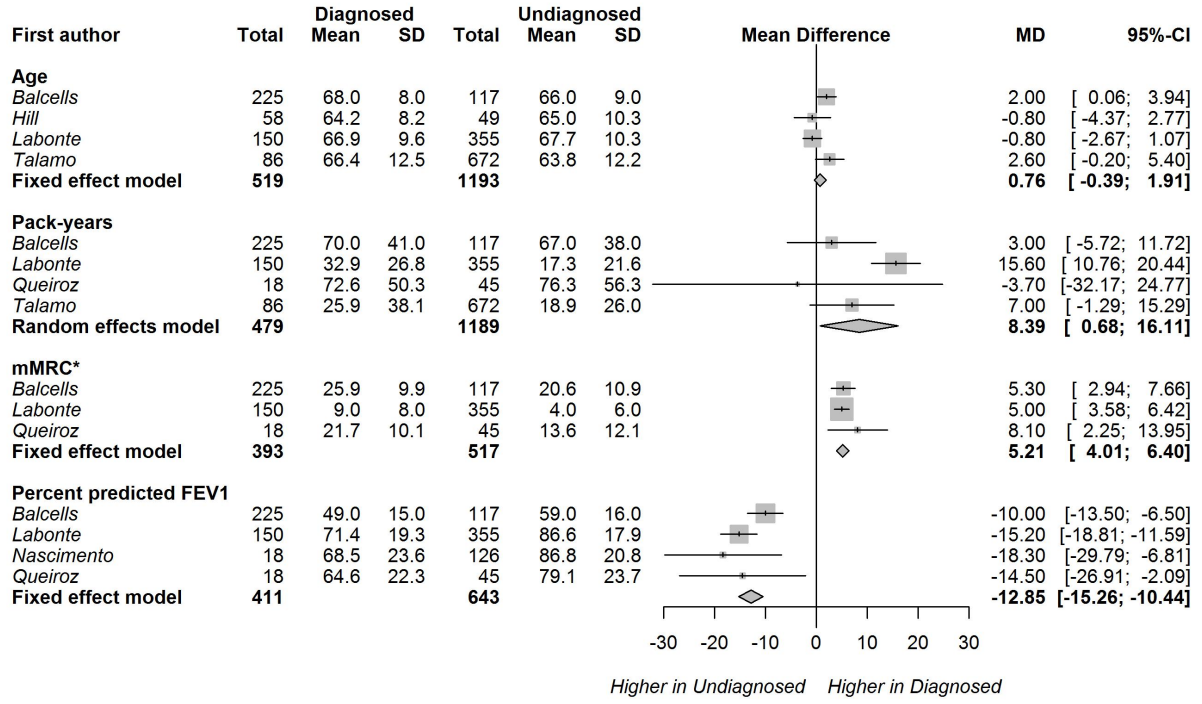


Figure 2-3 Mean difference (MD) in age, pack-years of smoking, mMRC dyspnea score, and percent of predicted FEV_1 between diagnosed and undiagnosed categories.

Persistent airflow limitation was defined as post-bronchodilator $FEV_1/FVC<0.7$. Squares represent individual study estimates with the size of the square corresponding to their weight in the pooled estimate (represented with diamonds).

* modified Medical Research Council (mMRC) Dyspnea scale[52] means and standard errors (SE) for the diagnosed and undiagnosed categories are multiplied by a factor of 10.

2.3.2 Adjusted analysis

Articles using regression modelling to assess the independent impact of risk factors on COPD diagnosis ('adjusted analysis') were pooled by risk factor type, and the results are presented in Figure 2-4 for the fixed ratio definition of persistent airflow limitation (5 articles), and Figure 2-5

for the LLN definition (2 articles with 5 datasets). Compared with the unadjusted analysis, the effect sizes of the risk factors were attenuated in these analyses. The presence of phlegm had a weak independent association with the diagnosis of COPD (OR 1.16, 95% CI 1.00-1.35, 2 studies) using the fixed ratio definition. The presence of wheezing (OR 1.20, 95% CI 0.99-1.44, 2 studies) and dyspnea (OR 1.13 95% CI 0.99-1.29, 2 studies) showed a trend towards association. Mild COPD (GOLD grade I OR 0.72, 95% CI 0.58-0.80) or moderate COPD (GOLD grade II, OR 0.71, 95% CI 0.58-0.86) were independently associated with a lower likelihood of diagnosis, compared with severe or very severe (reference GOLD grades III-IV). Sex and the presence of cough did not influence the likelihood of being diagnosed in the adjusted analyses. Overall, heterogeneity in the effect estimates between studies was very high (I^2>70.0% for all risk factors except sex).

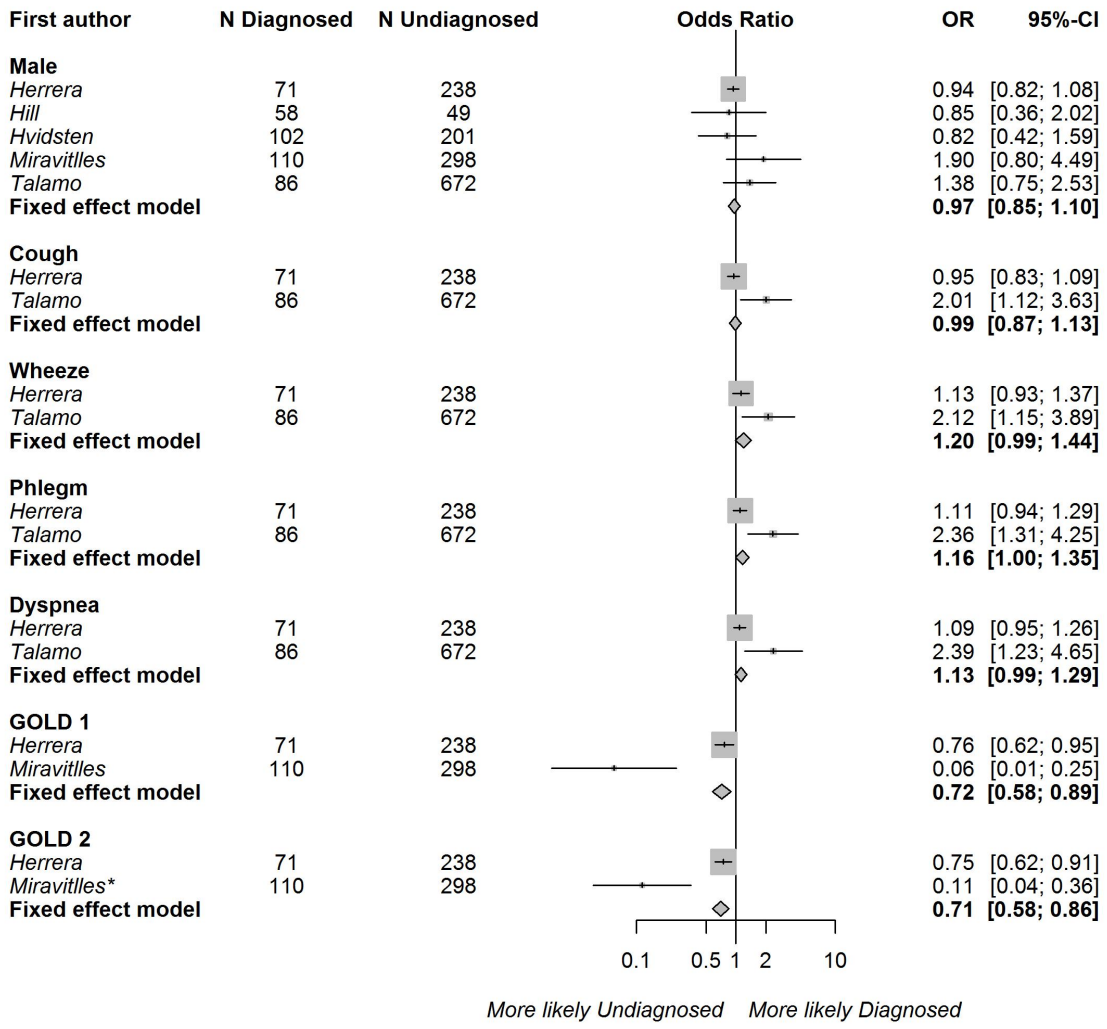


Figure 2-4 Associations between risk factors and the odds of receiving a COPD diagnosis using the regression coefficients from studies with multivariable regression modelling ('adjusted analysis') and persistent airflow limitation defined as post-bronchodilator $FEV_1/FVC<0.7$.

The reference categories were female, the absence of cough, wheeze, dyspnea, phlegm, and GOLD grades 3 and 4, respectively. Squares represent individual study estimates with the size of the square corresponding to their weight in the pooled estimate (represented with diamonds).

Regression models were adjusted for age (*Herrera, Hill, Hvidsten, Miravitlles, Talamo)*, sex (*Herrera, Hill, Hvidsten, Miravitlles, Talamo),* ethnicity *(Herrera, Talamo)*, body mass index *(Herrera, Hvidsten)*, education (*Herrera, Hvidsten, Miravitlles, Talamo)*, income *(Hvidsten)*, employment *(Talamo)*, risk factor to dust *(Herrera)*,

smoking *(Herrera, Hill, Hvidsten, Miravitlles, Talamo)*, respiratory symptoms, *(Herrera, Hill, Hvidsten, Talamo)*, self-rated health *(Hvidsten, Miravitlles)*, COPD severity *(Herrera, Miravitlles, Talamo)*, comorbidities *(Herrera, Hvidsten)*, prior healthcare use (*Herrera, Hill)*, and exacerbations *(Herrera)*.

*The reference category was changed from GOLD grade 1 to GOLD grades 3 and 4 by assuming a covariance of 0 between the dummy variables representing GOLD grades 1 and 2.

†*Herrera et al.*[104] reported prevalence ratios from Poisson regression models.

Three risk factors were pooled in my assessment of studies using adjusted analysis based on the LLN definition of persistent airflow limitation. This analysis indicated a more strongly positive association between the presence of phlegm and being diagnosed with COPD (OR 1.71, 95% CI 1.15-2.56), although there was heterogeneity between datasets (I^2 75.2%). Patient sex and the presence of cough had no independent effects.

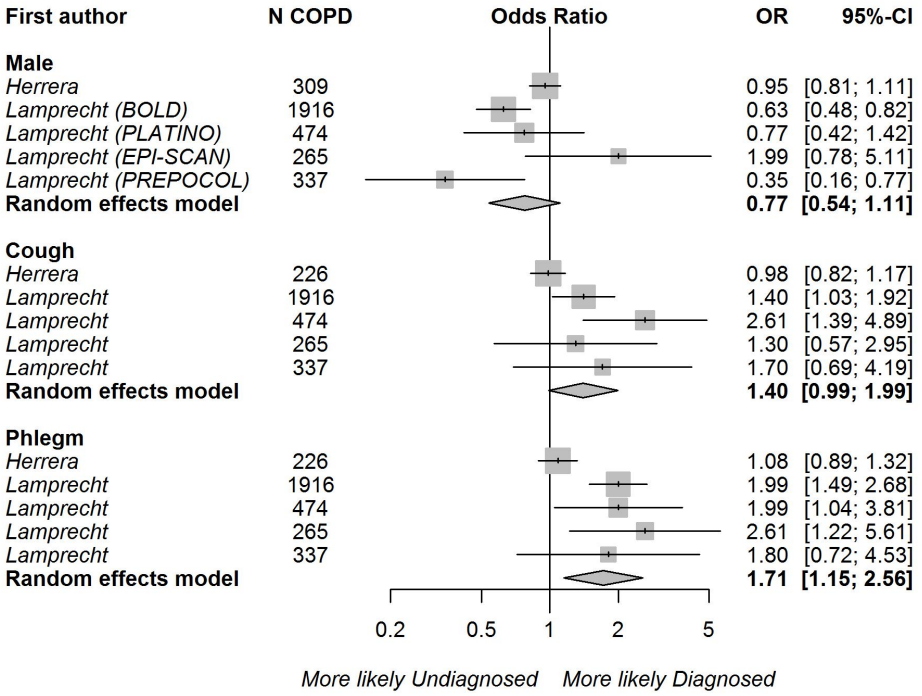


Figure 2-5 Associations between risk factors and the odds of receiving a COPD diagnosis using the regression coefficients from studies with multivariable regression modelling ('adjusted analysis') and persistent airflow limitation defined as post-bronchodilator $FEV_1/FVC<LLN$.

The reference categories were female, and the absence of cough and phlegm, respectively. The results for each dataset (BOLD, PLATINO, EPI-SCAN, PREPOCOL) analysed in Lamprecht et al.[47] were pooled separately. Squares represent individual study estimates with the size of the square corresponding to their weight in the pooled estimate (represented with diamonds).

Regression models were adjusted for age (*Herrera, Lamprecht)*, sex *(Herrera, Lamprecht)*, ethnicity *(Herrera)*, body mass index *(Herrera)*, education *(Herrera, Lamprecht)*, risk factors to dust *(Herrera)*, smoking *(Herrera, Lamprecht)*, respiratory symptoms (*Herrera, Lamprecht)*, COPD severity *(Herrera, Lamprecht),* comorbidities *(Herrera)*, and prior healthcare use *(Herrera, Lamprecht)*.

2.4 Discussion

I conducted a systematic review and meta-analysis to compare patient and disease factors between patients with undiagnosed persistent airflow limitation and those with diagnosed COPD. In the 16 observational studies included in this review, the presence of respiratory symptoms and GOLD grade III or IV disease severity were strongly associated with a prior diagnosis of COPD among individuals with persistent airflow limitation on spirometry. These findings were relatively consistent across analysis methods and alternate definitions of persistent airflow limitation. Greater disease severity was the most important characteristic of diagnosed patients in two out of three pooled analyses. In particular, patients with mild or moderate COPD (as measured by GOLD grades) were 78% less likely to have received a diagnosis than patients with severe or very severe COPD in the unadjusted analysis (based on contingency tables), and mean percent predicted FEV_1 was 13% lower in diagnosed than undiagnosed patients. Disease severity

was also the only risk factor that was associated with a diagnosis in both the unadjusted and adjusted (based on regression modelling) analyses. In the adjusted analysis, patients with moderate COPD were 29% less likely to have received a diagnosis than patients with severe or very severe COPD.

Among respiratory symptoms, the presence of dyspnea was the most strongly associated with a previous diagnosis in the unadjusted analysis. Patients with 'diagnosed' COPD scored 0.52 points higher on the mMRC dyspnea scale. One study[108] provided evidence that the mean score on the mMRC scale could have been used to distinguish undiagnosed from diagnosed patients using commonly accepted criteria ('more dyspnea' if mMRC score ≥2 v. 'less dyspnea' if mMRC score <2)[15]. Following dyspnea, the presence of wheeze and phlegm were also strongly associated with 'diagnosed' COPD in the unadjusted analysis. These associations were weaker in the adjusted analysis but were still present. Interestingly, the presence of coughing was not well associated with a previous diagnosis in any of the pooled analyses. Overall, aside from the attenuated results in the adjusted analysis (discussed in detail below), my findings suggest a strong association between the presence of dyspnea, phlegm, or wheeze and a COPD diagnosis. This association is likely because patients with respiratory symptoms are more likely to seek care, and doctors are more likely to test for COPD in patients with symptoms[15].

Overall, these findings suggest that a diagnosis of COPD is likely to be delayed in patients with a lower burden of respiratory symptoms and lung function decline that progresses more slowly, meaning that opportunities for early intervention may be lower in these patients. Patients with fewer respiratory symptoms are also less likely to be screened for COPD following the U.S. Preventive Services Task Force recommendation[65]. However, my results suggest that screening or case detection methods that rely exclusively on the presence of respiratory

symptoms may be missing undiagnosed patients. Symptoms should be assessed in combination with a history of exposure to risk factors for COPD when considering a diagnosis[15].

Importantly, sex, age, and smoking status were not independently associated with receiving a diagnosis of COPD in any of the pooled analyses. Because these are major risk factors for the presence of COPD[15], physicians should be more likely to diagnose COPD in older patients who are current or past smokers, which should have resulted in an independent association between these factors and a diagnosis of COPD. The lack of such association in any of my analyses may indicate that the relation between these risk factors and the presence of COPD is not sufficiently recognised by physicians. This is in contrast to the strong association of GOLD grade and symptoms with diagnosis status, which suggests that a diagnosis of COPD is more commonly made based on the degree of impairment in lung function and/or patient respiratory symptoms. This hypothesis might also explain my finding that smoking history in terms of pack-years was associated with a previous diagnosis of COPD while current smoking status was not, as only smoking history is related to cumulative lung function impairment.

The effects of risk factors on the likelihood of being diagnosed were weaker in the adjusted analyses than in the unadjusted analyses. The adjusted analyses were based on pooled coefficients from regression modelling. Although the inclusion of covariates is expected to reduce the effects sizes compared to odds ratios derived from contingency tables (as in the unadjusted analysis), one study in the adjusted analysis[104] had unusual results that received disproportionate weighting. In contrast to all other studies in this review, Herrera et al.[104] found that respiratory symptoms were not associated with the likelihood of having received a diagnosis of COPD. In the adjusted analysis, these results were pooled with one other study[98], which found that the presence of respiratory symptoms were strongly associated with the likelihood of

receiving a diagnosis. This discrepancy between studies may be due to differences in the population that was sampled (primary care clinic[104] versus general population[98]). In general, studies in clinic settings might have observed smaller differences between undiagnosed and diagnosed patients because they sampled from a subset of patients that were prompted to seek care because of symptoms.

This systematic review has several strengths. First, I used data from a total of 16 articles in the meta-analysis, and these articles were mostly population-based studies that scored high in quality. Second, there were a robust number of studies for many risk factors; patient sex was assessed in 10 studies in total, followed by disease severity in 9 studies, and respiratory symptoms and smoking history in 8 studies. The methods used to measure disease severity, respiratory symptoms, and smoking history were relatively consistent across studies, which facilitated pooling of their findings. Lastly, I conducted several pooled analyses to assess the sensitivity of my findings to alternate definitions of COPD (fixed ratio and LLN) and analysis methods (unadjusted and adjusted analyses). Except for one study[104], my findings were consistent.

This systematic review also has several limitations. First, half of the pooled samples were based on data from three large prevalence studies (EPI-SCAN, PLATINO, and BOLD). This resulted in overrepresentation of patients in Spain and Latin America, and differences in patient and physician behaviour and healthcare services use can result in findings that vary across settings. Second, although the total number of studies for each risk factor was robust, the number of studies assessing each risk factor within pooled analyses tended to be small. This was partly because separate articles using the same dataset could not be combined in our pooled analyses. Third, with the exception of dyspnea, all other respiratory symptoms in the pooled analyses were

measured as binary variables (either present or absent), and all symptoms were measured cross-sectionally. Given my finding that symptoms are characteristic of a COPD diagnosis, a more nuanced assessment of their severity and temporal variability might result in an even greater ability to distinguish between undiagnosed and diagnosed patients. In addition, because respiratory symptoms were self-reported in all studies, reporting bias might have exaggerated the difference in symptoms between the undiagnosed and diagnosed groups. Finally, several studies reported additional comparisons of risk factors between diagnosed and undiagnosed patients. Examples include education, income, comorbidities, quantity and type of care, and a previous diagnosis of asthma. However, due to inconsistent definitions and different categorizations, I could not pool these estimates across studies. An important knowledge gap is the impact of environmental risk factors on the likelihood of receiving a diagnosis, which was rarely measured in the included studies.

2.5 Conclusions

The findings from this systematic review have important implications for research and policy around COPD diagnosis, for example, in estimating the return on investment in screening and case detection strategies for COPD. The true burden of COPD is the sum of the disease burden in diagnosed and undiagnosed patients. My results indicate that undiagnosed patients generally have milder disease and therefore a lower disease burden, meaning that strategies aiming to reduce the underdiagnosis problem are unlikely to result in immediate and dramatic improvements in patient-related outcomes such as symptoms. However, the gap in disease severity and symptom burden between diagnosed and undiagnosed patients also indicates a delay in COPD diagnosis. Given the potential for disease modification at early stages of COPD,

reducing this delay could be associated with substantial improvement in long-term patient outcomes and a reduction in mortality and costs.

Chapter 3: Heterogeneity in the Respiratory Symptoms of Patients with Mild-to-Moderate COPD

3.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a common inflammatory lung condition that affects close to 400 million people worldwide[35]. COPD is characterised by persistent airflow limitation and symptoms such as breathlessness, chronic cough, sputum production, wheezing, and chest tightness[15]. Respiratory symptoms are a major burden in many patients, and are associated with an increased frequency of exacerbations[110], worse disease prognosis[72,111,112], lower health status[113,114], reduced quality of life[115], and higher healthcare resource utilisation[116].

The three major components of the natural history of COPD are lung function status, patterns of exacerbations, and symptom burden[15]. Modern guidelines such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) appreciate the importance of all three components in disease management decisions. The GOLD guidelines recommend evaluating symptoms separately from airflow limitation and history of exacerbations in providing therapeutic recommendations[15].

It is increasingly recognised that COPD is a heterogeneous disease. Individuals can vary markedly in their rate of lung function decline[28] and frequency of exacerbations[117,118] over the course of their disease. For example, COPD patients in the Lung Health Study had an annual rate of change in FEV_1 that ranged from rapidly declining to modestly increasing (95% CI -83 mL/yr to +15 mL/yr)[28]. Similarly, the annual rate of exacerbations observed in the MACRO clinical

trial varied from 0.47 to 4.22[118]. Quantifying this variation at an individual level is critical to enabling precise risk factor and disease management[14].

In contrast, heterogeneity in the burden of symptoms has not received the same level of attention as these other disease components. This is despite the fact that the degree of symptom impairment is increasingly recognised as an important determinant of patient management strategies, and one that is only partially dependent on the severity of airflow limitation[72,74,113,119]. Previous studies have reported that patient symptoms tend to vary over the day, week, or season[74,120–122], but variation between individuals in the occurrence of symptoms has been less well characterised. Understanding the extent and drivers of this heterogeneity can help improve our understanding of the natural history of COPD and ultimately help formulate disease management strategies that provide optimal therapeutic strategies for each patient.

Using data from a population-based prospective cohort, I assessed the burden of self-reported respiratory symptoms in patients with persistent airflow limitation in order to (1) characterise variation in the occurrence of symptoms between individuals, and (2) determine the proportion of between-individual variability in symptoms that can be explained by lung function versus all other observable characteristics. I hypothesised that there is high variability in the occurrence of symptoms between individuals, and that an individual's clinical and demographic characteristics explain a larger fraction of this heterogeneity than lung function alone.

3.2 Methods

I used data from the Canadian Cohort of Obstructive Lung Disease (CanCOLD), which is a multicentre prospective longitudinal cohort study conducted across Canada[45]. Individuals ≥40 years old were recruited using random digit dialing and multi-level sampling to ensure

representativeness of the general Canadian population. Participants were followed for a maximum of 3 years with in-person visits at baseline and 18-month intervals. From the entire cohort of CanCOLD participants (N=1,561), I selected any visits in which the participant had persistent airflow limitation, defined as post-bronchodilator FEV1/FVC< lower limit of normal (LLN)[41]. As a result, I could have included any combination of the three study visits per participant. Participants who had airflow limitation at one visit but not at any of their subsequent visits were excluded, as their airflow limitation was not considered persistent. I also excluded participants who did not meet the clinical definition of COPD because they were asymptomatic throughout follow-up and had no smoking history[15]. The sample selection procedure is shown in Figure 3-1.

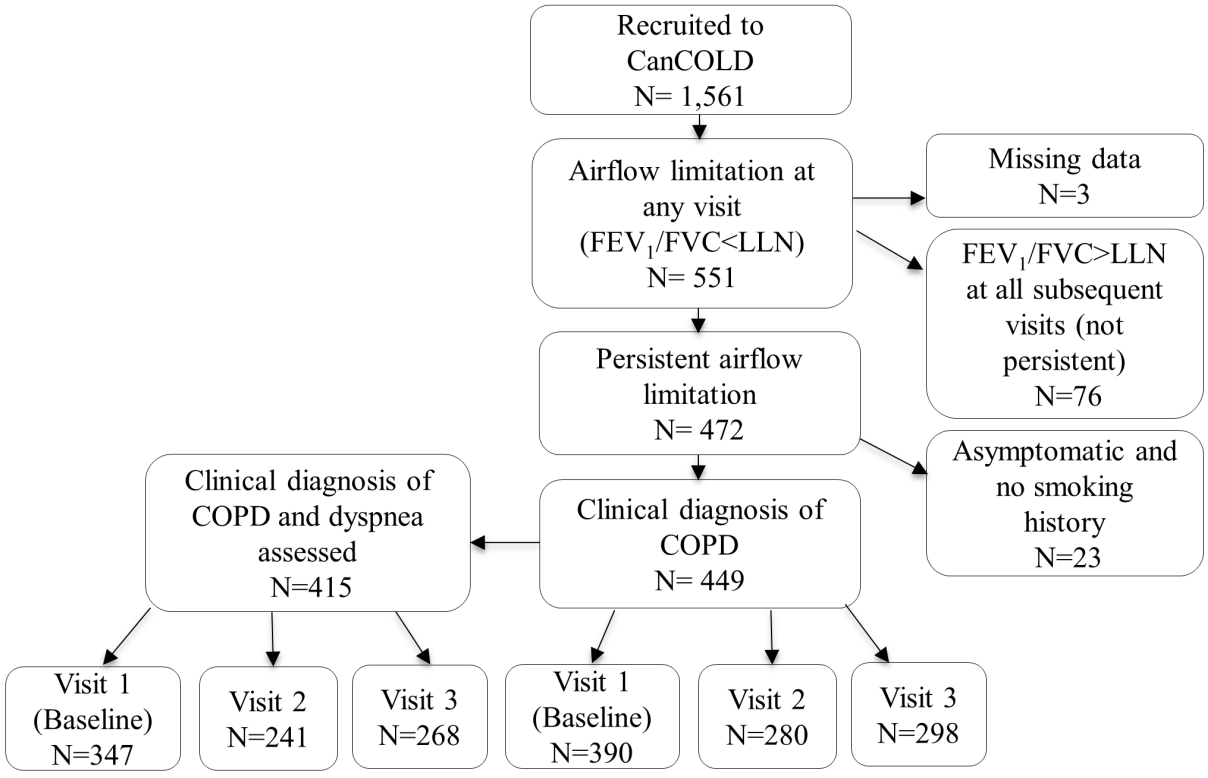


Figure 3-1 Sample selection procedure.

Information was collected during each visit on the presence of cough, phlegm, wheeze, and dyspnea using separate questions for each symptom. Participants reported whether they (1) usually coughed in the absence of a cold, (2) brought up phlegm from the chest in the absence of a cold, and (3) experienced any wheezing or whistling in the chest. Dyspnea (4) was measured using the Medical Research Council (MRC) dyspnea scale[52], which was converted to a binary variable by assuming that a score of 2-5 indicated the presence of dyspnea. The questionnaire used to assess symptoms is reproduced in Appendix B.1. Dyspnea and whether the participant experienced any symptoms were assessed in a subset of the data that included 856 visits from 415 participants because 34 participants were unable to walk and therefore did not complete the MRC dyspnea test. Other variables that were assessed at each visit and included in this analysis were: demographic information, smoking status and history, number of comorbidities, previous diagnosis of anxiety, major or minor depression, history of physician-diagnosed COPD (including emphysema and chronic bronchitis), and history of physician-diagnosed asthma, all self-reported using validated questionnaires with a recall period spanning the length of time between visits[45]. Participants also reported the frequency and type of all respiratory-related medication use, and previous exacerbations of any severity[15], both with a 12-month recall period.

3.2.1 Statistical analysis

I used separate mixed effect logistic regression models for cough, phlegm, wheeze, dyspnea, and any symptoms to model heterogeneity. A random effect term captured the variability among individuals (heterogeneity) that was not attributable to the independent variables in the model. I initially determined the total heterogeneity in the occurrence of symptoms using an intercept-only random-effects logistic regression model for each symptom (the null model, i.e., no

independent variables). I used this model to determine the individual-specific probability of experiencing each symptom, and estimated the interquartile (25%-75%) range of probabilities to measure heterogeneity in the occurrence of symptoms.

I subsequently assessed the proportion of the total heterogeneity in symptoms that could be explained by all measured characteristics of individuals. For this, I included patient age, sex, body mass index (BMI), ethnicity, number of comorbidities, diagnosis of anxiety or minor/major depression, smoking status, pack-years of smoking, any exacerbations in the past 12 months, medication possession ratio (MPR)[123] for all respiratory related medications, post-bronchodilator forced expiratory volume in 1 second (FEV_1), previous diagnosis of asthma, and COPD diagnosis status as independent variables in each model (the full models). In order to determine the variance explained by the independent variables (i.e., participants' measured characteristics), I calculated the proportion of the estimated variance in the random effect of the full model for each symptom (with all the independent variables), compared to the estimated variance in the random effect of the null model with no independent variables[124]. I repeated this process using a reduced model with FEV_1 as the only independent variable (as opposed to the full model) to determine the proportion of total heterogeneity explained by lung function alone.

I conducted sensitivity analyses in which percent predicted FEV_1 and GOLD grade were used in place of FEV_1 as indicators of lung function (collinearity prevented these variables from being included in the model at the same time). Seasonality was not included in the main analysis because the recall period was >1 year and therefore spanned all seasons; however, season was assessed in a sensitivity analysis to account for the possibility that patients were more likely to recall their recent symptom burden (which could be affected by the current season). All analyses were performed in SAS (version 9.4, 2016).

3.3 Results

The characteristics of participants are shown in Table 3-1. There were 968 visits from 449 participants in the final sample (53% male, mean age 67 years). 91% of participants had mild to moderate disease (grade I-II), 8% had severe disease (grade III), and 1% had very severe disease (grade IV) as measured by GOLD grades[15]. 71% of participants with persistent airflow limitation on spirometry had not been previously diagnosed. The average follow-up time was 36 months; 28% of participants underwent only one study visit, and 44% of participants were assessed at all three study visits. There were 390, 280, and 298 participants at visit 1 (baseline), 2, and 3 respectively. The characteristics of the subset of the data used to analyse dyspnea and any symptoms were very similar (Appendix B.2).

Table 3-1 Characteristics of study participants at study visits.

	Visit 1 (n=390)	**Visit 2** (n=280)	**Visit 3** (n=298)
Age	65.3 (10.3)	67.1 (10.1)	68.2 (9.5)
Male (vs. female)	54.1%	53.2%	52.3%
BMI	27.3 (5.2)	27.3 (5.1)	27.3 (5.1)
Caucasian (vs. non-Caucasian)	97.4%	97.1%	98.0%
Comorbidities*			
0 comorbidities	59.2%	53.2%	54.4%
1 comorbidity	32.3%	33.6%	26.8%
≥2 comorbidities	8.5%	13.2%	18.8%
Anxiety/Depression (vs. no)	19.5%	21.8%	20.8%
Smoking between visits (vs. no)	76.2%	29.3%	26.5%
Lifetime pack-years smoked	28.0 (26.5)	26.6 (25.5)	27.3 (25.4)
Any exacerbations† (vs. no)	7.9%	11.1%	15.4%
Medication Possession Ratio‡	79.9% (108.4)	81.5% (112.4)	79.3% (110.3)
FEV_1 (L)	2.1 (0.8)	2.1 (0.8)	2.1 (0.7)
% Predicted FEV_1	74.4 (18.1)	74.9 (19.1)	75.7 (18.8)
Diagnosed COPD (vs. undiagnosed)	24.6%	28.9%	32.2%
Asthma (vs. no)	20.8%	27.1%	29.9%
Symptoms (present vs. absent)			
Cough	47.7%	47.1%	40.6%

	Visit 1 (n=390)	**Visit 2** (n=280)	**Visit 3** (n=298)
Phlegm	33.8%	31.8%	28.2%
Wheeze	51.3%	43.6%	42.6%
Dyspnea§	53.3%	46.5%	44.8%
Any symptoms§	83.9%	77.2%	74.6%

Means (and standard deviations) are reported unless otherwise indicated.

* Participants reported whether they had ever been diagnosed with coronary artery disease, hypertension, diabetes, lung cancer, stroke, and tuberculosis at each study visit

† COPD exacerbations of any severity (mild, moderate, severe[15]) over the past 12 months

‡ 12-month medication possession ratio[123] for all respiratory-related medications

§ Determined for the subset of participants in which dyspnea was measured (N=415)

3.3.1 Objective 1: Heterogeneity in the occurrence of symptoms

Most participants did not report having cough, phlegm, wheeze, or dyspnea at each study visit, but only 11% of participants were completely asymptomatic throughout the study period. The asymptomatic participants tended to have mild airflow obstruction (mean of 87% predicted FEV_1, 18% SD). The proportion of patients that reported a given symptom at least once during follow-up ranged from 43% for phlegm (95% CI 38-47%, the least common symptom) to 61% for dyspnea (95% CI 57-66%, the most common symptom). Symptoms were generally stable within participants: 64% of participants reported the same level of cough throughout their follow-up (95% CI 59-70%, the least stable symptom), and 74% for phlegm (95% CI 69-78%, the most stable symptom).

There was substantial variation in the individual-specific probabilities for the occurrence of symptoms that were estimated from the models (Figure 3-2). The median probabilities of an individual experiencing cough, wheeze, and dyspnea were 0.43, 0.42, and 0.50, respectively. In

contrast, the median probability of experiencing phlegm was 0.16 and >0.99 for any symptoms. The interquartile range of probabilities was 0.17-0.73 for cough, 0.03-0.53 for phlegm, 0.13-0.78 for wheeze, 0.19-0.81 for dyspnea, and 0.78->0.99 for any symptoms. Median probabilities are depicted with blue lines and interquartile ranges are depicted with grey boxes in Figure 2.

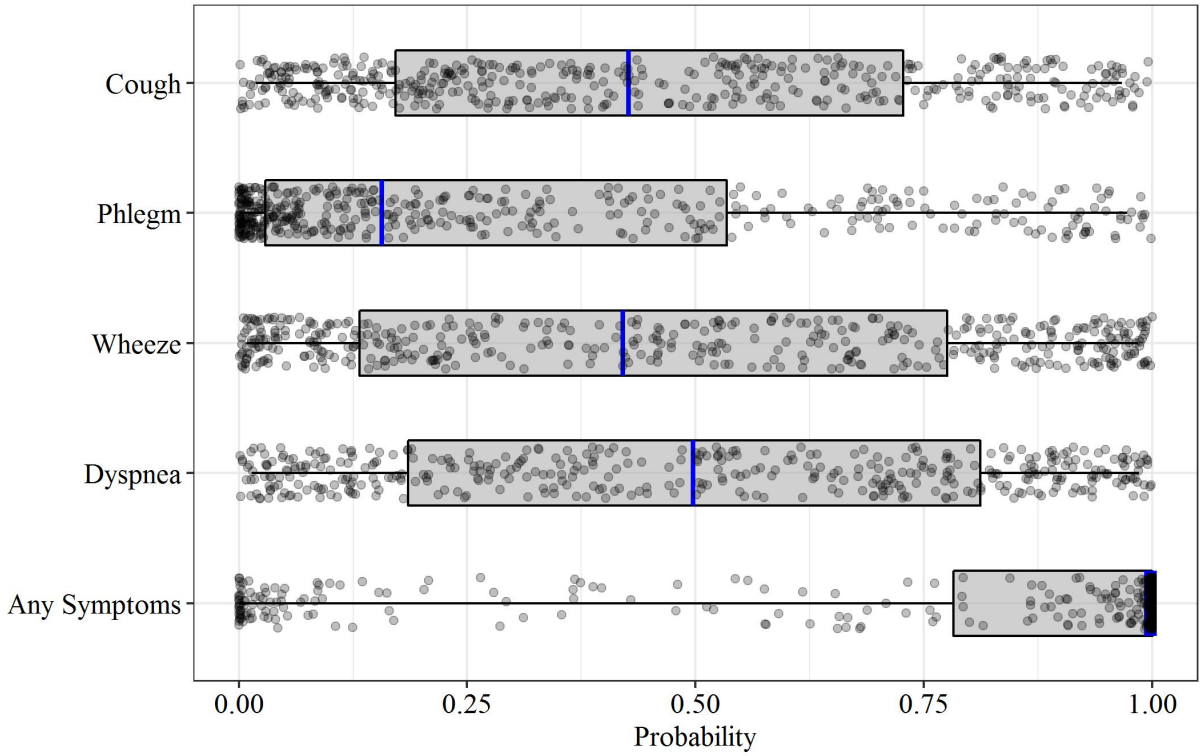
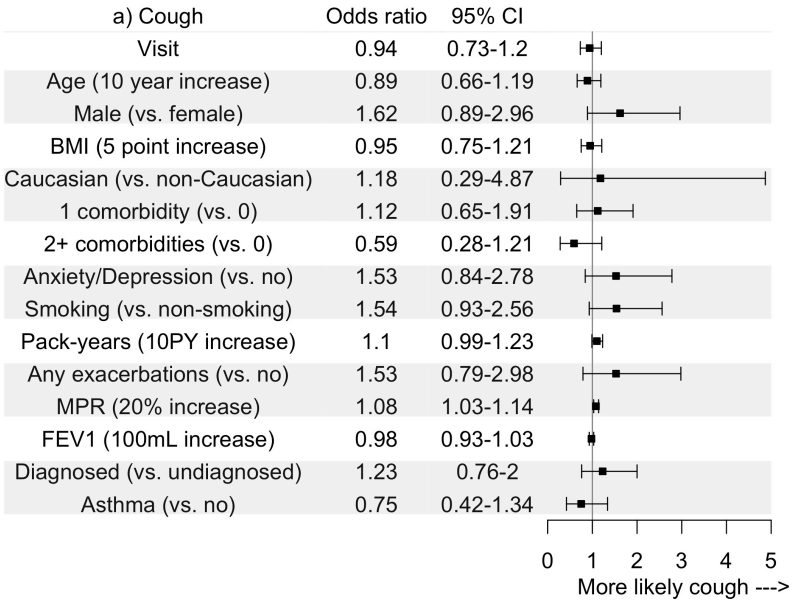


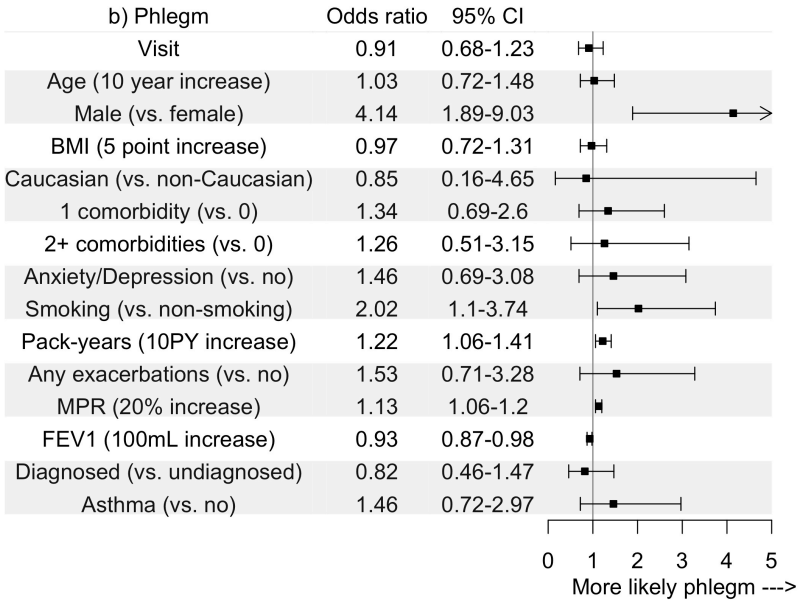
Figure 3-2 The distribution of individual-specific probabilities of the occurrence of symptoms.

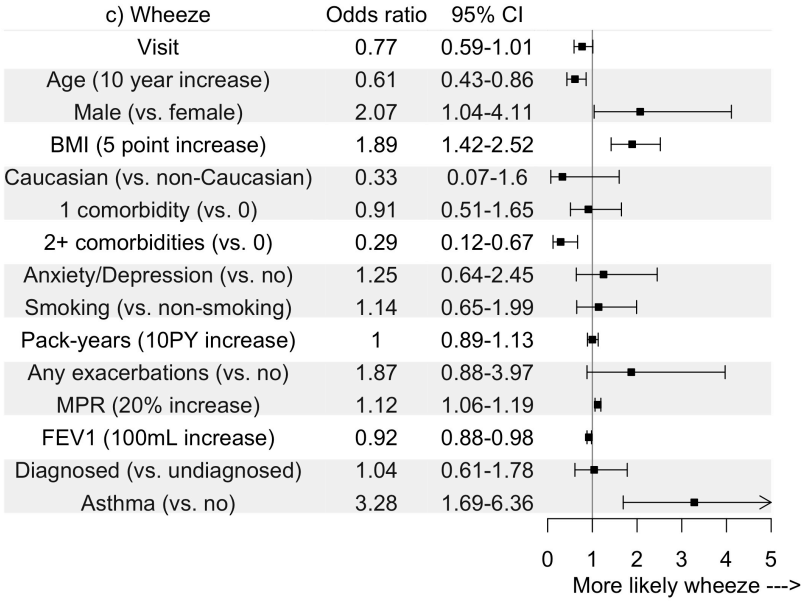
The box spans the lower and upper quartiles (25%-75%) of individuals around the median (blue line). Individual random effects are drawn from a normal distribution with a mean of 0 and standard deviation of the fitted random effects. The statistics shown by the boxes were determined from 1000 repetitions for each individual, and the points show the results of one repetition.

3.3.2 Objective 2: Influence of lung function on symptom heterogeneity

The logistic regression models revealed relatively consistent associations between patient and disease characteristics and the presence of cough, phlegm, wheeze, dyspnea and any symptoms. Comparisons of the strength of associations across individual symptoms are shown in Figure 3-3, and with any symptoms in Figure 3-4. Lung function, sex, pack-years of smoking, BMI, and MPR were associated with most patient-reported symptoms. Lung function was most strongly associated with the presence of any symptoms (OR per 100 mL increase in FEV_1 0.85, 95% CI 0.79-0.91), and least strongly associated with the presence of cough (OR 0.98, 95% CI 0.93-1.03). These results were similar when lung function was assessed as percent predicted FEV_1 or GOLD grade in sensitivity analyses (results not shown). Higher pack-years of smoking, BMI, and MPR were all associated with an increased odds of reporting most symptoms. Males were more likely than females to report the presence of phlegm (OR 4.14, 95% CI 1.89-9.03), wheeze (OR 2.07, 95% CI 1.04-4.11), and any symptoms (OR 3.78, 95% CI 1.54-9.31). Summer (vs. winter) was associated with increased reporting of cough (OR 2.04 95% CI 1.13-3.68), phlegm (OR 2.04, 95% CI 1.01-4.13), wheeze (OR 2.95 95% CI 1.54-5.66) and any symptoms (OR 3.13, 95% CI 1.40-6.97) when it was included in sensitivity analyses.


a) Cough
Odds ratio
95% CI
Visit 0.94 0.73-1.2
Age (10 year increase) 0.89 0.66-1.19
Male (vs. female) 1.62 0.89-2.96
BMI (5 point increase) 0.95 0.75-1.21
Caucasian (vs. non-Caucasian) 1.18 0.29-4.87
1 comorbidity (vs. 0) 1.12 0.65-1.91
2+ comorbidities (vs. 0) 0.59 0.28-1.21
Anxiety/Depression (vs. no) 1.53 0.84-2.78
Smoking (vs. non-smoking) 1.54 0.93-2.56
Pack-years (10PY increase) 1.1 0.99-1.23
Any exacerbations (vs. no) 1.53 0.79-2.98
MPR (20% increase) 1.08 1.03-1.14
FEV1 (100mL increase) 0.98 0.93-1.03
Diagnosed (vs. undiagnosed) 1.23 0.76-2
Asthma (vs. no) 0.75 0.42-1.34
0 1 2 3 4 5
More likely cough --->


b) Phlegm
Odds ratio
95% CI
Visit 0.91 0.68-1.23
Age (10 year increase) 1.03 0.72-1.48
Male (vs. female) 4.14 1.89-9.03
BMI (5 point increase) 0.97 0.72-1.31
Caucasian (vs. non-Caucasian) 0.85 0.16-4.65
1 comorbidity (vs. 0) 1.34 0.69-2.6
2+ comorbidities (vs. 0) 1.26 0.51-3.15
Anxiety/Depression (vs. no) 1.46 0.69-3.08
Smoking (vs. non-smoking) 2.02 1.1-3.74
Pack-years (10PY increase) 1.22 1.06-1.41
Any exacerbations (vs. no) 1.53 0.71-3.28
MPR (20% increase) 1.13 1.06-1.2
FEV1 (100mL increase) 0.93 0.87-0.98
Diagnosed (vs. undiagnosed) 0.82 0.46-1.47
Asthma (vs. no) 1.46 0.72-2.97
0 1 2 3 4 5
More likely phlegm --->


c) Wheeze
Odds ratio
95% CI
Visit 0.77 0.59-1.01
Age (10 year increase) 0.61 0.43-0.86
Male (vs. female) 2.07 1.04-4.11
BMI (5 point increase) 1.89 1.42-2.52
Caucasian (vs. non-Caucasian) 0.33 0.07-1.6
1 comorbidity (vs. 0) 0.91 0.51-1.65
2+ comorbidities (vs. 0) 0.29 0.12-0.67
Anxiety/Depression (vs. no) 1.25 0.64-2.45
Smoking (vs. non-smoking) 1.14 0.65-1.99
Pack-years (10PY increase) 1 0.89-1.13
Any exacerbations (vs. no) 1.87 0.88-3.97
MPR (20% increase) 1.12 1.06-1.19
FEV1 (100mL increase) 0.92 0.88-0.98
Diagnosed (vs. undiagnosed) 1.04 0.61-1.78
Asthma (vs. no) 3.28 1.69-6.36
0 1 2 3 4 5
More likely wheeze --->

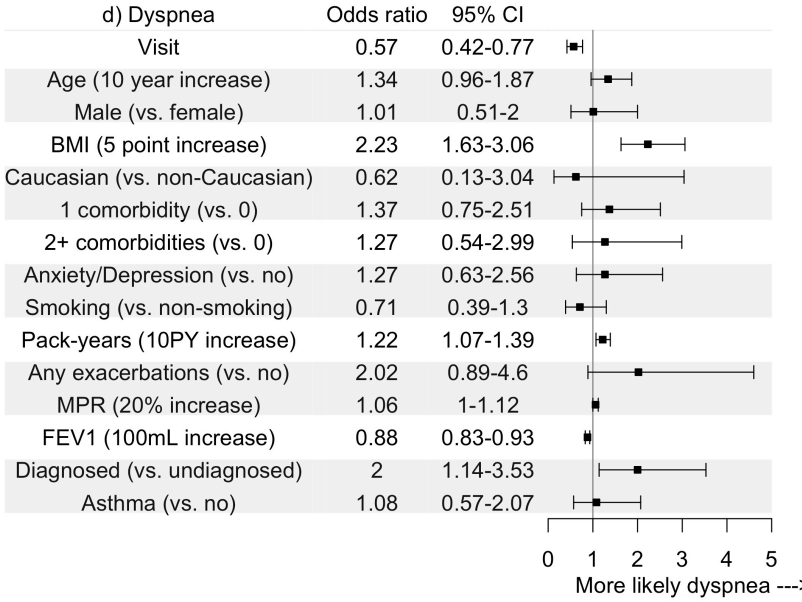

d) Dyspnea
Odds ratio
95% CI
Visit 0.57 0.42-0.77
Age (10 year increase) 1.34 0.96-1.87
Male (vs. female) 1.01 0.51-2
BMI (5 point increase) 2.23 1.63-3.06
Caucasian (vs. non-Caucasian) 0.62 0.13-3.04
1 comorbidity (vs. 0) 1.37 0.75-2.51
2+ comorbidities (vs. 0) 1.27 0.54-2.99
Anxiety/Depression (vs. no) 1.27 0.63-2.56
Smoking (vs. non-smoking) 0.71 0.39-1.3
Pack-years (10PY increase) 1.22 1.07-1.39
Any exacerbations (vs. no) 2.02 0.89-4.6
MPR (20% increase) 1.06 1-1.12
FEV1 (100mL increase) 0.88 0.83-0.93
Diagnosed (vs. undiagnosed) 2 1.14-3.53
Asthma (vs. no) 1.08 0.57-2.07
0 1 2 3 4 5
More likely dyspnea --->

Figure 3-3 Odds ratios for the associations between independent variables and the presence of a) cough, b) phlegm, c) wheeze, and d) dyspnea.

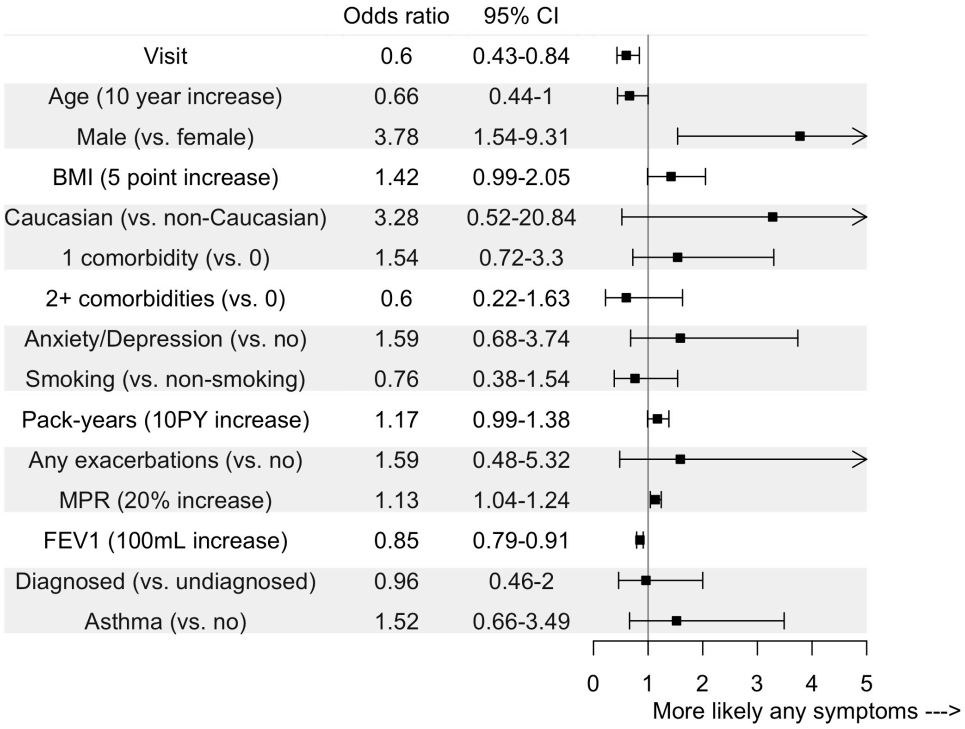


Figure 3-4 Odds ratios for the associations between independent variables and the presence of any symptoms.

The proportion of between-individual variation in the occurrence of symptoms that could be attributed to participants' measured characteristics (all independent variables in the full models) was 26%, 39%, 39%, 49%, and 91%, for cough, phlegm, wheeze, dyspnea, and any symptoms, respectively (Table 3-2). The proportion of variation explained by FEV_1 alone ranged from 2% (for wheeze) to 78% (for any symptoms, Table 3-2).

Table 3-2 Percentage of between-individual variation in symptoms explained by individual's lung function and all measured characteristics combined.

	Cough	Phlegm	Wheeze	Dyspnea	Any Symptoms
FEV_1	3%	8%	2%	28%	78%
All measured characteristics*	26%	39%	39%	49%	91%

* Visit, Age, Sex, BMI, Caucasian, Comorbidities, Anxiety/Depression, Smoking status, Pack-years of smoking, any exacerbations in the past 12 months, MPR, Diagnosed COPD, Asthma Diagnosis, FEV_1

3.4 Discussion

In this chapter, I characterised heterogeneity in the occurrence of respiratory symptoms between patients with COPD and assessed the extent to which commonly measured patient and disease characteristics explained the observed heterogeneity in symptoms. Respiratory symptoms were very common in this sample despite over 90% of patients having mild to moderate COPD, and only 29% of them having been diagnosed with COPD. Dyspnea was the most common symptom, followed by cough and wheeze. Individual-specific probabilities for the occurrence of symptoms were highly variable between individuals and for different symptoms. The interquartile range of probabilities was the largest for wheeze and dyspnea, indicating greater variability between individuals in the presence of these symptoms than for cough and phlegm. For phlegm, the majority of individuals had a probability of experiencing phlegm near 0 (visible in Figure 3-2 as a higher density of points at the left edge of the plot). In contrast, the individual-specific probabilities for cough, wheeze, and dyspnea were more evenly spread across the range of possible values. This indicates that phlegm is more stable in nature, and that individuals who do not currently have phlegm are unlikely to report it in the future. Indeed, a pan-European study

reported that daily and weekly variability in dyspnea, wheeze, and cough were higher than that for phlegm[125]. My findings extend these observations on symptom variability within individuals to variability between individuals in the occurrence of symptoms. As a result, tools for assessing COPD severity that involve the measurement of symptoms (such as the GOLD ABCD assessment tool),[15] are likely to be more or less variable over time, depending on the symptom measured.

The proportion of heterogeneity explained by the measured characteristics of participants differed substantially between symptoms. Most heterogeneity in the occurrence of any symptoms, and half the heterogeneity in dyspnea was explained by the demographic and clinical characteristics of participants included in the models. In contrast, these characteristics explained less than half the heterogeneity in phlegm and wheeze, and only a quarter of the heterogeneity in cough, indicating that other characteristics not included in these models are more important drivers of these symptoms. Cough in particular may be less predictable than dyspnea or the presence of any symptoms using many easily measured patient characteristics. Indeed, age, sex, BMI, smoking history, and lung function were weakly correlated with cough frequency[126] in previous studies. Instead, cough frequency was driven by current smoking intensity and percentage of sputum neutrophils[126]. A unique aspect of this study is that the assessment of heterogeneity was not limited to the patient characteristics included in these models. I quantified total between-individual variation in the burden of symptoms independent of the measured characteristics of participants. The proportion of heterogeneity that was not explained by measured characteristics highlights the potential for other factors, such as biologic disease markers, to improve predictions of symptom burden.

Although lung function has traditionally been regarded as the primary driver of respiratory symptoms[73], I found that FEV_1 explained the majority of between-individual variation in only the occurrence of any symptoms, and a substantial minority of variation in dyspnea. This finding is in line with the observation of high symptom variability within levels of disease severity[127], and high short-term variability in symptoms that is not due to changes in lung function[72,119]. My results extend these previous studies by examining the role of FEV_1 in each symptom individually. These findings suggest that lung function is an important but not dominant driver of the occurrence of dyspnea, but it explains very little between-individual variation in the occurrence of phlegm, cough, and wheeze. These symptoms are expected to be more variable within levels of disease severity defined by FEV_1. My results highlight the importance of moving beyond FEV_1 to incorporate other disease attributes, such as the presence of specific symptoms and exacerbation risk, when classifying disease severity. Given the large differences in the drivers of each symptom that I observed, it is likely that variation between patients in the burden of specific symptoms arises from different disease mechanisms. This can provide insights for refined COPD phenotyping.

In addition to analysing heterogeneity in symptoms, I documented associations between symptoms and many demographic and clinical characteristics of participants. In particular, I observed substantial sex-based differences in the reporting of all symptoms apart from cough and dyspnea. Controlled for disease severity, smoking history, and other variables, male patients were over three times more likely to be symptomatic, and four times more likely to report experiencing phlegm. Whether this is a biological phenomenon, or due to gender-related differences in the experience of symptoms[128], remains to be further assessed. I also observed positive associations between the occurrence of all symptoms and MPR. The direction of this

association is likely due to the long recall period over which symptoms were assessed, and reflects the underlying disease activity rather than short-term variation in symptoms due to treatment. As a result, high treatment intensity was indicative of greater disease activity and therefore more symptomatic disease.

Unique features of this study are its reliance on a large, nationally representative sample of the general Canadian population, the use of standardised spirometry in lung function assessment, validated questionnaires, and a long follow-up time. My sample consisted primarily of patients with mild to moderate COPD, a population that is often underrepresented in large cohort studies. Further, the majority of participants in this study had undiagnosed airflow obstruction. Because patients with a higher symptom burden are more likely to seek care that leads to a diagnosis[129], samples of diagnosed patients do not accurately represent symptoms in the entire population with permanent airflow obstruction. Finally, the associations determined from conventional regressions describe the relation between patient characteristics and the presence of symptoms for an average participant. My use of a random effect term in these models enabled me to extend these results by describing the extent to which these population-level associations apply to a given individual. I found that variation between individuals in the presence of any symptoms and dyspnea were reasonably well described by these population-level associations, but this was not the case for cough, phlegm, and wheeze. The assessment of variation at an individual-level is critical to fully characterising heterogeneity in the natural history of COPD, and ultimately to enabling effective use of symptoms in risk prediction tools and case finding algorithms for COPD.

This study also has several limitations. Patients reported their respiratory symptoms with a recall period that spanned the length of time between study visits, which could reach a

maximum of three years. The long duration of the recall period is likely to have resulted in inaccuracies in symptom reporting. However, my inclusion of comorbid anxiety and depression reduces the likelihood that psychological factors resulted in reporting bias. In addition, I only assessed the presence of symptoms, not their intensity. A more granular measurement of patient symptoms could provide a more nuanced assessment of symptom variability. Future studies should conduct similar analyses of symptom heterogeneity in patients with severe to very severe COPD, and in subgroups of patients defined by phenotypes or the GOLD ABCD grading system. The impact of individual symptoms on disease outcomes, such as the rate of exacerbations and the slope of lung function decline, should also be assessed. Given the tremendous heterogeneity in the burden of symptoms and their drivers, a detailed classification of patients according to their symptoms might enable better risk stratification to inform treatment decisions.

3.5 Conclusion

I assessed a sample of the general population with mostly mild-moderate COPD and found substantial variation in the occurrence of respiratory symptoms between individuals. Lung function explained a small proportion of between-individual variation in the occurrence of cough, phlegm, and wheeze. Commonly measured patient and disease characteristics explained very little heterogeneity in the occurrence of cough in particular. Overall, the observed differences in symptom variation may reflect the divergent etiology of symptoms associated with COPD. Defining phenotypes based on symptoms and evaluating their relation to disease outcomes is a key area of future research.

Chapter 4: Healthcare System Encounters before COPD Diagnosis: a Registry-Based Longitudinal Cohort Study

4.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease of the airways that affects approximately 384 million people globally[35], and resulted in the deaths of 3.2 million people in 2015 alone[130]. Despite the high prevalence of COPD, an estimated 81% of COPD patients worldwide have not received a diagnosis at any given time[47]. These patients are not receiving treatment and risk factor mitigation for the disease, and are likely to experience worse outcomes over the long-term[54]. In high income countries, undiagnosed COPD patients tend to have less severe disease than diagnosed patients[129]. However, previous studies indicate that healthcare services use among these patients is substantial[46,131].

Numerous case detection and screening strategies have been proposed to diagnose patients with COPD earlier[59]. These strategies typically rely on opportunistic encounters between undiagnosed COPD patients and the healthcare system[59]. The patterns of healthcare services use among undiagnosed COPD patients are therefore critical factors in determining their success. In a population-based study of nearly 40,000 COPD patients, a sharp increase in respiratory-related physician consultations in the five years preceding a diagnosis of COPD was documented[76]. The authors concluded that there was a missed opportunity for an earlier diagnosis of COPD in 85% of patients, and suggested implementing a case finding approach based on patient risk factors[76]. However, this study only examined respiratory-related resource use, and most interactions between undiagnosed COPD patients and the healthcare system likely occur for non-respiratory

reasons[131]. This study also did not assess healthcare utilisation in a comparator group. In order to enable efficient case detection strategies, it is necessary to identify the encounters that are best at distinguishing COPD from non-COPD patients.

To address this knowledge gap, I documented the type and frequency of outpatient visits in a population-based sample of COPD patients before diagnosis. I assessed the rate and probability of primary care, specialist, and pharmacist visits in the five years preceding a diagnosis of COPD. I compared these results to a matched population of non-COPD subjects to identify the types of visits that were most predictive of a patient having COPD.

4.2 Methods

4.2.1 Study design

I conducted a population-based, retrospective cohort study using health administrative data. Ethics approval was obtained from Population Data BC (H13-00684). All inferences, opinions and conclusions drawn in this research are those of the authors and do not reflect the opinions or policies of the Data Steward(s).

4.2.2 Data sources

The province of British Columbia (BC), Canada, had a population of 4.8 million in 2017[132]. To administer the public healthcare system in BC, healthcare utilisation records of all legal residents are collected in centralised databases. These administrative databases comprehensively capture information on (1) hospitalisations[133], which include admission date, discharge date, and diagnoses coded using the International Classification of Diseases 9th or 10th revisions (ICD-9, ICD-10) revisions, (2) physician billing claims[134], which include service date, diagnoses, and

practitioner type, and (3) medication dispensation records[135], which include service date and type for all drugs dispensed outside a hospital setting. In BC, general practitioners and specialists can practice within the community or be employed by hospitals. There are no private healthcare institutions that provide similar services. Demographic and census information are also recorded[136,137], including date of birth, sex, and socioeconomic status (SES) based on income quintiles in the geographic neighbourhood of residence. These databases were linked at the individual level using a unique, anonymous identifier. Administrative databases in Canada have been shown to have low rates of missing, unreported, or misclassified information[138,139].

4.2.3 Study population

Figure 4-1 depicts the study design. I created a retrospective longitudinal cohort of patients who fulfilled a validated case definition for COPD between January 1, 1996 and December 31, 2015. Patients with three or more physician billing claims and/or one hospitalisation for COPD in any 2-year window were defined as having physician diagnosed COPD[140]. This case definition has a specificity of 95%[140]. I defined the index date as the date of first healthcare resource use of any type (outpatient or inpatient) with COPD as the main diagnostic code. Patients who fulfilled the case definition but were <40 years on the index date were excluded, as there is a higher likelihood of misdiagnosis in these patients.

Following the principle of incident density sampling[141], the comparator non-COPD cohort was composed of subjects who, as of the same day of follow-up for each COPD patient, were not diagnosed with COPD. Controls either never developed COPD during follow-up, or were diagnosed with COPD later in the study period. A comparator subject was matched to each COPD patient using the following criteria: 1) year of birth within 5 years, 2) sex, 3)

sociodemographic status within one income quintile, and 4) no COPD diagnosis date, or a diagnosis date that occurred later than their matched COPD patient. Comparator subjects were assigned the same index date as their matched COPD patient. COPD patients and comparator subjects were required to be in the dataset for at least five years prior, and 1 year following the index date. To ensure that comparator subjects were in the province around the index date, COPD/comparator pairs in which the comparator had no healthcare resource use of any type in the year following the index date were excluded. COPD patients had an instance of resource use at the index date by definition, thus satisfying this criterion. I assessed healthcare encounters in the five years prior to the index date for COPD and comparator subjects. I excluded all pairs in which the COPD patient had a diagnostic code for spirometry within 1 to 5 years of index, but the test did not result in a diagnosis of COPD.

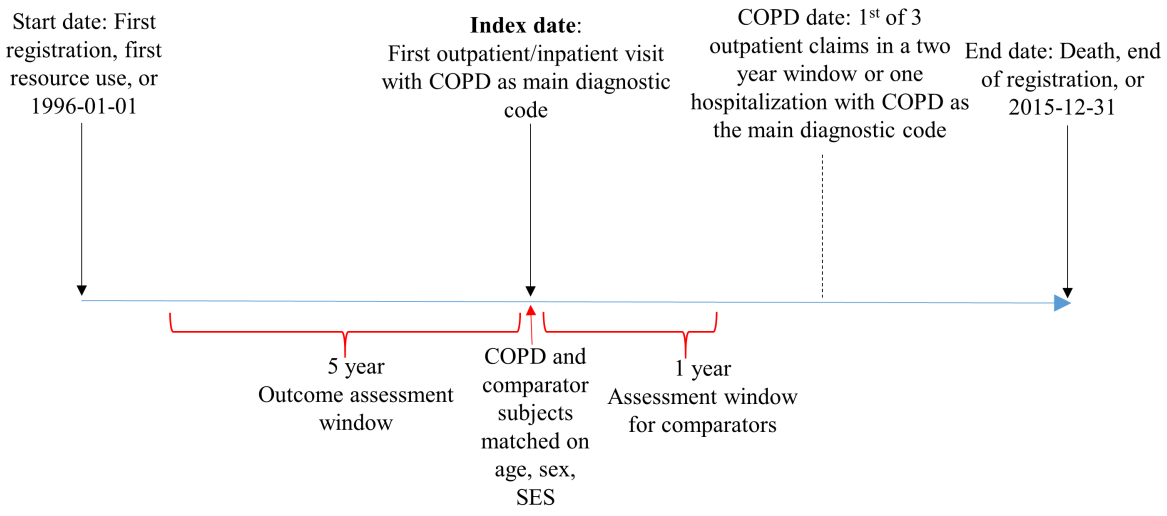


Figure 4-1 Schematic illustration of study design.

The 1-year assessment window for comparators was to ensure comparator subjects had at least one instance of resource use in the year after the index date.

4.2.4 Healthcare system encounters

For each subject, I determined the number of outpatient visits in each of the five one-year periods prior to the index date. I assessed visits to (1) pharmacists, (2) primary care physicians, (3) specialist physicians, and (4) primary care physicians for respiratory-related reasons. Physician visits types were distinguishable using specialty codes, and all specialties, regardless of their field, were included in the specialist physician assessment. Respiratory-related visits were those with a primary diagnostic code for respiratory diseases other than COPD (ICD-9 460-466, 470-478, 480-487, 490-496, 500-508, 510-514, 516-519, ICD-10 J00-J99) or for respiratory symptoms (ICD-9 786, ICD-10 R05-R07). I did not assess hospitalisations as the focus of this study was on community-based case detection.

I categorised the types of COPD-related inhaler medications dispensed at pharmacist visits using Health Canada's unique Drug Identification Numbers. I defined the following medication groups: inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), long-acting muscarinic agents (LAMA), short-acting beta-agonists (SABA), and short-acting muscarinic agents (SAMA). Combination therapies were single inhaler ICS/LABA, SABA/SAMA, and LAMA/LABA, or LAMA and LABA dispensed as separate inhalers on the same date. I used a master drug list (Appendix C.1) to identify all other respiratory medications. Over-the-counter medications were not recorded in this dataset.

4.2.5 Analysis

All analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC). I initially created a descriptive summary of the rate of outpatient visits per patient year, stratified by COPD status. Second, I assessed the medical indications that prompted COPD patients to visit a primary care

physician before diagnosis. Medical indications were grouped by disease type based on the main diagnostic code for each visit. Within disease types, main diagnostic codes could be for either symptoms or disease diagnoses. In a small minority of cases, a visit was attributed to more than one medical indication (i.e. >1 main diagnostic code), and these were counted as separate visits. Third, I calculated the mean number of pharmacist visits per patient year in which a respiratory medication was dispensed. When more than one medication of different classes were dispensed at the same visit, these were counted separately. Last, I assessed the probability that COPD patients had any opportunity for case detection in the five years before diagnosis. This was done by determining the proportion of COPD and comparator subjects with at least one visit of each type in the cumulative years before diagnosis (i.e., year 1, then years 1 and 2, etc.).

I tested for differences in the rate of outpatient visits between COPD patients and comparator subjects before the index date. I constructed separate generalised linear regression models (negative binomial distribution, log link) for each of the four visit types. The rate ratio (RR) gives the ratio of visit rates between COPD patients and comparators. I used generalised estimating equations to account for clustering of data between matched pairs of observations. Period number (1-5 range), calendar year at the beginning of the period, age, sex, and SES on the index date were included in all models to adjust the exposure estimates for the overall effects of these variables over the study period. To assess trends in the rate of healthcare visits as COPD patients approached diagnosis, I constructed a second model for each of the dependent variables. The independent variables were identical to the original model, with the addition of an interaction term between period and the group-defining variable (COPD/comparator). The sum of the coefficients for period and the interaction term gave the rate of change in healthcare visits in the COPD group relative to the comparator group.

I conducted a sensitivity analysis on the subset of COPD patients who were prescribed LAMA in the year before or after their index date. In BC, physicians prescribing this drug must provide evidence that the ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) is < 0.7 and $FEV_1 \leq 65\%$ of predicted[142], meaning that nearly all patients in this subgroup had moderate to very severe airflow obstruction according to the Global Initiative for chronic Obstructive Lung Disease (GOLD) guidelines[15]. Therefore, the specificity of the case definition for COPD is close to 100% in this subgroup. I performed a second sensitivity analysis in which all participants with missing data were excluded. In a third sensitivity analysis, I constructed a new cohort with the additional criterion that comparator subjects never developed COPD at any point during the study period.

4.3 Results

The sample selection flow chart is shown in Figure 4-2. 149,213 patients fulfilled the case definition of COPD and had data available for at least five years prior to the index date. 112,635 COPD/comparator pairs were included following the selection process. 28.3% of COPD patients received an initial diagnosis of COPD during hospital admission; the remaining were diagnosed in outpatient settings. 12.3% of COPD patients were matched to a comparator subject who developed COPD later in follow-up. 51.0% of pairs were male, and the mean age at the index date was 68.6 (SD 12.2) years. A descriptive summary of the sample characteristics is shown in Table 4-1.

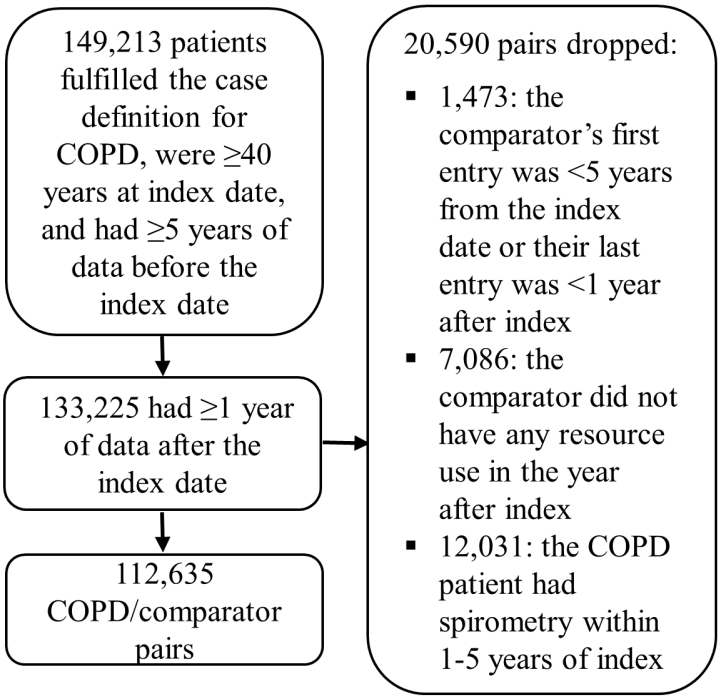


Figure 4-2 Cohort selection process.

Table 4-1 Characteristics of patients meeting the case definition of COPD and matched comparator subjects.

	COPD patients (N= 112,635)	**Comparator subjects** (N= 112,635)
Age	68.6 (12.2)	68.7 (12.2)
Male (vs. female)*	51.0%	51.0%
SES†‡		
Quintile 1	25.9%	25.9%
Quintile 2	21.3%	21.3%
Quintile 3	18.7%	18.7%
Quintile 4	17.3%	17.3%
Quintile 5	15.0%	15.0%
Year of index date		
2001-2005	28.4%	28.4%
2006-2010	40.1%	40.1%
2011-2015	31.5%	31.5%

* Sex was unknown in 0.05% (N=57) of COPD patients and 0.05% (N=57) of comparators.

† SES was unknown in 1.80% (N=2,023) of COPD patients and 1.80% (N=2,023) of comparators. Unknown observations for sex and SES were coded as missing and included as a separate category in regression analysis.

‡ Quintile 5 is the highest socioeconomic status.

4.3.1 Rate of outpatient encounters

Pharmacist, primary care, and specialist physician visits were more common among COPD patients than comparator subjects throughout the five-year assessment period (Figure 4-3). In the year prior to being diagnosed, COPD patients had an average of 17.0 (Interquartile Range [IQR] 5.0-20.0) visits to a pharmacist, 12.6 (IQR 5.0-16.0) primary care visits, 10.5 (IQR 3.0-14.0) specialist visits, and 1.8 (IQR 0.0-2.0) visits to a primary care physician for respiratory-related reasons. In contrast, comparator subjects had an average of 10.2 (IQR 3.0-13.0), 8.2 (IQR 3.0-11.0), 6.9 (IQR 2.0-9.0), and 0.5 (IQR 0.0-1.0) pharmacist, primary care, specialist, and respiratory-related primary care visits in the year before index, respectively.

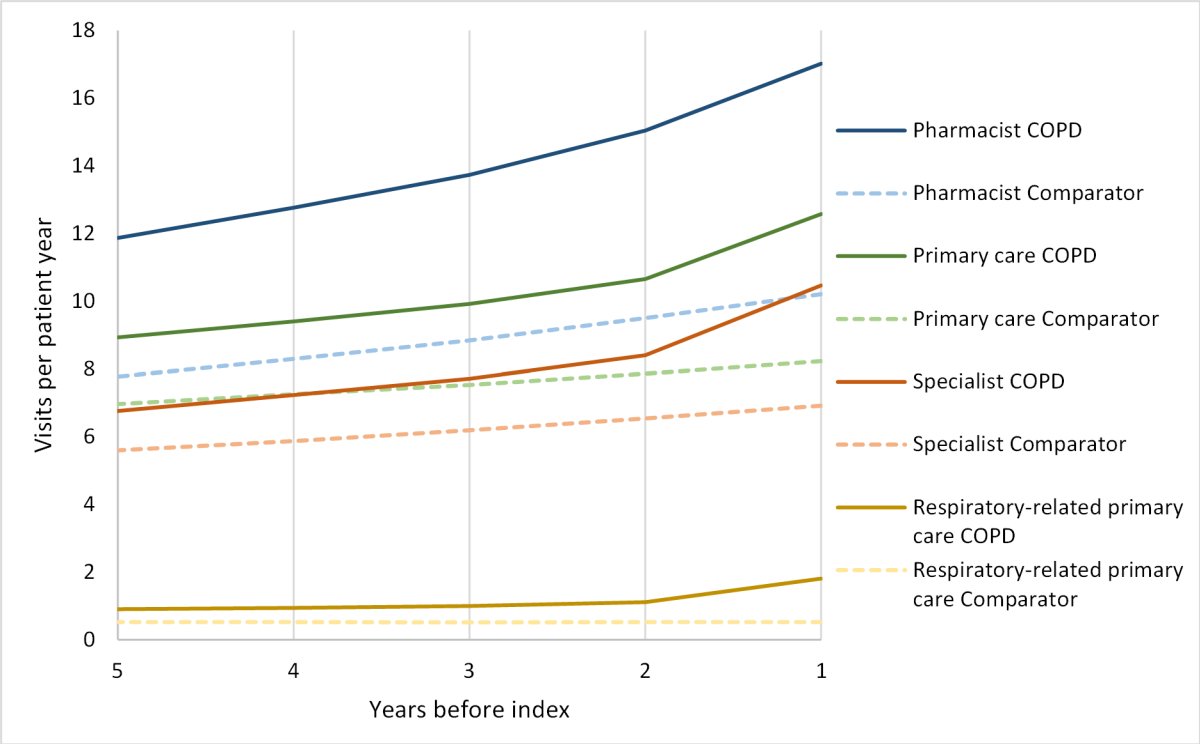


Figure 4-3 Mean number of outpatient visits per patient year in each of the five years before the index date.

COPD patients and their comparator non-COPD subjects are shown.

The regression analysis indicated that COPD patients prior to diagnosis incurred all types of visits at higher rates than comparator subjects (Table 4-2). Relative to comparator subjects, COPD patients were most likely to visit a primary care physician for respiratory related reasons (rate ratio [RR] 2.17 95%CI 2.14–2.19). COPD and comparator subjects with lower SES had a higher rate of primary care and pharmacist visits. For all outcomes, healthcare visits increased as subjects approached the index date. Models with an additional interaction term between period and the group-defining variable indicated that the rate of primary care visits increased by 8.5% more visits per year (95%CI 8.1–8.9%) in COPD than comparator subjects. This figure was 7.3% (95%CI 6.8–7.8%) for pharmacist visits, 10.8% (95%CI 10.2–11.4%) for specialist visits, and

21.9% (95%CI 20.8–23.0%) for respiratory-related primary care visits. Coefficients for female, age, SES, and calendar year were similar to the main models and are therefore not shown. I observed similar results in the sensitivity analysis of 9,079 patients with spirometry-confirmed moderate to very severe COPD near the index date[15] (Appendix C.2), for the 110,556 COPD/comparator pairs with no missing data (Appendix C.3), and for the cohort of 106,439 COPD/comparator pairs in which the comparator never developed COPD during follow-up (Appendix C.4).

Table 4-2 Parameter estimates and confidence intervals from the multivariable regression model of the rate of outpatient visits among COPD patients and comparator non-COPD subjects.

	All-cause primary care visits		Respiratory-related primary care visits		Specialist physician visits		Pharmacist visits	
	Rate Ratio	95% CI	Rate Ratio	95% CI	Rate Ratio	95% CI	Rate Ratio	95% CI
COPD (vs. comparator)	1.40	1.39-1.41	2.17	2.14-2.19	1.35	1.34-1.37	1.62	1.60-1.63
Period	1.06	1.06-1.06	1.14	1.14-1.14	1.07	1.07-1.08	1.06	1.06-1.06
Female (vs. male)	1.16	1.15-1.16	1.27	1.26-1.29	1.08	1.07-1.09	1.18	1.17-1.20
Age	1.01	1.01-1.01	1.00	1.00-1.00	1.02	1.02-1.02	1.01	1.01-1.01
SES								
1 (vs. 5)	1.17	1.16-1.19	1.11	1.09-1.13	1.02	1.00-1.03	1.32	1.30-1.35
2 (vs. 5)	1.10	1.09-1.11	1.08	1.06-1.10	0.99	0.98-1.01	1.12	1.10-1.14
3 (vs. 5)	1.06	1.04-1.07	1.05	1.03-1.07	0.99	0.97-1.00	1.06	1.04-1.08
4 (vs. 5)	1.03	1.02-1.05	1.02	1.00-1.04	0.99	0.97-1.00	1.04	1.03-1.06
Calendar year	1.00	1.00-1.00	0.97	0.96-0.97	1.01	1.01-1.01	1.02	1.02-1.02

Parameter estimates for the category of observations that were missing for sex and socioeconomic status are not shown due to their small numbers (see Table 4-1 for details).

The most common reason for visits to a primary care physician among COPD patients was circulatory disease (mean of 1.96 diagnostic codes/year, SD 3.77), followed by respiratory disease (1.16 diagnostic codes/year, SD 2.14, Figure 4-4). The frequency of circulatory disease diagnoses increased by 20.4% from two years before COPD diagnosis to year one before, and by 62.9% for respiratory disease diagnoses over the same time period.

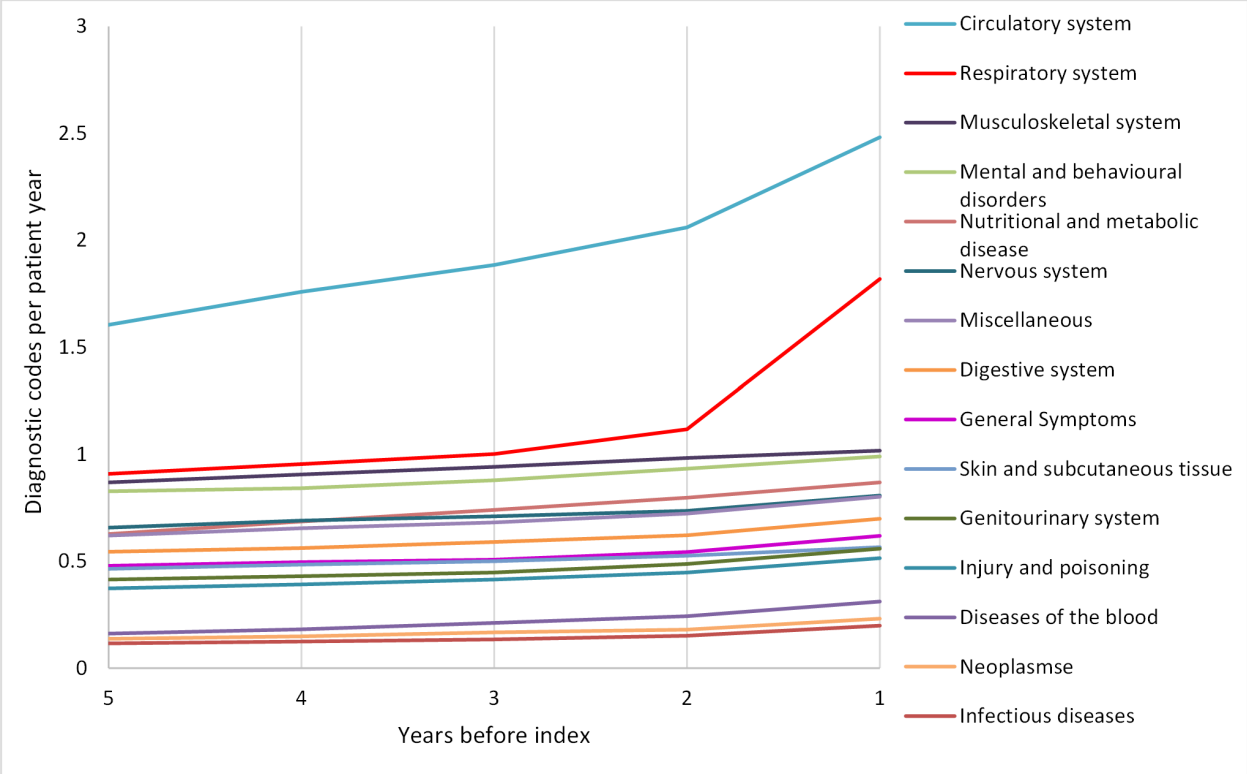


Figure 4-4 Mean number of ICD diagnostic codes per patient year at the primary care visits of COPD patients before the index date.

In 97.7% out of 5,665,378 total visits analysed, there was only one diagnostic code per visit.

Disease categories with less than <0.1 diagnostic codes per year are not shown.

COPD patients had a mean of 1.61 (SD 4.48) pharmacist visits per year in which respiratory medications were dispensed (Table 4-3). This increased to 2.46 (SD 5.57) visits in the final year before diagnosis. In contrast, these figures were 0.31 visits per year (SD 1.66) and 0.36 visits (SD 1.86) for comparator subjects, respectively. SABA was the respiratory medication most commonly dispensed to COPD patients before diagnosis; with a mean of 0.58 (SD 1.96) pharmacist visits with a SABA dispensed per year. Non-respiratory medications were dispensed 53 percent more frequently to COPD patients than to comparator subjects.

Table 4-3 Mean number of pharmacist visits per 100 patient years with respiratory and other medications dispensed.

	COPD patients					Comparator subjects				
Years before index	**5**	**4**	**3**	**2**	**1**	**5**	**4**	**3**	**2**	**1**
ICS	26	28	29	33	43	6	6	6	6	6
LABA	3	3	4	4	5	1	1	1	1	1
ICS/LABA	10	12	15	20	31	2	2	2	3	4
LAMA	1	1	2	3	5	0	0	0	0	0
LABA	3	3	4	4	5	1	1	1	1	1
LAMA/LABA	0	0	0	0	0	0	0	0	0	0
SABA	44	48	52	61	85	8	8	8	9	9
SAMA	8	10	12	16	27	1	1	1	2	2
SAMA/SABA	2	3	4	4	6	0	0	0	0	0
Other Respiratory Medications	21	24	26	30	42	10	11	11	13	14
Non-Respiratory Medications	1141	1226	1320	1441	1612	766	817	871	937	1007

4.3.2 Probability of outpatient encounters

The proportion of COPD patients that incurred at least one visit in any of the five years before the index date was ≥99.0% for pharmacist, primary care, and specialist visits, and 85.3% for respiratory-related primary care visits (Figure 4-5). These proportions were similar for comparator subjects, with the exception of fewer respiratory-related primary care visits (66.2%). The highest proportion of COPD patients visited a primary care physician in the year prior to diagnosis (97.2%), followed by pharmacist (95.4%), specialist (93.6%), and respiratory-related primary care visits (60.3%).

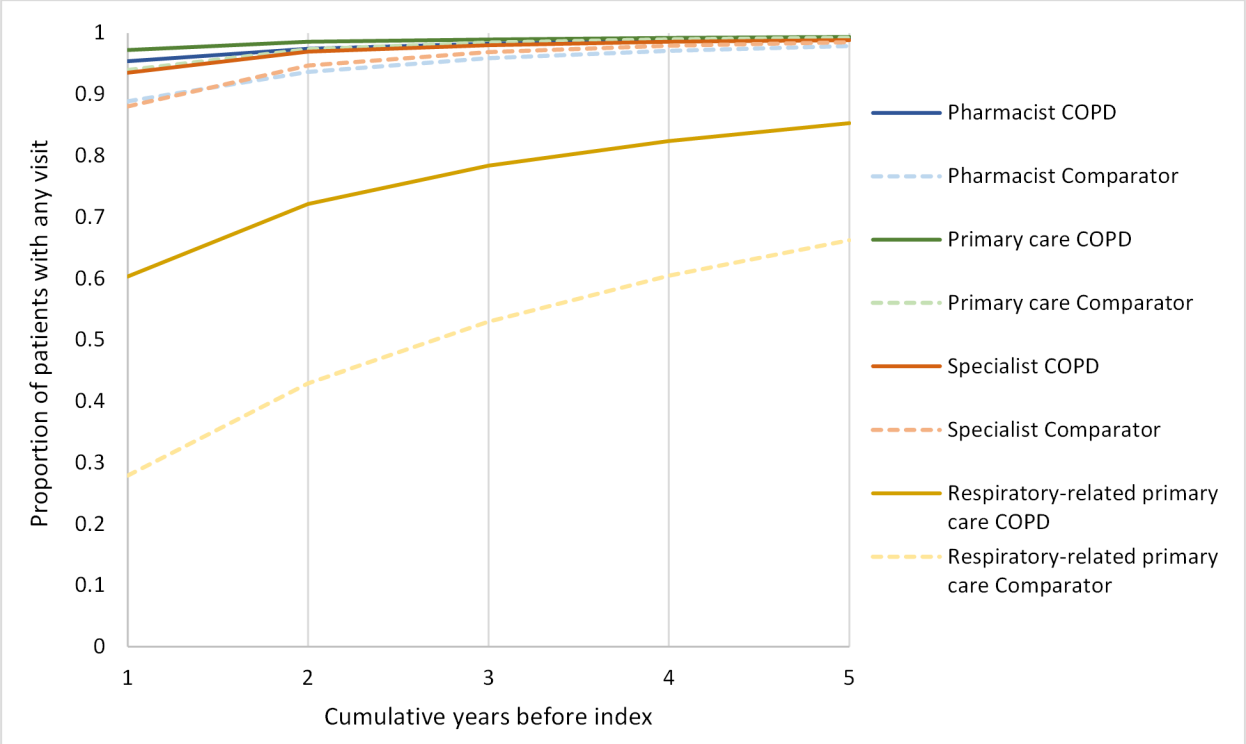


Figure 4-5 Proportion of subjects with at least one outpatient visit in any of the five years before index.

COPD patients and their comparator non-COPD subjects are shown.

4.4 Discussion

In this chapter, I conducted a longitudinal study of healthcare encounters before COPD diagnosis in a sample of the general population. Nearly all patients had at least one encounter in an outpatient setting in the five years before they were diagnosed with COPD. They interacted most frequently with pharmacists, followed by primary care physicians, and then with specialist physicians. The rate of visits of every type increased as COPD patients approached diagnosis, and healthcare encounters were particularly high in the year before diagnosis. Outpatient visits occurred at a substantially higher rate in COPD patients than in matched non-COPD comparator subjects. My findings indicate that case detection technologies implemented in primary care settings have frequent opportunities to diagnose COPD earlier.

COPD is a progressive disease that is characterised by airway, and in certain patients, systemic inflammation[143]. Due to this inflammation and also to shared risk factors, patients with COPD have higher rates of comorbidities than subjects without the disease[144]. Cardiovascular comorbidities are especially common among COPD patients[23]. The most common reason for visiting a primary care physician before being diagnosed with COPD was circulatory disease, followed by respiratory diseases other than COPD or respiratory symptoms. Gershon et al.[131] also found that circulatory diseases were the most common reason for outpatient visits in undiagnosed COPD patients. In my analysis, the frequency of circulatory and respiratory disease diagnoses spiked in the year before COPD diagnosis. The increase in healthcare encounters leading up to diagnosis might reflect these systemic manifestations of the disease. It is also possible that COPD was the underlying cause of some of these circulatory-related visits, as symptoms such as dyspnea and fatigue are shared between diseases[145]. It is likely that these increased encounters were what eventually led to the COPD diagnosis. Increased awareness of

the risk of COPD among patients with cardiovascular disease in particular might lead to earlier detection. However, the presence of frequent healthcare encounters is not in itself sufficient to warrant suspicion of COPD, as the pattern of increased healthcare services use leading up to diagnosis is common to other disease areas[146,147]. Case detection methods such as risk assessment questionnaires[70,148] or screening spirometry[66] should be implemented at these types of routine visits in order to identify patients at high risk of having COPD.

These results indicate that there are substantial opportunities to diagnose COPD earlier. 85% of COPD patients visited a primary care physician for a respiratory-related reason in the five years before they were diagnosed with COPD. This proportion is almost identical to that found by Jones et al.[76] in the UK. Moreover, due to my exclusion criteria, none of the COPD patients in the main analysis received spirometry despite visiting a primary care physician for either respiratory symptoms or other respiratory diseases. Many of these patients were also receiving treatment for respiratory symptoms despite not having been diagnosed with COPD. Influential guidelines, such as GOLD, recommend considering a diagnosis of COPD in patients with respiratory symptoms or risk factors for COPD[15]. Risk factors can include other respiratory diseases such as asthma, environmental, or early childhood exposures, for example to childhood respiratory infections, that can result in lung damage long before the clinical manifestation of COPD[149]. This suggests that programs systematically attempting to diagnose COPD earlier through the use of case detection methods have the potential to substantially increase testing for COPD. Given that almost all COPD patients had at least one respiratory consultation in the five years before diagnosis, and many were already receiving respiratory medications, respiratory-related primary care visits might provide particularly high value opportunities for case detection.

This type of visit was much more common among COPD patients than in comparator subjects, which would increase the prior predictive value of any diagnostic test.

This study has several strengths. I characterised healthcare services use in a large sample of the general population. I used routinely collected data rather than self-reporting by physicians or patients, which is particularly important given that information or recall bias might affect the accuracy of self-reports. A limitation of this study is the lack of data on individual patient characteristics such as spirometry and disease severity, which limited us to studying healthcare services use before COPD diagnosis, rather than in undiagnosed COPD patients. However, I observed similar results in the subset of patients who had spirometry-confirmed moderate to severe COPD near the time of diagnosis. My use of a highly specific case definition may have resulted in a sample of patients with more severe COPD and higher healthcare service use than in the general population of undiagnosed COPD patients. The definition of comparator subjects allowed subjects to develop COPD after the index date. However, due to the high prevalence of undiagnosed COPD[46,150], some comparator subjects may have already had COPD at the index date. If the comparator group included patients with COPD, my results would be biased towards the null. Another limitation is that I only followed patients for 5 years before diagnosis. I imposed this criterion to ensure identical follow-up between matched COPD and comparator subjects while still maintaining a large sample size. The probability of a patient having undiagnosed COPD also decreases as time to diagnosis increases. Finally, my results are most relevant to high income countries, as more limited access to care could result in lower or no healthcare services use among undiagnosed COPD patients in low- and middle- income countries.

4.5 Conclusions

I documented frequent interactions between COPD patients and the healthcare system prior to COPD diagnosis. This suggests that there are many opportunities to implement case detection strategies in outpatient settings, and that it is possible to improve early detection while relying on only opportunistic healthcare encounters. COPD patients interacted most frequently with pharmacists before diagnosis, but the greatest difference between COPD and non-COPD subjects was in the rate of primary care visits for respiratory-related reasons. Either of these types of visits might present high value opportunities for case detection. Increased testing for COPD during the routine visits of at-risk patients has the potential to substantially improve early detection. The cost-effectiveness of case detection strategies implemented during pharmacist or primary care visits should be investigated in a simulation experiment.

Chapter 5: Cost-Effectiveness of Case Detection Strategies for the Early Detection of COPD

5.1 Introduction

Chronic obstructive pulmonary disease (COPD) is the third most common cause of mortality among chronic diseases globally[151], and is the leading medical cause of hospital admission in Canada[152]. Patients with COPD typically experience periods of increased impairment known as exacerbations, as well as a progressive loss of lung function that is typically irreversible[15]. As a result, risk factor management to preserve lung function early in the disease progression is regarded as the most important component of treatment[54]. However, early interventions to reduce the burden of COPD require an early diagnosis, and estimates from Canada indicate that 70% of patients with COPD are currently undiagnosed[46,150], with up to one third of COPD patients initially diagnosed in hospital following an exacerbation[44,153]. A late diagnosis of COPD can represent a missed opportunity, as treatment for smoking cessation and pharmacotherapy to reduce symptoms and the risk of exacerbations can improve quality of life and long-term outcomes[54,59].

Screening and case detection strategies offer potential solutions to the problem of underdiagnosis in COPD. Screening involves testing healthy individuals in the general population for COPD[8]. In contrast, case detection is opportunistic, and involves targeted testing of high-risk individuals during their routine healthcare encounters[8,60–62]. Influential clinical guidelines recommend against screening for COPD among asymptomatic adults due to the lack of evidence that it improves disease outcomes[6,63]. However, two recent randomised controlled

trials found that opportunistic case finding strategies resulted in a higher yield of new COPD cases than usual care[154,155]. A subsequent economic analysis showed that an active case finding approach, in which symptomatic patients at risk of COPD were recruited for diagnostic spirometry, can be cost-effective[155,156]. However, existing case detection strategies are extremely heterogeneous[59], and the decision space around selection characteristics, case detection technology, and frequency of testing should be more fully explored.

The objective of this chapter was to address these questions using a 'whole disease' model of COPD. The Evaluation Platform in COPD (EPIC) was recently developed and has been extensively validated to project the outcomes of COPD-related policies for the general Canadian population[80]. In contrast to existing trial-based economic evaluations[154,155], model-based decision analysis offers a more flexible approach to policy design through a fuller evaluation of scenarios and a broader scope of evidence. The objective of this study was to determine the cost-effectiveness of primary care-based case detection scenarios, which vary in terms of their initial eligibility criteria, case detection technology, follow-up intervals, and subsequent disease management.

5.2 Methods

This chapter was conducted in two phases, and the methods are reported accordingly. In the first section, I describe my methods for evaluating the cost-effectiveness of case detection; in the second section, I describe my expansion of the EPIC model to simulate the case detection pathway. The case detection scenarios evaluated, their implementation in EPIC, and key parameters for the costs of case detection and effectiveness of treatment are summarised in Sections 5.2.1 to 5.2.3. I describe the cost-effectiveness analysis in Section 5.2.4. In the second

phase (Section 5.2.5), I describe the development of modules for simulating respiratory symptoms, primary care visits, COPD diagnosis, treatment, and case detection in EPIC. Diagnosis, symptoms, and primary care visits were the subjects of Chapters 2–4, respectively, and the results of these chapters informed their development in EPIC. I have adhered to the consolidated health economic evaluation reporting standards (CHEERS) statement for reporting economic evaluations of health interventions[157].

5.2.1 Case detection scenarios

I evaluated 16 strategies for improving early detection of COPD during routine primary visits. Scenarios were defined by three sets of selection characteristics for inclusion, two types of case detection methods, and two different time intervals between case detection.

Scenarios were grouped based on their eligibility criteria for selecting patients to receive case detection: all patients (Scenario 1: '*S1*'), patients reporting any respiratory symptoms at baseline (Scenario 2: '*S2*'), and current or former smokers ('ever smokers') ≥50 years of age at baseline (Scenario 3: '*S3*'). Within each set of eligibility criteria, scenarios were further characterised by the case detection method employed: the COPD diagnostic questionnaire (CDQ)[158] or the handheld flow meter, and the time interval between implementation (Table 5-1).

Table 5-1 Case detection scenarios evaluated.

Case detection method	Testing interval	Sensitivity, Specificity	Reference
S0: No case detection			
(S1) *All patients*			
S1a: CDQ ≥17 points	3 years, 5 years	91%, 49%	[159]
S1b: Screening spirometry (with bronchodilator)	3 years, 5 years	80%, 94%	

S1c: CDQ + Screening spirometry (with bronchodilator)	3 years, 5 years	72%, 97%	
(S2) *Symptomatic patients* (any respiratory symptoms)			
S2a: Screening spirometry (without bronchodilator)	3 years, 5 years	81.5%, 88.9%	[6]
(S3) *Smoking history* (ever smokers ≥ 50 years)			
S3a: CDQ ≥19.5 points	3 years, 5 years	64.5%, 65.2%	[66]
S3b: CDQ ≥16.5 points	3 years, 5 years	87.5%, 38.8%	
S3c: Screening spirometry (without bronchodilator)	3 years, 5 years	79.9%, 84.4%	
S3d: CDQ + Screening spirometry (with bronchodilator)	3 years, 5 years	74.4%, 97%	[159]

I evaluated two types of case detection methods: the handheld flow meter and the COPD diagnostic questionnaire (CDQ). Handheld flow meters are used for performing screening spirometry based on the ratio of FEV_1 to forced expiratory volume in 6 seconds (FEV_6) < 0.7[66]. I assessed handheld flow meters with prior administration of a bronchodilator (scenarios: *S1b*, *S1c*, *S3d*)[159], and without a bronchodilator (scenarios: *S2a*, *S3c*)[45,59], depending on their implementation in the study from which I derived their performance characteristics.

The CDQ is a 5-item symptom and risk factor assessment questionnaire with a total score of 38 points[68,158]. Different score cut points have been used to identify patients for referral to diagnostic spirometry. In separate scenarios, I evaluated scoring cut points of ≥19.5 (*S3a*) and ≥16.5 (*S3b*) among ever smokers[66], and ≥17 (*S1a*) among all patients[159], again following the studies from which I derived their performance characteristics. In two scenarios (*S1c* and *S3d*), the CDQ and screening spirometry were implemented sequentially at the same primary care visit (Table 5-1).

Within each group of scenarios (*S1a, S1b, S1c, S2a, S3a, S3b, S3c, S3d)*, I evaluated 3- and 5-year intervals between instances of case detection. In cases where an individual had no primary care visits at the scheduled interval, case detection was deferred to the next year in which they had a primary care visit.

5.2.2 Evaluating case detection scenarios

The Evaluation Platform in COPD (EPIC) simulates the development and progression of COPD in the general population of Canadians ≥40 years old. From this simulated population, I created a cohort of individuals meeting the eligibility criteria for case detection at baseline (i.e. *S1*- all patients, *S2*- symptomatic patients, *S3*- ever smokers). To be eligible for cohort inclusion, individuals were also required to have undiagnosed COPD or to not have COPD ('non-COPD' individuals), and to have had at least one primary care visit in the previous 12 months as this was seen as an opportunity for study recruitment.

Case detection occurred at routine primary care visits and resulted in one of four outcomes: a diagnosis of COPD in individuals with COPD (true positive), no diagnosis of COPD in individuals with COPD (false negative), a diagnosis of COPD in individuals with no COPD (false positive), or no diagnosis of COPD in individuals with no COPD (true negative). Individuals who tested negative after case detection (true negatives and false negatives) did not receive any further testing. Individuals who tested positive after case detection (true positives and false positives) underwent an additional primary care visit to assign a diagnosis of COPD using post-bronchodilator diagnostic spirometry. Diagnostic spirometry had 100% accuracy in ruling out a diagnosis of COPD in non-COPD individuals. Therefore, individuals with COPD (true positives) were definitively diagnosed, and non-COPD individuals were not diagnosed. The

cohort creation and case detection pathway are depicted in Figure 5-1. Details on the development and parameterization of the case detection module are provided in Section 5.2.5.6.

COPD could be diagnosed at primary care visits without the use of case detection, both among individuals with COPD (routine diagnosis) and non-COPD individuals (routine overdiagnosis). An additional primary care visit with diagnostic spirometry was required to correctly diagnose individuals with COPD, or to reverse the diagnosis among non-COPD individuals. Among individuals with COPD, a second pathway to diagnosis was during hospitalisation due to severe exacerbation. Details on the development and parameterization of the routine diagnosis module are provided in Section 5.2.5.4.

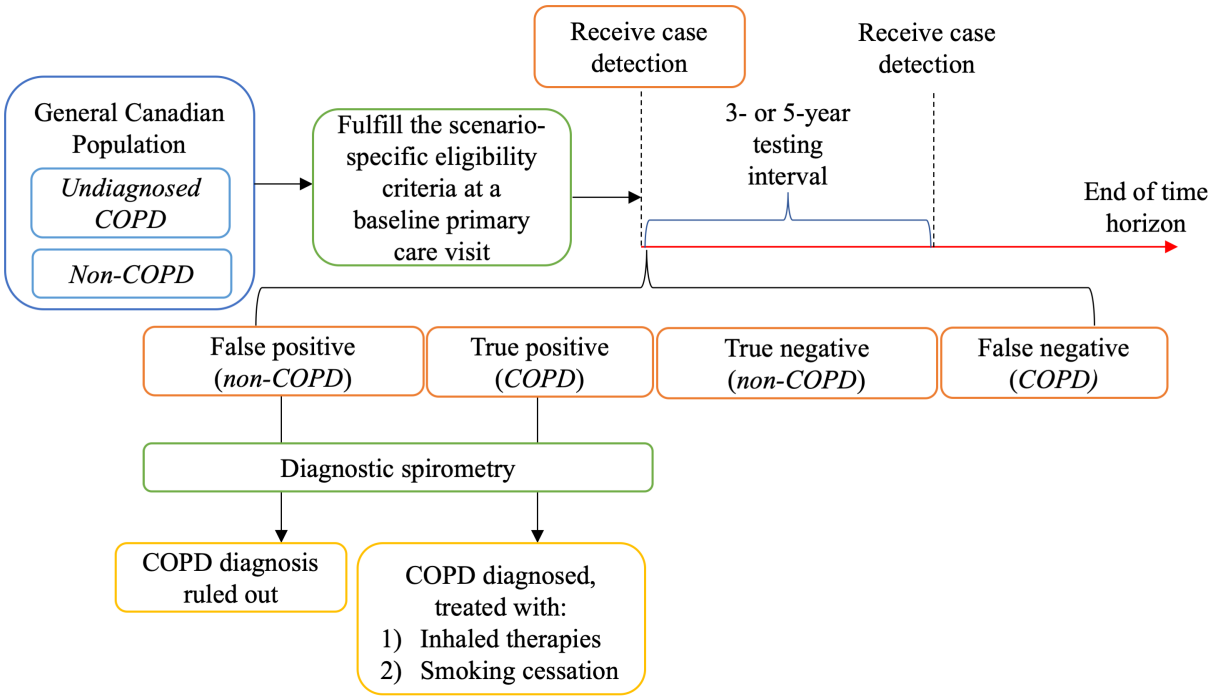


Figure 5-1 Framework for applying case detection strategies.

5.2.3 Parameter inputs

5.2.3.1 Treatment effectiveness

All individuals diagnosed with COPD (through case detection or routine diagnosis) were treated with inhaled therapies, and among current smokers, treated for smoking cessation. Inhaled therapies were provided to all individuals with a diagnosis of COPD according to the GOLD ABCD criteria, which is based on exacerbation history in the previous 12 months and respiratory symptoms[15]. The full treatment algorithm is described in Section 5.2.5.5. Using evidence from landmark clinical trials[160–162], the effectiveness of inhaled therapies was applied as a reduction in the rate of all exacerbations (parameter values are provided in Table 5-2). Following a previous modelling study[156], symptom relief from treatment, outside an exacerbation episode, was assessed as a 0.0367 increase in quality adjusted life year (QALY) among diagnosed COPD patients with any respiratory symptoms.

All newly diagnosed individuals who were current smokers received three months of nicotine replacement therapy (NRT). This was associated with an increase in the odds of successful smoking cessation in the year following diagnosis of 1.38. (This parameter was derived through a calibration process that is described in Section 5.2.5.5.) Nicotine replacement therapy had no effect on smoking cessation in subsequent years following diagnosis.

Inhaled therapies and treatment for smoking cessation were assigned to individuals probabilistically based on an adherence of 70%. That is, in 30% of person-time in the model, individuals who met the criteria for inhaled therapy or NRT did not receive treatment, or for inhaled therapies, were not upgraded to the recommended treatment.

5.2.3.2 Costs

Case detection, COPD diagnosis, and treatment were all associated with costs. These costs were converted to 2015 Canadian dollars using the healthcare component of the Consumer Price Index.

5.2.3.2.1 Case detection and diagnosis costs

Case detection was administered during routine primary care visits. I assumed that case detection comprised the major topic of a primary care visit. According to a previous study, major topics require a median of 5.3 minutes out of a total visit length of 15.7 minutes, or 34% of the total visit time[163,164]. The time to administer case detection was costed at 34% of the total cost of a primary care visit, which was derived from the BC Medical Service Plan fee schedule[165]. The CDQ was assigned only this time-related cost. Screening spirometry was assigned the cost of the primary care physician's time, plus the cost of administering spirometry with a handheld flow meter. Screening spirometry could be administered with or without a bronchodilator, and these had separate costs as determined from BC fee codes[165]. All costs related to case detection are shown in Table 5-2.

The cost of an outpatient diagnosis was composed of the cost of post-bronchodilator diagnostic spirometry plus the duration of an additional primary care visit for interpreting the results, derived from BC fee codes[165] (Table 5-2). An inpatient diagnosis of COPD had no cost in addition to that of hospitalisation for COPD exacerbation[80].

5.2.3.2.2 Treatment costs

The cost of inhaled pharmacotherapies was determined from medication dispensation records in BC health administrative data. I calculated the average annual cost of patients dispensed short-acting beta-agonists (SABA), long-acting muscarinic antagonists (LAMA), long-acting muscarinic antagonist and long-acting beta-agonist combination therapy (LAMA/LABA), and triple therapy with inhaled corticosteroids (ICS), LAMA, and LABA as a single inhaler or monotherapies at least once in 2014 (the last year for which full data was available)[166]. These costs are provided in Table 5-2. All newly diagnosed individuals who were current smokers received 3 months of NRT at a cost of C$350, which was based on the costs reported in a previous Canadian study[167].

The direct costs of maintenance COPD therapy, stratified by GOLD grade, were determined from Canadian studies[84,168] and are shown in Table 5-2. To avoid double counting of treatment costs, I reduced the total maintenance costs by the proportion of total costs attributed to pharmacotherapy at each GOLD grade[169]. The direct costs of exacerbations were determined from the literature[87,88]; they have been described and provided previously[80].

5.2.3.3 Health status

The derivation and validation of background utilities by GOLD grade[84,86], and the reduction in QALY due to exacerbations[84], have been previously described[80]. A false positive diagnosis of COPD was not associated with a disutility following previous findings in another chronic disease[170] (Table 5-2).

Table 5-2 Model parameters specific to the evaluation of case detection.

	No COPD	GOLD 1	GOLD 2	GOLD 3	GOLD 4
Global parameters					
Annual discount for QALY	1.5%				
Annual discount for costs	1.5%				
Time horizon	20 years				
Health Outcomes					
Background Utility[84]	0.86[85]	0.81	0.72	0.68[86]	0.58[86]
QALY reduction from mild-moderate exacerbations[*84]		0.0225	0.0155	0.0488	0.0488
QALY reduction from severe-very severe exacerbations[*84]		0.0728	0.0683	0.0655	0.0655
Disutility from false positive diagnosis[170]	0				
Costs†					
Direct maintenance costs without treatment‡ [84,169]		$135	$330	$864	$1178[168]
Outpatient diagnosis[165]	$58.79				
Screening spirometry without bronchodilator[165]	$23.38				
Screening spirometry with bronchodilator[165]	$29.27				
Administration of Case Detection Questionnaire (CDQ)[165]	$11.10				
Treatment					
Odds ratio of NRT for successful smoking cessation[171,172]	1.38				
Annual costs of NRT[167]	$350.36				
Adherence to NRT	70%				
Inhaled therapies	*SABA*	*LAMA*	*LAMA/ LABA*	*ICS/LAMA/LABA*	
Rate reduction for all exacerbations§	0	0.22[160]	0.23[161]	0.34[162]	
Utility gain from treatment§‖[156]	0.0367				
Annual cost[166]	$50.51	$335.55	$613.73	$1084.98	
Medication adherence	70%				

General model parameters have been reported previously[80].

* The QALY reduction due to exacerbation was determined by dividing the 3-month disutility from an exacerbation[84] by four. See the original publication for more details[80].

† The price year for all costs was 2015 Canadian dollars.

‡ Maintenance costs were composed of physician visits (generalist and specialist), rehabilitation programmes, laboratory tests and devices, and oxygen therapy[84].

§ Only individuals with COPD benefited from treatment (rate reduction in exacerbations or utility gain from treatment). Inhaled therapies had no effect on non-COPD individuals.

‖ Only individuals with symptoms (the presence of cough, phlegm, wheeze, or dyspnea) received the additional utility benefit due to treatment.

5.2.4 Analysis

5.2.4.1 Reference case

The main outcomes of this analysis were total costs and QALYs accumulated over a 20-year time horizon. The target population for this policy was the Canadian general population ≥40 years of age. In order to maintain the same total population across case detection scenarios with different eligibility criteria (*S1*- all patients, *S2*- symptomatic patients, *S3*- ever smokers), I standardised the analysis to the *S1* (all patients) scenario. Total costs and QALYs of the *S2* and *S3* scenarios were adjusted to include the average costs and QALYs of individuals not meeting the selection criteria for that scenario. As a result, the expected per patient costs and QALYs were comparable across all case detection strategies and could be ranked. Unless otherwise specified, results are reported for a cohort of 1,000 individuals who were eligible for any case detection strategy.

For each of the 16 case detection scenarios, I calculated incremental costs and QALYs relative to a comparator, no case detection scenario. I determined the preferred case detection

scenario using the efficiency frontier approach[173]. Using this approach, the scenario with the lowest incremental cost-effectiveness ratio (ICER) compared to the current standard of care (no case detection) was identified as the initial default scenario. Scenarios that were more costly and less effective than the default scenario were subject to 'extended dominance' and were not considered further. Of the remaining scenarios, the case detection scenario with the lowest ICER relative to the default became the new preferred scenario. This iterative process stopped when there were no remaining scenarios with an ICER below the willingness to pay (WTP) threshold of $50,000/QALY.

After determining the preferred scenario, I ranked the remaining scenarios using incremental net monetary benefit (INMB) at a WTP threshold of $50,000/QALY. Scenarios were considered cost-effective if they fell below this threshold. Costs and QALYs were discounted annually at a rate of 1.5%, and the analysis was conducted from the perspective of the Canadian healthcare system following guideline recommendations[173].

5.2.4.2 Sensitivity analyses

I conducted one-way sensitivity analyses around the effectiveness of treatment for individuals diagnosed with COPD. Following previous assessments of medication adherence in the general population[174], I reduced overall medication adherence to 0.5 and 0.3 in separate sensitivity analyses. Guidelines recommend providing treatment for smoking cessation to all current smokers regardless of COPD status[6,175]. Therefore, I conducted a sensitivity analysis in which treatment for smoking cessation at the time of COPD diagnosis was removed. Finally, I reduced the utility benefit due to symptom relief from treatment to 0.01, as this was the threshold for cost-effectiveness in a previous economic evaluation of case detection[156]. Following the same

study, I removed the utility benefit from the impact of treatment on symptoms. In each sensitivity analysis, I reassessed INMB and ranked the scenarios.

5.2.5 Model development

5.2.5.1 Evaluation Platform in COPD (EPIC)

EPIC is a whole disease, discrete event microsimulation model of COPD in Canada. The development, internal and external validation of the model has been described in detail elsewhere[80]. In brief, EPIC is a dynamic population model that simulates Canadian adults ≥40 years old. It is composed of a series of modules, each of which addresses a different aspect of disease. EPIC has modules for: (1) the demography and risk factors of the general Canadian population 40 years and older; (2) COPD occurrence as defined by forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) less than the lower limit of normal[40]; (3) individualised lung function trajectories measured by FEV_1 and the Global Initiative for chronic Obstructive Lung Disease (GOLD) COPD severity grades[15,28]; (4) the occurrence and severity of COPD exacerbations; (5) mortality related to COPD exacerbations and background mortality; and, (6) payoffs, including costs and quality adjusted life years (QALYs) for all individuals in the model. COPD occurrence, exacerbation start and end, change in smoking status, and death due to background mortality are modelled as events in EPIC. These modules performed well in tests of external validity[80].

In order to assess the cost-effectiveness of case detection strategies for COPD, I constructed new modules for symptoms, primary care visits, COPD diagnosis, and treatment. The development of each new module is described below. All modules were validated to ensure

model results matched those of the input data source, and in some cases, external calibration targets. The results of validation are shown in the corresponding appendix for each module.

5.2.5.2 Symptom module

Symptoms were added to EPIC based on the results of Chapter 2, which indicated they were a key factor in determining whether a patient with COPD was diagnosed. (Lung function, which was also strongly associated with a previous diagnosis, was already modelled in EPIC.) Simulated individuals in EPIC were assigned a binary value for the presence of cough, phlegm, wheeze, and dyspnea, annually. Separate linear mixed-effects logistic regression models were developed for each symptom using data from the population-based Canadian Cohort of Obstructive Lung Disease (CanCOLD)[45]. These equations were developed in Chapter 3; a detailed description of the dataset and equations can be found in Section 3.2. In brief, separate equations were fitted to participants with COPD (N=502) and those without COPD (N=1071). I used the subset of independent variables assessed in Chapter 3 that were modelled in EPIC. The log odds of experiencing a symptom was a function of age, sex, current smoking status, and for COPD patients, FEV_1. I determined the covariance of the random effect term for participants from each symptom model, which I used to construct a multivariate normal distribution for symptoms. I sampled from this distribution to assign a unique random-effects term to individuals in EPIC for each symptom. The use of random effects captured additional heterogeneity in symptoms that could not be attributed to the independent variables in the model, as well as the tendency for symptoms to cluster within individuals and to differ in their stability over time[150]. Model specifications and the results of internal validation are provided in Appendix D.1.

5.2.5.3 Primary care visits module

The results of Chapter 4 indicated that undiagnosed COPD patients frequently encountered primary care physicians before diagnosis, and that these types of visits could be used as opportunities for case detection. Individuals in EPIC were assigned an annual number of primary care visits based on their age, sex, smoking status, the presence of symptoms, and for COPD patients, FEV_1. Because the health administrative data used in Chapter 4 did not have information on symptoms, smoking status, or FEV_1, I used self-reported healthcare resource use data from CanCOLD to model primary care visits in EPIC. I developed separate regression models for COPD (N=502) and non-COPD (N=1070) patients. Participants in CanCOLD reported how many times they had seen their doctor in the past 12 months at in-person visits that occurred at 18 month intervals for a maximum of 3 years of follow-up[45]. I used generalised linear models with a negative binomial distribution and logarithmic link to model the rate of primary care visits for all individuals in EPIC. I used this to generate a count of annual primary care visits for all individuals. Model specifications and the results of internal validation are provided in Appendix D.2.

5.2.5.4 Diagnosis module

COPD patients in EPIC could be already diagnosed at the start of the simulation (baseline diagnosis), or during follow-up (incident diagnosis). The results of Chapter 2 informed the patient and disease characteristics that were modelled in EPIC in order to simulate diagnosis in current practice. However, I required patient-level data from CanCOLD (N=467) to develop logistic regression models for the odds of diagnosis based on age, sex, smoking status, the presence of symptoms, FEV_1, and primary care visits. Diagnosis in CanCOLD was based on

self-report of having ever received a physician diagnosis of COPD, chronic bronchitis, or emphysema at each study visit. The regression equation for baseline diagnosis was fitted using data from the initial study visit only. Follow-up diagnosis was fitted using all study visits. In both cases, a diagnosis of COPD could only occur if the individual had ≥1 primary care visit in the preceding year. The regression equation for incident diagnosis is shown in Equation 5.1:

Equation 5-1
$$logit(p) = \beta_0 + \beta_1 \times age + \beta_2 \times sex + \beta_3 \times smoking\ status + \beta_4 \times cough + \beta_5 \times phlegm + \beta_6 \times wheeze + \beta_7 \times dyspnea + \beta_8 \times FEV1 + \beta_9 \times primary\ care\ visits + \beta_{10} \times case\ detection$$

where p is the probability of a patient with COPD being diagnosed during follow-up, and the βs are the input parameters for the probability of diagnosis. β_1 through β_9 were obtained from the logistic regression model that was fitted to data from CanCOLD. β_{10} was not available in the data and was determined through a process described in Section 5.2.5.6.

Non-COPD individuals in EPIC could receive a false positive diagnosis of COPD (overdiagnosis) annually. I developed a logistic regression model to predict the odds of overdiagnosis among non-COPD subjects in CanCOLD (N=1,011). Model covariates were age, sex, smoking status, the presence of symptoms, and primary care visits. Overdiagnosed patients were re-assessed annually, and at each re-assessment there was a probability for the diagnosis to be corrected. This parameter was not reported in the literature and was determined through a calibration process. The calibration target was a stable proportion of false positive diagnoses at the 3% prevalence observed in CanCOLD, which is similar to previous observations[131]. This resulted in a probability of 0.50 for correcting overdiagnosis at any given year.

The results of Chapter 4, as well as a previous study[44], indicate that approximately one third of COPD patients are initially diagnosed in hospital. COPD patients in EPIC could be

diagnosed during instances of hospitalisation due to severe exacerbation. At each hospitalisation, COPD diagnosis occurred with a certain probability. This parameter was not reported in the literature and was determined through a calibration process. The probability of hospital diagnosis and the intercept of the incident diagnosis equation were calibrated simultaneously to maintain a stable proportion of undiagnosed COPD at the same prevalence observed in CanCOLD[150]. This corresponded to a probability of 0.50 for inpatient diagnosis, and 35% of diagnoses occurring in hospital, which is in line with previous reports. Model specifications and the results of internal validation are provided in Appendix D.3.

5.2.5.5 Treatment module

Treatment was implemented in EPIC according to the GOLD ABCD criteria[15]. At outpatient diagnosis, I assumed that individuals were treated with a LAMA if they had dyspnea, or a SABA if they did not. All overdiagnosed individuals received a SABA. An individual's medication could be changed annually or after an exacerbation. Individuals who experienced a moderate exacerbation could receive a LAMA or a SABA, depending on whether they had dyspnea or not, respectively. Individuals who were hospitalised due to an exacerbation, or who had ≥2 moderate exacerbations in the previous 12 months, received combination therapy. This could be either a LABA/LAMA, or an ICS/LAMA/LABA if they were also experiencing dyspnea. The full treatment algorithm is shown in Appendix D.4.1. The overall prevalence of inhaled therapies in EPIC are shown in Appendix Figure D.4.2. They are relatively reflective of overall trends in medication use among COPD patients in British Columbia (BC)[166].

The effectiveness of 3-months of NRT on the odds of successful smoking cessation was determined through calibration. I used the one-year effectiveness of NRT from a large meta-

analysis[171] as the starting point for calibration. The calibration target was the marginal effect of the smoking cessation intervention on the proportion of non-smokers in the Lung Health Study, over 11-years[172] (Appendix D.4.3). This resulted in an odds of successful smoking cessation of 1.38 due to the intervention. Background smoking cessation and incidence rates have been validated with overall trends in smoking in the general Canadian population, and have been previously described[80].

5.2.5.6 Case detection module

Case detection strategies increased the odds of true positive and false positive diagnoses according to their sensitivity and specificity, which I derived from previous case detection studies reported in the literature[66,159]. In order to maintain accurate estimates of sensitivity and specificity, the selection characteristics for each strategy followed those used in the studies from which the performance characteristics were derived.

The effect of case detection was added as a parameter to the regression equations for prevalent diagnosis, incident diagnosis (Equation 5-1) and false positive diagnosis. I used the sensitivity and specificity of each case detection method (shown in Table 5-1) to determine the coefficient for case detection (β_{10} in Equation 5-1). I solved for β_{10} such that the average probability of diagnosis equalled the sensitivity of the case detection method (for COPD patients), and the average probability of false positive diagnosis equalled the specificity of the case detection method (for non-COPD individuals). To accomplish this, I converted the sensitivity (for COPD patients) and the specificity (for non-COPD individuals) of the case detection method into odds, and divided by the odds of routine diagnosis for each patient to derive the average (log) odds ratio for the effect of case detection, as shown in Equation 5-2.

Equation 5-2

$$\beta_{10} = \log\left(\frac{1}{n}\sum_{i=1}^{n}\frac{\text{odds of diagnosis with case detection}}{\text{odds of routine diagnosis}_{\text{i}}}\right)$$

For a given case detection method, the 'odds of diagnosis with case detection' is the $sensitivity/(1-sensitivity)$ for COPD patients, and the $specificity/(1-specificity)$ for non-COPD individuals. The 'odds of routine diagnosis$_i$' is the estimated probability of the i^{th} patient being diagnosed without case detection from the logistic regression model (Equation 5-1 for COPD patients). The coefficient for each case detection method (β_{10}) and an example calculation are shown in Appendix D.5.

Following guideline recommendations[6], I assessed an additional scenario in which only patients with respiratory symptoms at the baseline visit were eligible for case detection (scenario *S2a*, Table 5-1). I was unable to find an example in the literature of the case detection methods of interest implemented in this subgroup of the population. Therefore, I performed an analysis of CanCOLD to determine the sensitivity and specificity of a theoretical screening spirometry intervention (based on pre-bronchodilator $FEV_1/FEV_6<0.7$) implemented among participants with any respiratory symptoms[176]. I repeated the process described above to convert these performance characteristics into coefficients for diagnosis.

5.3 Results

5.3.1 Reference case

All case detection scenarios resulted in higher total costs and QALYs than no case detection. Scenarios with more inclusive eligibility criteria (*S1*- all patients) had higher total costs than more restrictive scenarios (*S2*- symptomatic patients and *S3*- smoking history). Scenarios using

the CDQ at its lowest threshold for referral to diagnostic spirometry produced the greatest number of total QALYs (*S1a, S3b*). Case detection methods with a high specificity, such as the CDQ and screening spirometry applied in combination (*S1c* and *S3d*), resulted in fewer total QALYs. Total costs and QALYs were higher when case detection was administered at 3-year intervals than at 5-years; however, these scenarios were not always more cost-effective (Table 5-3).

Table 5-3 Total costs and QALYs for case detection scenarios.

Scenario	**Testing Interval**	**Cost** ($/ Patient)	**QALYs** (QALYs/ Patient)	**ICER** ($/QALY)	**INMB*** (Ranking)
S0: No case detection	NA	$2,043	12.546	*Reference*	*Reference*
All patients					
(S1a) CDQ ≥17 points	3 years	$2,318	12.560	18,791	457 **(1)**
(S1a) CDQ ≥17 points	5 years	$2,239	12.556	18,985	321 **(2)**
(S1b) Screening spirometry	3 years	$2,246	12.554	24,811	206 **(6)**
(S1b) Screening spirometry	5 years	$2,182	12.552	22,211	174 **(8)**
(S1c) CDQ + Screening spirometry	3 years	$2,268	12.551	45,047	25 **(16)**
(S1c) CDQ + Screening spirometry	5 years	$2,199	12.550	37,084	54 **(15)**
Symptomatic patients					
(S2a) Screening spirometry	3 years	$2,173	12.553	18,096	229 **(4)**
(S2a) Screening spirometry	5 years	$2,134	12.551	16,757	180 **(7)**
Smoking history					
(S3a) CDQ ≥19.5 points	3 years	$2,123	12.548	29,100	57 **(14)**
(S3a) CDQ ≥19.5 points	5 years	$2,097	12.548	21,688	71 **(12)**
(S3b) CDQ ≥16.5 points	3 years	$2,178	12.553	17,641	247 **(3)**
(S3b) CDQ ≥16.5 points	5 years	$2,138	12.552	15,542	210 **(5)**
(S3c) Screening spirometry	3 years	$2,143	12.550	22,946	118 **(9)**
(S3c) Screening spirometry	5 years	$2,113	12.549	19,404	110 **(10)**
(S3d) CDQ + Screening spirometry	3 years	$2,151	12.549	27,066	91 **(11)**
(S3d) CDQ + Screening spirometry	5 years	$2,116	12.548	26,435	65 **(13)**

The 'All patients' strategy encompassed the entire population of interest. 59% of the population was included in the 'Symptomatic' strategy, and 46% in the 'Smoking history' strategy. To maintain a constant reference population,

per patient costs and QALYs were adjusted to include individuals not selected by the strategy. For the symptomatic strategy, the costs (and QALYs) shown are the sum of the costs (QALYs) of individuals not included in the symptomatic strategy, and the costs (QALYs) of those included, weighted by the proportion in each group. The results of smoking history strategy were adjusted in the same fashion.

***** INMB is expressed incrementally in comparison to no case detection (scenario S0). Positive INMB indicates that the scenario is more cost-effective than no case detection at a willingness to pay threshold of $50,000/QALY.

The cost-effectiveness plane is shown in Figure 5-2**.** All scenarios were cost-effective compared to no case detection. A scenario in which the CDQ ≥16.5 points was delivered to ever smokers at 5-year intervals (scenario *S3b*) had the lowest ICER relative to no case detection. Therefore, the first step on the efficiency frontier was from the status quo (no case detection) to scenario *S3b*, which was the new default scenario. The CDQ ≥19.5 points among ever smokers (*S3a*), screening spirometry among ever smokers (*S3c*), the CDQ and screening spirometry among ever smokers (*S3d*), the CDQ and screening spirometry among all patients (*S1c*), and screening spirometry among symptomatic individuals (*S2a*) at 5-year intervals, were subject to extended dominance relative to scenario *S3b*.

Relative to the new default scenario (*S3b*), the remaining scenarios were: the CDQ ≥17 points among all patients (*S1a*), screening spirometry among all patients (*S1b*), screening spirometry among symptomatic individuals (*S2a*) at 3-year intervals, and the CDQ ≥16.5 points among ever smokers (*S3b*) at 3-year intervals. The CDQ ≥17 points delivered to all patients (*S1a*) at 3-year intervals had the lowest ICER, and because there were no remaining scenarios on the cost-effectiveness plane, this was the final step on the efficiency frontier. The CDQ ≥17 points delivered to all patients at 3-year intervals (scenario *S1a*) was associated with an incremental cost of $180 per eligible patient, and an incremental effectiveness of 0.009 QALYs

per eligible patient compared to the CDQ ≥16.5 points delivered to ever smokers at 5-year intervals (scenario *S3b*), resulting in an ICER of $21,108/QALY. The preferred case detection strategy in this analysis was the CDQ ≥17 points delivered at 3-year intervals to all patients ≥40 years of age (scenario *S1a*).

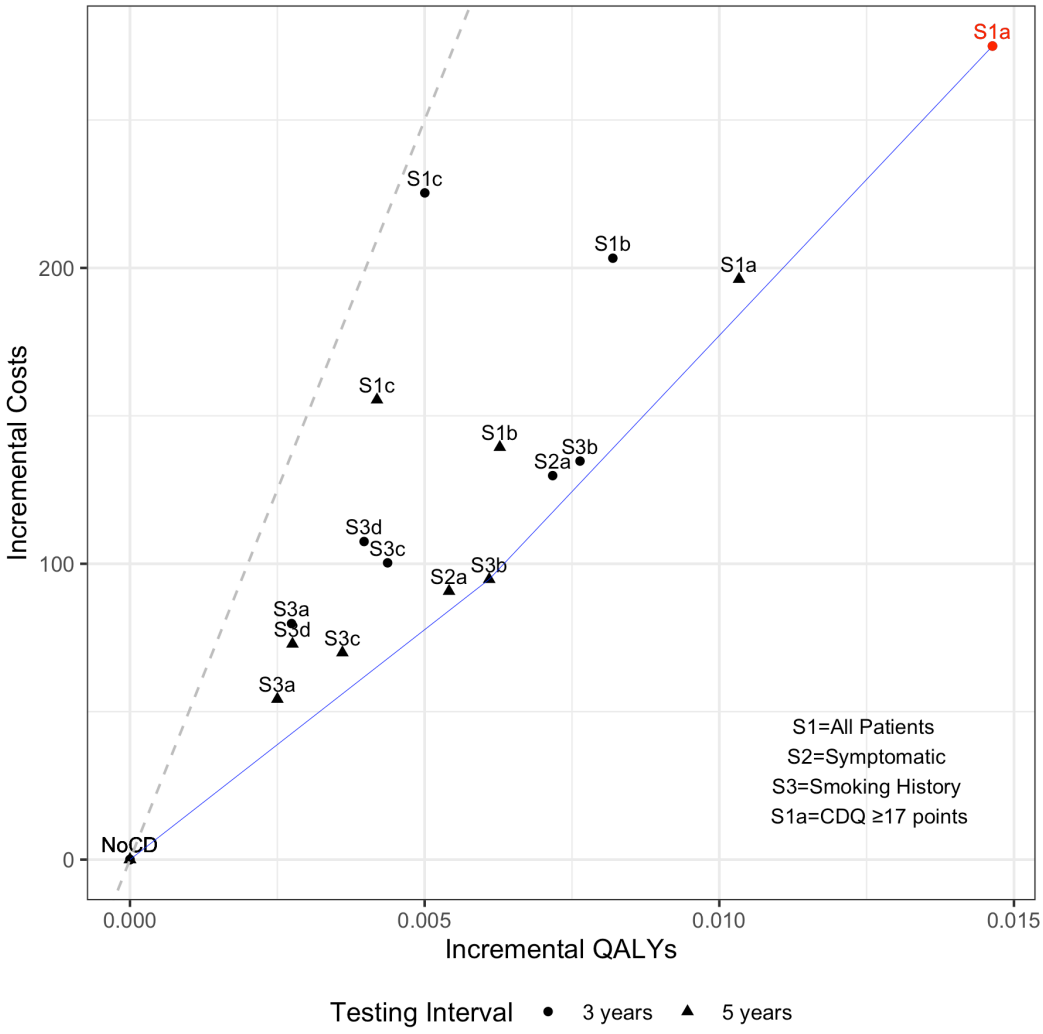


Figure 5-2 Cost-effectiveness plane for case detection scenarios.

Refer to Table 5-3 for a full legend of scenarios.

The solid blue line indicates the cost-effectiveness frontier. The grey dashed line indicates the WTP threshold ($50,000/QALY). The preferred scenario is highlighted in red.

For a cohort of 1,000 individuals eligible to receive case detection, the preferred case detection scenario (*S1a*) resulted in total costs of $2,318,121 and total QALYs of 12,560. The comparator scenario with no case detection had total costs of $2,043,113 and total QALYs of 12,546. Therefore, case detection with the CDQ ≥17 points delivered to all patients at 3-year intervals (*S1a*) resulted in an additional 15 QALYs at a cost of $275,008 relative to no case detection.

In the same cohort of 1,000 individuals, the total patient years diagnosed with COPD increased from 356 diagnosed-years without case detection, to 890 diagnosed-years with case detection. Case detection increased the rate of treatment by 124 patient years for SABA, 46 patient years for LAMA, 304 patient years for LAMA/LABA, and 28 patient years for ICS/LAMA/LABA. This resulted in 13 fewer mild exacerbations, two fewer moderate, and three fewer severe exacerbations, and no change in the number of very severe exacerbations (<0.2 difference). Case detection resulted in an additional two patient years in GOLD grade II, and <1 patient year difference between all other GOLD grades. These results are depicted graphically in Appendix D.6.

5.3.2 Sensitivity analyses

These results were sensitive to several key parameters related to the treatment of newly diagnosed patients (Figure 5-3). I removed 3-months of NRT for smoking cessation among newly diagnosed patients. As in the reference case, the preferred case detection scenario using

INMB was the CDQ ≥17 points delivered to all patients (*S1a*) at 3-year intervals. The INMB of most scenarios was unchanged or slightly lower, and the CDQ ≥19.5 points delivered to ever smokers (*S3a*) at 5-year intervals was no longer cost-effective.

When medication adherence was reduced to 50%, results were similar to the reference case. The preferred scenario using INMB was again the CDQ ≥17 points delivered to all patients (*S1a*) at 3-year intervals, although its INMB was lower than in the reference case. The CDQ ≥19.5 points delivered to ever smokers (*S3a*) at 3-year intervals was not cost-effective. At 30% medication adherence, the preferred scenario using INMB was still the CDQ ≥17 points delivered to all patients (*S1a*), but at 5-year intervals. The INMB of all scenarios decreased; in addition to the CDQ ≥19.5 points delivered to ever smokers (*S3a*) at 3-year intervals, the CDQ and screening spirometry among all patients (*S1c*) was no longer cost-effective.

The cost-effectiveness of case detection was most sensitive to changes in the utility benefit due to symptom relief from treatment. This parameter was 0.0367 in the reference analysis, which was derived from a previous modelling study[156]. When the utility benefit was reduced to 0.01 in a sensitivity analysis, the INMB of all scenarios decreasing substantially. The preferred scenario was the CDQ ≥16.5 points delivered to ever smokers (*S3b*) at 5-year intervals, which had an ICER of $32,200/QALY compared to no case detection. The only other cost-effective scenarios were screening spirometry among symptomatic patients (*S2a*), the CDQ ≥17 points delivered to all patients (*S1a*) at 3-year intervals, screening spirometry among all patients (*S1b*), the CDQ ≥19.5 points among ever smokers (*S3a*), and screening spirometry among ever smokers (*S3c*), all delivered at 5-year intervals. Case detection was not cost-effective when the utility benefit due to symptom relief from treatment was removed (Figure 5-3).

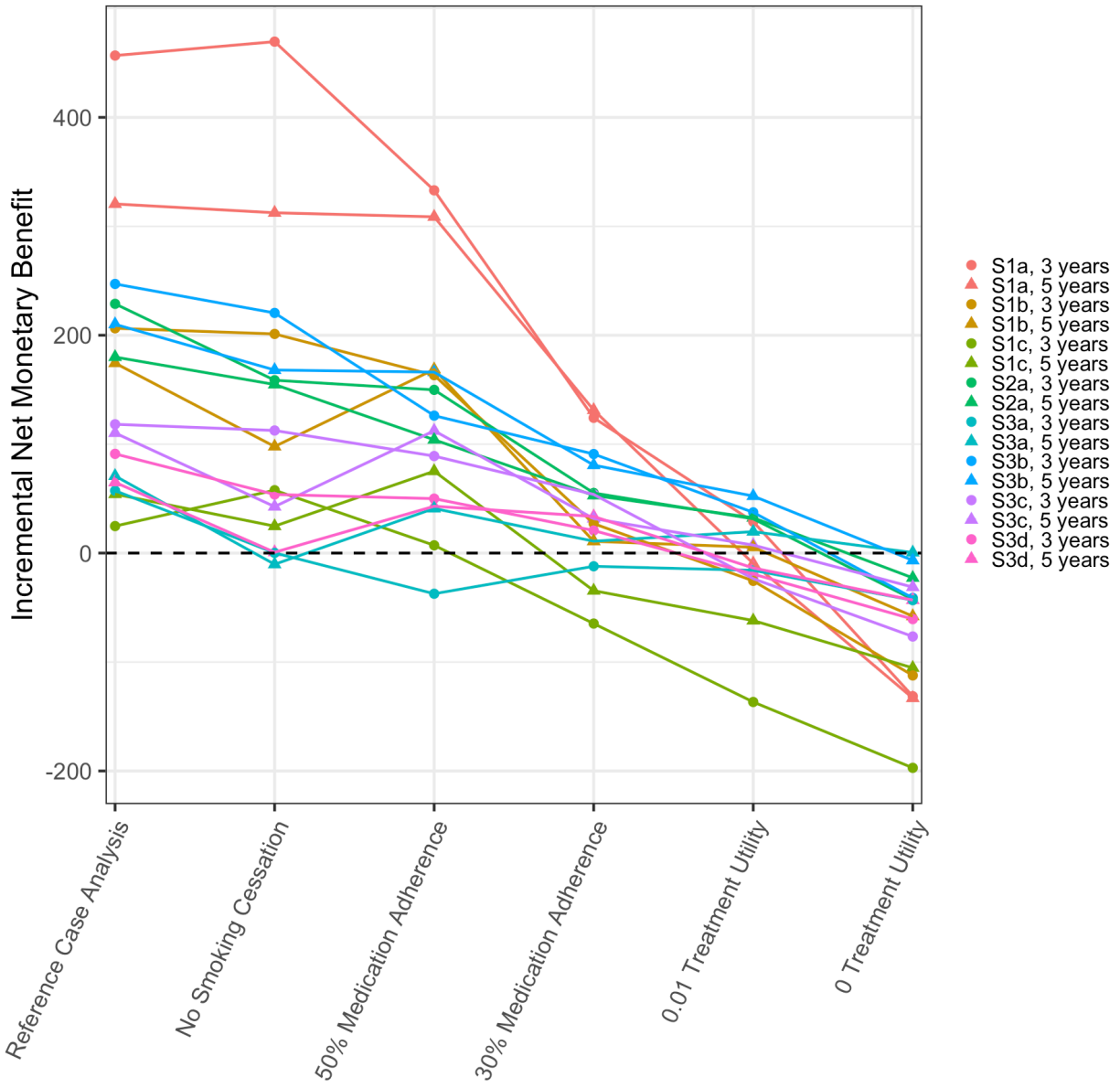


Figure 5-3 Sensitivity analyses of the incremental net monetary benefit of case detection scenarios compared to no case detection.

5.4 Discussion

5.4.1 Summary of results

I used a previously validated microsimulation model of COPD in the general Canadian population to assess the cost-effectiveness of early detection strategies for COPD. My results indicate that primary care-based case detection is highly cost-effective. Variations in the eligibility criteria for testing, the use of questionnaire- or spirometry-based case detection methods, and 3- or 5-year testing intervals were nearly all cost-effective compared with the status quo. The key feature in determining the value of case detection was treatment for newly diagnosed patients. In particular, the degree of symptom relief due to inhaled therapies. When this aspect of treatment was removed, case detection was no longer cost-effective.

5.4.2 Comparison with other research

Previous guidelines have recommended against screening for COPD among asymptomatic adults in the general primary care population[6]. These recommendations apply to the use of diagnostic spirometry to test for COPD directly, and to methods such as screening spirometry and questionnaires, although the authors noted a lack of evidence on the value of screening tools in this population[6]. In contrast, I found that both questionnaires and screening spirometry, implemented at routine primary care visits, could be cost-effective methods for early detection. Similarly, a recent trial-based economic evaluation found that an active case finding approach to COPD detection using a mailed symptom assessment questionnaire was highly cost-effective[155,156]. My results extend this analysis and suggest that all primary care patients, regardless of symptoms, should routinely receive risk assessment questionnaires.

5.4.3 Policy implications

The value of early detection for COPD is largely determined by the degree of adherence to best-practice recommendations for treatment, and the extent to which newly diagnosed patients benefit from symptom relief. Large clinical trials have demonstrated the effectiveness of inhaled therapies at reducing symptoms[160–162,177], including among patients with mild COPD[178]. The impact of improved symptom control on health-related quality of life has also been well documented[72,115]. However, despite the importance of symptom relief to the value of early detection, the preferred case detection strategy in this analysis targeted all patients, rather than only patients with symptoms at the baseline primary care visit. In Chapter 3, I found substantial heterogeneity in the presence of respiratory symptoms between patients with COPD, and the stability of symptoms also varied within patients over time[150]. Similarly, I found that symptoms performed poorly as selection criteria for COPD screening[176], and in this study, they had lower value when used as eligibility criteria for case detection.

The preferred scenario in this analysis targeted all patients ≥40 years of age to receive questionnaire-based case detection during their routine visits to a primary care physician. There are an estimated 1.8 million Canadians who currently have undiagnosed persistent airflow limitation[46,179], meaning there are 15.6 million Canadians ≥40 years who do not have COPD[180]. Extrapolating the per patient costs of the preferred case detection scenario to this population, the budget impact of this policy would be approximately $40.3 billion over 20 years (undiscounted). The budget impact of a more restrictive scenario, such as one targeting patients ≥50 years with a smoking history, would be much smaller ($27.4 billion). However, its effectiveness would also be lower; resulting in a total of 158.0 million QALYs, compared to 218.3 million QALYs with the preferred case detection scenario.

The case detection tools evaluated in this study differed mainly in terms of their performance characteristics (sensitivity and specificity) and mode of delivery. Both the questionnaire-based methods and screening spirometry were cost-effective compared to the status quo. In British Columbia, these case detection tools were relatively low in cost, although similar in cost to a questionnaire-based case detection tool used in a previous randomised controlled trial[156]. In all scenarios, case detection resulted in only small increases in per-patient costs. As a result, minimizing the use of diagnostic spirometry with a highly specific tool was less valuable. Scenarios in which the CDQ and screening spirometry were implemented sequentially had a specificity of 97%. These scenarios were typically associated with lower costs, but they also had lower value. The sensitivity of the case detection tool was the more important component of performance. The CDQ at a low threshold for referral to diagnostic spirometry was the preferred case detection tool. However, there was also support for the use of screening spirometry, particularly under conditions of poor adherence to inhaled therapies or diminished effectiveness of treatment. In these cases, the higher unit costs of screening spirometry were offset by their increased specificity. In addition, following previous evidence[170], I did not assign a disutility to healthy patients who received a false positive diagnosis of COPD. These patients only incurred the additional costs of diagnostic spirometry. It is possible that I underestimated the costs of a false positive diagnosis, including unnecessary lung imaging, initiation of treatment without diagnostic spirometry, and additional physician visits[63,64].

5.4.4 Clinical implications

The effectiveness of inhaled therapies was almost entirely influenced by the additional utility due to symptom relief from treatment, rather than their effect on the rate of exacerbations. Earlier

initiation of treatment through case detection resulted in only a slight reduction in the overall rate of exacerbations. Because undiagnosed patients are more likely to have mild disease[129], a lower rate of exacerbations, and exacerbations that are less severe[80], this aspect of treatment was less influential. Case detection tools that specifically target patients with more severe COPD and a high risk of exacerbations[181] might be more effective at preventing severe exacerbations and increase the value of this aspect of treatment. However, proper adherence to inhaled therapies, with the aim of relieving symptoms in patients with mild disease, is most critical to the benefit of an early diagnosis.

Recent evidence indicates that inhaled therapies might be associated with improved lung function in patients with mild-moderate COPD[178], and there is emerging evidence that early treatment can have a disease-modifying effect in these patients[160]. Treatment also has an indirect impact on lung function by reducing the rate of exacerbations, which are in turn associated with accelerated lung function decline[57]. Previous studies suggest this effect can be substantial, and greatest in patients with mild COPD[56,57]. However, I did not model the effect of treatment on lung function through either of these mechanisms. Therefore, my approach to assessing treatment effect can be regarded as conservative. My results address the long-standing debate on the value of early detection in patients with mild disease. Many authors have questioned the importance of detecting asymptomatic patients with limited therapeutic options[6,63]. This analysis indicates that even relatively small improvements in health outcomes due to early detection can be cost-effective over a long time horizon.

5.4.5 Strengths and limitations

This study has several strengths. First, EPIC is an independently validated, open population model that simulates the demography and risk factors of the Canadian population, including their temporal trends during the period of evaluation. Given that the performance of case detection strategies is highly dependent on local settings and subsequent management decisions, the use of 'whole disease' platforms such as EPIC can result in more consistent evaluations. They can also be updated more easily to account for changes to 'downstream' technologies such as treatment. Second, my use of an individual-level simulation offered greater flexibility in the design of case detection strategies, including different permutations of eligibility criteria, case detection method, and treatment.

My study has several limitations. First, my approach to assessing case detection methods used a generic application of performance characteristics rather than a direct assessment of the case detection tool (e.g., in a randomised trial). As a result, I was highly reliant on previous studies that evaluated the effectiveness of case detection tools. I was also required to use similar selection criteria to what had been employed in those studies. This limited my ability to test even more subgroups of patients. Second, EPIC is not probabilistic, meaning that I could not explore parameter uncertainty in a probabilistic sensitivity analysis. Finally, with the exception of instances when case detection was delayed because a patient had no primary care visits, I modelled perfect uptake of the case detection tool at the scheduled intervals. My analysis should be extended to model gradual market penetration of case detection strategies in a population-level budget impact analysis. This type of analysis can also account for budget constraints, which might lead to a different case detection scenario being adopted than the one selected using the efficiency frontier approach.

5.4.6 Conclusions

An early diagnosis of COPD, accompanied by timely and appropriate care, is very likely to be an efficient use of resources. Regular implementation of a screening questionnaire during the routine encounters of primary care patients ≥40 years of age is cost-effective compared to no case detection. Providing treatment to reduce the respiratory symptoms of newly diagnosed patients is the most important component of early detection. Future studies should evaluate the cost-effectiveness of the preferred case detection strategy in this analysis using a randomised control trial. Model-based evaluations such as this one should be extended to assess the impact of implementing case detection strategies in other healthcare settings, such as in pharmacist clinics. In summary, early detection strategies are a high value approach to improving the long-term health outcomes of patients with COPD.

Chapter 6: Conclusions

6.1 Contributions and implications

In this thesis, I used a variety of methodological approaches to characterise undiagnosed COPD patients, quantify heterogeneity in their respiratory symptoms (which were a key factor in determining whether a patient with COPD had received a diagnosis), assess the healthcare encounters of patients before COPD diagnosis, and evaluate the cost-effectiveness of case detection strategies. My results indicate that undiagnosed COPD patients are identifiable, that they are in frequent contact with the healthcare system, and that strategies for improving early detection provide good value for money. These results can help practitioners recognize undiagnosed COPD patients during their routine healthcare encounters and inform strategies for improving their detection. Many authors have argued that an earlier diagnosis of COPD would have substantial public health benefits[13], however, objective evaluations of early detection strategies were lacking. This thesis contains one of only two economic evaluations of case detection strategies for COPD[156]. It is also the only simulation study, which facilitated synthesizing evidence from diverse sources and more fully exploring the decision space created by early detection policies. My results provide an important message for policy-makers: early detection strategies for COPD are cost-effective and should be implemented, and for clinicians: patients with risk factors for COPD should receive case detection regularly. Given the large burden of COPD on patients and the healthcare system, better recognition of risk factors for COPD and the importance of early detection can have substantial public health benefits.

6.1.1 Improving recognition of risk factors for COPD

The value of early detection for COPD is one of the most debated issues in the respiratory research community[7,61]. The results of this thesis suggest that clinicians and policy-makers should take a proactive approach towards diagnosing COPD. In a systematic review and meta-analysis (Chapter 2), I found that undiagnosed patients tended to have less severe airflow obstruction and fewer respiratory symptoms than diagnosed patients. However, common risk factors for COPD, including older age and current smoking, were not associated with a diagnosis. This suggests that diagnoses of COPD are currently being made based on lung function impairment and patient symptoms rather than risk factors for the disease, which may be contributing to the delay in diagnosis. The importance of respiratory symptoms in determining a previous diagnosis may be partly explained by current guidelines that recommend limiting screening or case detection for COPD to symptomatic individuals[6].

In Chapter 3, I characterised heterogeneity in the presence of respiratory symptoms between patients with COPD using a longitudinal cohort of the general Canadian population. I found that the presence of cough, phlegm, dyspnea, and wheeze were highly heterogeneous between patients within COPD. Lung function and other commonly measured clinical characteristics explained a minority of this heterogeneity. Within patients, symptoms also differed in their stability over time. These results, and related work[176], suggest that respiratory symptoms alone provide a poor signal for the presence of COPD. In order to improve the diagnosis of COPD in the community, risk factors for COPD should prompt an investigation of disease, rather than relying on patient impairment due to symptoms or airflow limitation.

In my evaluation of the cost-effectiveness of case detection strategies (Chapter 5), symptom relief from inhaled therapies was critically important to the value of case detection.

However, using smoking history as eligibility criteria to receive case detection, or targeting all patients, was preferred to a strategy in which only patients with a history of symptoms were tested for COPD. Taken together, the results of this thesis indicate that reducing the burden of undiagnosed COPD will require more attention to risk factors for COPD, rather than exclusively evaluating patient symptoms. Guidelines for screening should be updated to reflect this focus[6]. These guidelines should also promote the use of case detection tools, such as the COPD diagnostic questionnaire, during routine healthcare encounters, instead of using diagnostic spirometry in the general population of primary care patients.

6.1.2 Early detection of COPD is cost-effective

Case detection strategies rely on opportunities for diagnosis. Previous authors have suggested that the routine healthcare encounters of at-risk patients should be used to opportunistically test for COPD[60–62]. The results of this thesis support this conclusion. Patients with undiagnosed COPD frequently encounter the healthcare system, and missed opportunities for an earlier diagnosis are common. Using administrative health records for the province of British Columbia (Chapter 4), I determined that COPD patients had an average of 14 visits to pharmacists, and 10 visits to primary care physicians in each of the five years before diagnosis. Over the same time period, 85% of patients visited a primary care physician for a respiratory-related reason that did not result in a diagnosis of COPD. Due to the exclusion criteria used in this study, none of these patients received spirometry to test for COPD, and many were already receiving respiratory medications. These results indicate that case detection strategies relying on opportunistic encounters between undiagnosed COPD patients and the healthcare system have opportunities to

diagnose COPD earlier. There is a need for systematic strategies to increase the use of spirometry in practice.

Regular administration of questionnaire-based assessments of COPD risk during routine primary care visits can be a high value, evidence-based approach to early detection. The use of screening spirometry with handheld flow meters (both with and without bronchodilators) was also supported in my evaluation of the cost-effectiveness of case detection strategies. However, in most cases, case detection strategies with a high sensitivity were preferred to highly specific tools such as screening spirometry. The use of case detection tools should be integrated into regular practice among primary care patients ≥40 years of age.

The lack of treatment options for patients with mild disease is the most commonly cited argument against investing resources in early detection strategies[7]. The hallmarks of COPD therapy are risk factor modification and inhaled therapies[15]. There is mounting evidence that early administration of respiratory medications can reduce symptoms[15], the risk of exacerbations[178], and potentially, lung function decline[57,58]. In my evaluation of the cost-effectiveness of case detection strategies, symptom relief due to inhaled therapies was the most important component of treatment following diagnosis. These results indicate that current guideline recommendations for therapy, applied to undiagnosed patients in mild disease stages, can improve their long-term health outcomes. However, the cost-effectiveness of case detection is contingent upon high adherence to inhaled therapies following diagnosis. If a diagnosis does not result in treatment that reduces the symptoms of COPD patients, case detection is unlikely to be cost-effective. Therefore, in addition to increased testing for COPD, the importance of providing evidence-based treatment to newly diagnosed patients must be emphasised.

6.1.3 Disease heterogeneity should be quantified

The overarching themes of this thesis were evidence generation on the natural history of disease, followed by whole disease modelling to evaluate policy. Whenever possible, I generated evidence that can facilitate precision medicine, which requires information on heterogeneity in the disease characteristics of patients. In Chapter 2, I addressed a key knowledge gap on the heterogeneity of respiratory symptoms in patients with COPD, which are a core component of its natural history. I found that heterogeneity between individuals in the presence of symptoms was substantial, and that very little of this variation was explained by easily-measured patient and disease factors. Future developments in precision medicine, such as the discovery of biomarkers, might reduce this unexplained heterogeneity. This type of evidence can improve our understanding of the burden of symptoms, or identify disease phenotypes to inform management decisions. The equations describing between-patient variability in symptoms in this work became the key component of the symptom module of EPIC, which was used to evaluate case detection strategies. Because heterogeneity in the symptoms of simulated individuals was explicitly incorporated, future studies can use this model as a platform to evaluate technologies in precision medicine.

6.1.4 Whole disease modelling can inform policy development

Whole disease models such as EPIC are a flexible platform for exploring the decision space created by a policy or intervention. These types of models are in contrast to *de novo* modelling, which are purpose-built decision models for evaluating a specific policy. The vast majority of previous COPD simulations have been *de novo* models[182]. As discussed in Chapter 1, I used a whole disease model because of the need to account for the downstream impacts of early

detection, especially treatment for newly diagnosed patients. The benefits and limitations of using a whole disease model to evaluate policy merits discussion.

Whole disease models are time-consuming to develop and tend to be very complex. As a result, conventional methods for evaluating structural and parameter uncertainty are difficult to implement and computationally-intensive. This is an important limitation of whole disease models, as guidelines recommend that all health economic evaluations assess parameter uncertainty[157]. In this thesis, there was a trade-off between the granularity at which any given case detection method could be modelled, and fully accounting for the decision space created by a policy or intervention. As an alternative to whole disease modelling, I could have created a *de novo* model to evaluate the cost-effectiveness of the COPD diagnostic questionnaire in a particular subgroup of the population. This approach may have may have produced more consistent estimates of parameters measured from a single population.

Whole disease modelling enables a broader approach to economic evaluation. The decision space for the evaluation of case detection strategies involves different permutations of eligibility criteria, case detection method, period of intervention, and disease management following diagnosis. A *de novo* model simulating a single case detection method in a particular population would have less ability to explore this decision space. It is also more likely to make simplifying assumptions about the distribution of risk factors, disease heterogeneity, and treatment effectiveness, all of which might impact the robustness of results. In contrast, whole disease models are a flexible platform for exploring this decision space, and can facilitate a wider range of economic evaluations. For example, in this research, I assessed different eligibility criteria for case detection, and identified the features of case detection methods (i.e. sensitivity versus specificity) and treatment that were most influential for the cost-effectiveness of early

detection. These results can inform the development of new case detection methods, or identify key targets for intervention.

Although whole disease models are more time consuming to develop than *de novo* models, the contributions I made to the development of EPIC will have lasting benefit to future evaluations. The decision space that can be explored now includes three additional aspects of disease: diagnosis, respiratory symptoms, and healthcare encounters. Because EPIC is freely accessible to other researchers, this can reduce duplicate efforts within the community and increase the reproducibility of my analyses. It also makes whole disease modelling a more sustainable approach to evaluation. For example, the value of case detection is likely to change if new therapies for COPD are introduced or with new evidence on existing therapies. My evaluation of case detection strategies could be repeated to incorporate these changes to treatment effectiveness, which would provide valuable evidence to decision-makers.

Finally, by evaluating decisions at any point along the care pathway, whole disease modelling can promote system-level optimization. This enables new possibilities for resource management, such as disinvestment and finding optimal care bundles. In this research, I focused on the value of an early diagnosis of COPD. However, there are many other points of intervention along the COPD care pathway. For example, additional resources could be allocated to drug discovery, where new therapies to modify disease progression might be developed. Alternatively, decision-makers could invest resources in improving access to pulmonary rehabilitation programs[183]. Whole disease models can evaluate a variety of interventions using a single platform with consistent assumptions. This enables a more realistic quantification of the opportunity cost of investment decisions, and can improve overall disease management.

6.2 Strengths of this research

There are several strengths to this work. I used a variety of methodological approaches to characterise undiagnosed COPD and evaluate strategies for improving its detection. I summarised existing evidence in a systematic review, conducted original analyses of a clinical cohort and administrative health records, and made significant contributions to a decision-analytic model of COPD.

The external validity of the data sources used in this research is one of its main strengths. My systematic review included studies from four continents and is likely to be representative of most high-income countries. The analyses in Chapter 3 used data from a population-based prospective cohort study, and administrative health records from the general population of COPD patients in Chapter 4. EPIC was developed to be representative of COPD in the Canadian general population. CanCOLD, a longitudinal cohort study, was the source of data for my analysis of heterogeneity in respiratory symptoms (Chapter 3), and for the additional modules I developed to simulate the case detection pathway in EPIC (Chapter 5). CanCOLD sampled adults ≥40 years from nine major urban sites in Canada with multi-level sampling to ensure representativeness of the general population. Because CanCOLD was developed to study the development and progression of COPD in the general population, the majority of subjects enrolled had mild to moderate COPD. This is in contrast to most clinical trials, which typically enrol patients in moderate to severe disease stages[184]. Therefore, CanCOLD is a unique data source for evaluating questions around undiagnosed COPD.

My use of a decision-analytic model for evaluating early detection strategies is another strength of this research. Using this approach, I incorporated multiple different sources of evidence, including from CanCOLD[45], landmark trials in COPD therapy[58,162,172,185], and

administrative health records from BC[166]. This facilitated a fuller exploration of the decision space than any single empirical study could provide. The decision-analytic model also allowed evidence on intermediate outcomes from these studies to be extrapolated to a long time horizon. This is critical for chronic diseases such as COPD, in which the benefits of an early diagnosis may not be realised until much later in the disease progression.

6.3 Limitations of this research

Decision-analytic models require many different assumptions and input data sources, and high-quality empirical data are not always available. There were two primary sources of uncertainty in the evidence used to populate parameters in EPIC. First, as discussed above, CanCOLD was the primary source of evidence for the case detection pathway simulated in EPIC. These data may not be representative of the general population of individuals without COPD. Non-COPD subjects in CanCOLD were selected because they were never smokers (healthy controls), or because they were ever smokers, and therefore at risk of developing COPD[45]. Ever smokers are likely to have more respiratory symptoms than the healthy population[186]. However, both groups of non-COPD subjects were used to simulate respiratory symptoms in the general, non-COPD population of EPIC. The frequency of respiratory symptoms may have been overestimated in this population as a result. The value of using symptoms as eligibility criteria for case detection may also have been underestimated. Other limitations of clinical studies such as healthy volunteer bias might also exist in CanCOLD.

A second source of uncertainty was the effectiveness of inhaled therapies in patients with mild COPD. To date, most clinical trials of treatment effectiveness in COPD have enrolled patients in moderate to severe disease stages. With one notable exception[58], early stage COPD

has been comparatively less studied. Given that most undiagnosed patients have mild COPD, applying the effectiveness of inhaled therapies to these patients might have overestimated the benefits of treatment. Finally, there was limited evidence on the effect of symptom relief due to treatment on health-related quality of life. This was the most influential parameter in determining the cost-effectiveness of case detection, and its value was based on a previous economic evaluation[156]. Quantifying the impact of treatment on health-related quality of life in patients with mild to moderate COPD would provide important evidence for future evaluations. To fill this knowledge gap, clinical trials or observational studies of inhaled therapies could administer the EQ-5D as a secondary outcome and provide a comparison of health-related quality of life between treatment groups.

Comorbidities are a key contributor to burden of COPD[187]. In Chapter 4, I found that circulatory disease was the most common reason for visits to a primary care physician among undiagnosed COPD patients. The presence of comorbidities is also likely to increase the probability that a patient with COPD has received a diagnosis, however, I was not able to investigate this factor in Chapter 2 due to the lack of existing literature. In part due to the lack of empirical data on comorbidities in patients with undiagnosed COPD, and also due to the complex interaction between COPD and other diseases, comorbidities are not currently modelled in EPIC. However, comorbidities influence the risk of COPD[188] and the outcomes of COPD patients[189]. Therefore, the value of case detection is very likely to be affected by comorbid conditions. This is particularly true for cardiovascular comorbidities, which are highly prevalent among COPD patients[23], and impact the management of COPD[190]. Primary care visits related to cardiovascular disease could also be used as opportunities for case detection. Future assessments

should explicitly incorporate the impact of cardiovascular comorbidities on the value of case detection.

Another important limitation of this analysis is that I modelled an accelerated decline in FEV_1 as the main disease process in COPD. Recent evidence has shown there are two primary biologic mechanisms for the development of COPD: an accelerated rate of lung function decline, or low maximum lung function due to abnormal lung development[19]. Despite evidence that disease progression and health outcomes differs between these groups, with important implications for treatment[191], I did not consider this second pathway to disease in my evaluation. Further, other markers of disease such as blood eosinophil and history of asthma are also known to affect patient response to treatment[149,191]. Computed topography scans have the potential to identify markers of early disease before airflow obstruction develops[192], and patients at risk of rapid progression could be identified and treated for smoking cessation and symptoms (if present)[193]. Incorporating these factors into a more nuanced treatment algorithm might affect the value of case detection.

Finally, there are other approaches to early detection that were not evaluated in this thesis. In addition to questionnaires and screening spirometry, algorithms based on electronic medical records could be used to identify patients with undiagnosed COPD[194]. These algorithms could flag patients who are at high risk of having undiagnosed COPD, which would prompt a physician to investigate a diagnosis at their next visit. If this strategy reduced the number of patients eligible to receive case detection, it might increase the feasibility of early detection strategies. However, in developing these algorithms, it should be noted that the results of this thesis suggest that a more sensitive instrument is preferred to a highly specific one. Simulation

studies such as this one are well positioned to investigate the cost-effectiveness of strategies using these types of technologies.

6.4 Future research directions

6.4.1 Knowledge translation to policy-makers, knowledge users, and patients

Expanding knowledge translation of this work is a key area for future research. Through peer-reviewed publications and conference presentations, I have communicated these results to care providers (e.g. at the Canadian and European Respiratory Congresses), and to technology assessment experts (e.g. at the Canadian Agency for Drugs and Technologies in Health Symposium). In addition, clinical experts and policy-makers were involved in the conceptualization and development of EPIC, and they remain active knowledge users. These stakeholders provided feedback on the relevant aspects of disease to model, the level of precision at which they needed to be represented, and assessed the model assumptions. However, further knowledge translation work remains. In particular, communicating the outputs of this research to stakeholders, and discussing the uncertainties and limitations of the model. The relevant stakeholders include other researchers, clinical guideline developers, government policy-makers, and patients with COPD.

My results on the value of early detection for COPD should be accessible to these decision-makers and knowledge users. The case detection policies recommended by this research have a very large budget impact. As a result, policy adoption is likely to be highly dependent on factors specific to each jurisdiction. Allowing decision-makers to reassess the value of case detection under local conditions would produce more policy-relevant results.

Currently, EPIC is publicly available as an R package (http://resp.core.ubc.ca/research/Specific_Projects/EPIC). Existing functions allow other researchers to run the analysis described in Chapter 5 under different inputs and examine the results. However, this requires the user to be familiar with R Statistical Software[92], which could be a substantial barrier to use. In future work, an existing model repository (http://resp.core.ubc.ca/ipress/prism) should be used to develop an interface in Excel for interacting with the model inputs and generating easily-understandable graphical outputs. This tool would facilitate policy-ready messages under conditions that are most relevant to decision-makers. It would also help communicate the uncertainties and variability in these results. Finally, other researchers in the scientific community could use this tool to replicate my analyses. This would increase model transparency and make my results more credible. Targeted knowledge translation such as this can increase the uptake of early detection strategies for COPD.

Patients are a key stakeholder group who have thus far, not taken part in the development of EPIC, or my evaluation of case detection strategies. Communicating the results of this research to patients with COPD is a critical next step. Future researchers should elicit patient feedback on the values for certain parameters, and whether all outputs relevant to early detection have been collected. Given its influence on the cost-effectiveness of case detection, patient perspectives on the importance of symptom relief due to treatment would be particularly valuable.

Patients could also help prioritise future developments to EPIC as it is expanded to include other aspects of disease. For example, given that patients often view health economic models as simulating disease too narrowly[195], they might emphasise the need to include comorbidities in future iterations of the model. Incorporating patient perspectives in this way

would increase the legitimacy of any subsequent results[195]. Finally, future researchers should discuss with patients the uncertainties and limitations of this research, and the degree to which this evidence should prompt changes in care. This information would be valuable to decision-makers and increase the acceptability of new policies related to the early detection of COPD.

6.4.2 Extending case detection to pharmacists

Some of the resistance to implementing early detection strategies for COPD can be attributed to an overburdening of primary care physicians. Because many diseases have shared symptoms and risk factors, physicians must consider a multitude of potential diagnoses during very short visits with patients. A strategy in which all primary care patients ≥40 years were targeted for case detection would apply to an estimated 17.4 million Canadians[180] and cost approximately $40.3 billion over 20 years (undiscounted). This is a major challenge to the feasibility of early detection strategies. Enlisting other healthcare providers to administer case detection is a promising solution.

In Chapter 4 of this thesis, I found that patients with COPD were in most frequent contact with pharmacists before diagnosis. In fact, the average annual visits to pharmacists reported in that chapter may have underestimated the frequency of encounters between undiagnosed COPD patients and pharmacists, as only visits in which patients were dispensed medications were recorded in the dataset. However, at these visits, patients with undiagnosed COPD were often dispensed respiratory medications. Pharmacists could target patients who are being dispensed respiratory medications without an existing respiratory disease diagnosis for case detection. These patients would be invited to complete the COPD diagnostic questionnaire. Patients who were found to be at risk of COPD using the questionnaire would be referred to their primary care

provider to investigate a diagnosis. Similar initiatives for improving detection of osteoarthritis in community pharmacy settings have been very successful[196]. In that study, community pharmacists recruited patients with symptoms, assessed their risk of osteoarthritis, and following examination, high risk patients were referred to their general practitioner to confirm a diagnosis[196]. There is general movement towards enabling pharmacist-provided care in Canada, which can increase the feasibility of this type of approach for COPD[197]. Financial incentives for collaboration between healthcare practitioners are becoming more widespread[197], and can encourage innovative new approaches to improving patient care. New reimbursement models will be necessary to integrate case detection into the regular practice of pharmacists.

6.4.3 Empirical evaluation of case detection strategies

In this thesis, I determined that early detection strategies for COPD were cost-effective. These results should be confirmed in a clinical trial setting. The preferred case detection strategy was the COPD diagnostic questionnaire (CDQ) implemented at 3-year intervals during the routine primary care visits of all patients ≥40 years. This strategy should be investigated using a pragmatic randomised control trial following previous empirical evaluations of case detection[155,156]. To reduce the pool of eligible participants and increase the feasibility of this study, patients ≥40 years could be randomly selected using electronic medical records. These patients would have their records flagged, which would prompt their primary care physician to administer the CDQ at their next visit. Patients recruited into the opportunistic case detection arm would be compared to patients who were flagged but did not receive case detection (the usual care arm). Outcomes such as the proportion of COPD patients diagnosed, and the costs of case detection would be collected. Linking the administrative health records of trial participants

would provide valuable information on the long-term outcomes of early detection. However, the results of this thesis suggest that even small improvements in disease outcomes due to improved diagnosis can have important benefits over a long time horizon. Therefore, evidence of the short-term cost-effectiveness of a case detection strategy would provide strong support for its value.

An observational study could also be used to evaluate case detection strategies. Existing variation in the use of case detection methods could be assessed in a longitudinal cohort of patients with COPD. Within this cohort, subjects who received case detection would be matched to control subjects who did not receive case detection. The rate of diagnosis, costs of case detection, and differences in the treatment patterns and healthcare resource use of diagnosed patients would be compared between groups. Although this type of study could provide valuable information on the associations between case detection and health outcomes, it would be at risk of confounding by disease severity and variation in physician or patient preferences for administering case detection. A rich dataset would be required to account for these factors.

6.5 Conclusions

Reducing the burden of undiagnosed COPD requires a proactive approach to disease diagnosis. Risk factors for COPD, such as smoking, should prompt an investigation of disease, rather than only the presence of respiratory symptoms. Symptoms are highly heterogeneous between patients with mild to moderate COPD, and restricting early detection strategies to symptomatic patients reduces their value. Screening questionnaires are a systematic, evidence-based method for assessing the risk of COPD. They should be used routinely in primary care settings to identify patients who require further testing for COPD. This strategy can facilitate interventions to preserve lung function while the disease is early in its progression. Symptom relief through

inhaled therapies, and treatment for smoking cessation among current smokers, can improve the long-term health outcomes of patients with COPD.

In summary, strategies for improving the early detection of COPD can be cost-effective and represent a high value use of resources. Given the mounting evidence from this thesis and similar work, there is a need to shift the focus from evaluating strategies for the early detection of COPD, to investigating barriers to their implementation. More broadly, the framework used in this thesis of evidence generation to understand the natural history of disease, followed by whole disease modelling to evaluate policy, can be transferred to other chronic diseases and used to improve patient care and health outcomes.

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Appendices

Appendix A

A.1 Search strategy

MEDLINE (OVID)
March 22, 2017

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---
1 *pulmonary disease, chronic obstructive/ or *bronchitis, chronic/ or *pulmonary emphysema/ (38797)
2 *airway obstruction/ (11509)
3 *bronchitis/ or *bronchiolitis/ or *bronchiolitis obliterans/ or *cryptogenic organizing pneumonia/ (18102)
4 *emphysema/ or *mediastinal emphysema/ or *subcutaneous emphysema/ or *alpha 1-antitrypsin deficiency/ (11041)
5 *Lung Diseases, Obstructive/ (13636)
6 limit 5 to yr="1980 -2001" (11016)
7 or/1-4,6 (84739)
8 di.fs. [Diagnosis] (2370855)
9 ep.fs. [Epidemiology] (1471514)
10 8 or 9 (3570350)
11 7 and 10 (23089)
12 Diagnostic Errors/ (35551)
13 Delayed Diagnosis/ (4539)
14 Early Diagnosis/ (22251)
15 Airway Obstruction/di [Diagnosis] (2772)
16 underdiagnos$.mp. (7477)
17 under diagnos$.mp. (2788)
18 undiagnos$.mp. (16208)
19 "Diagnostic Techniques and Procedures"/ (2914)
20 Diagnosis, Differential/ (432511)
21 "not diagnos$".mp. (5636)
22 misdiagnos$.mp. (26521)
23 or/12-22 (533328)
24 11 and 23 (4893)
25 "Risk Factors"/ (717586)
26 logistic models/ (119410)
27 risk assessment/ (224203)

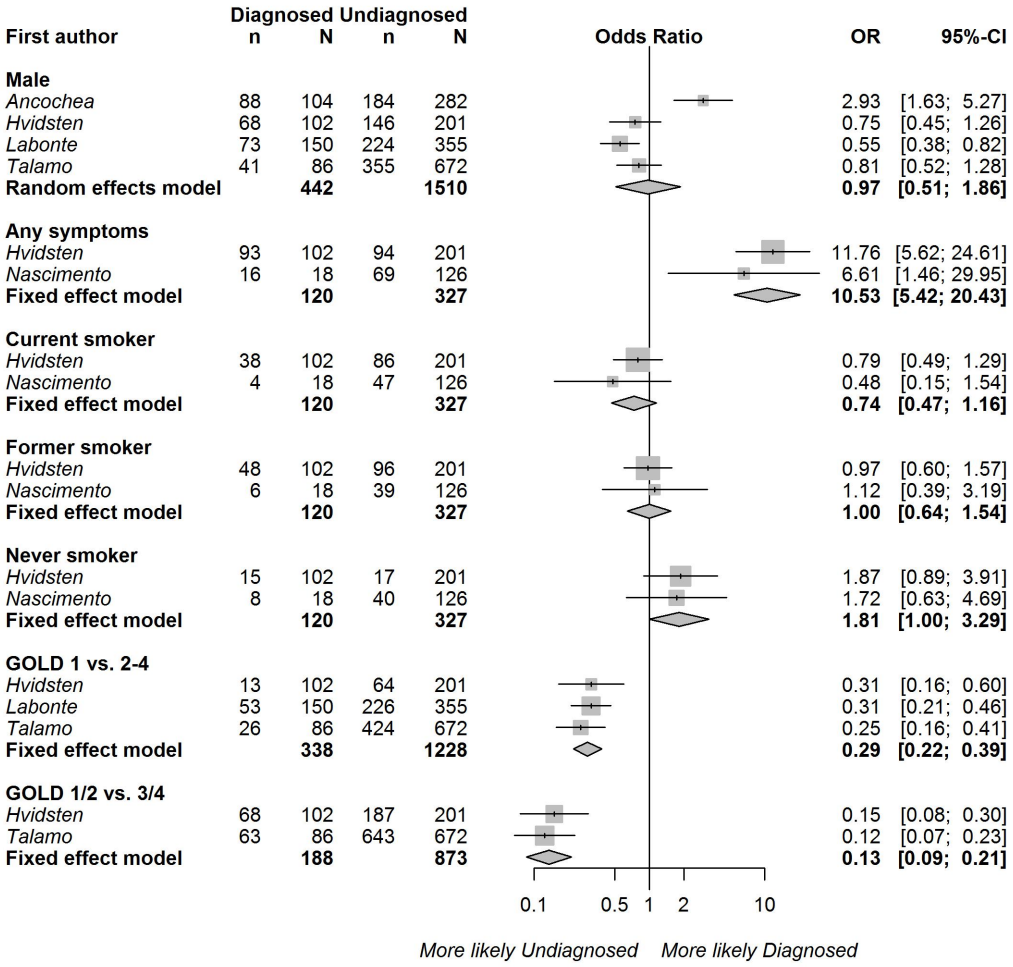
28 risk factors/ (717586)
29 risk/ (115068)
30 protective factors/ (1844)
31 probability/ (54508)
32 odds ratio/ (79810)
33 risk factor$.mp. (954945)
34 risk assessment$.mp. (251708)
35 (characteri#tic? or characteri#e? or characteri#ation).mp. (2499735)
36 or/25-35 (3674000)
37 24 and 36 (992)
38 limit 37 to yr=1980 -current (981)

EMBASE (OVID)
April 11, 2017

Database: Embase <1974 to 2017 August 14>
Search Strategy:
---
1 *chronic obstructive lung disease/ or *chronic bronchitis/ or *lung emphysema/ (68276)
2 *airway obstruction/ or *airflow limitation/ (10588)
3 *bronchitis/ or *chronic bronchitis/ or *bronchiolitis/ or *bronchiolitis obliterans/ or *bronchiolitis obliterans organizing pneumonia/ (24818)
4 *emphysema/ or *subcutaneous emphysema/ or *cigarette smoke-induced emphysema/ or *elastase-induced emphysema/ or *experimental emphysema/ or *alpha 1 antitrypsin deficiency/ (9667)
5 or/1-4 (103405)
6 di.fs. [Diagnosis] (2921008)
7 ep.fs. [Epidemiology] (976523)
8 6 or 7 (3661177)
9 5 and 8 (21021)
10 Diagnostic Error/ (50975)
11 Early Diagnosis/ (89985)
12 *Airway Obstruction/di [Diagnosis] (1452)
13 Diagnostic Procedure/ (80939)
14 Differential diagnosis/ (334345)
15 or/10-14 (535842)
16 9 and 15 (3600)
17 Risk Factor/ (828169)
18 regression analysis/ (116928)
19 multivariate analysis/ (141771)
20 risk assessment/ (424757)
21 risk factor/ (828169)
22 risk/ (496728)
23 probability/ (75672)

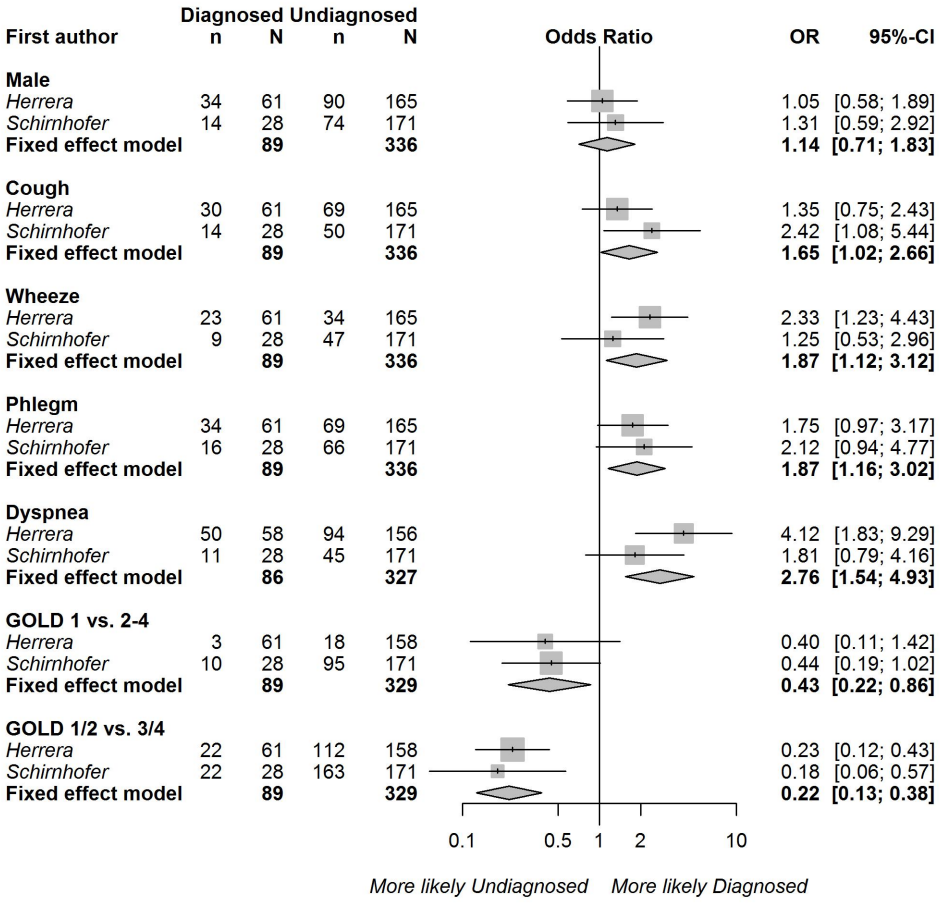
24 odds ratio/ (12341)
25 risk factor$.mp. (1080390)
26 risk assessment$.mp. (444895)
27 (characteri#tic? or characteri#e? or characteri#ation).mp. (3007687)
28 or/17-27 (4767936)
29 16 and 28 (717)
30 underdiagnos$.mp. (10792)
31 under diagnos$.mp. (5242)
32 undiagnos$.mp. (23402)
33 "not diagnos$".mp. (8488)
34 misdiagnos$.mp. (37341)
35 unrecogni$.mp. (33790)
36 Delayed Diagnosis/ (9134)
37 or/30-36 (123603)
38 9 and 37 (663)
39 29 or 38 (1299)
40 limit 39 to yr="1980 -current" (1296)
41 limit 40 to "english language" (1049)
42 40 not 41 (247)

A.2 Unadjusted analysis in the general population



Associations between diagnosed (v. 'undiagnosed') COPD and sex, the presence of any respiratory symptoms, smoking status, smoking history, and COPD severity based on the contingency tables of studies using random sampling of the general population ('unadjusted analysis'). Persistent airflow limitation was defined as post-bronchodilator $FEV_1/FVC<0.7$. Squares represent individual study estimates with the size of the square corresponding to their weight in the pooled estimate (represented with diamonds).

A.3 Unadjusted analysis using the lower limit of normal criterion



Associations between diagnosed (v. 'undiagnosed') COPD and sex, the presence of cough, wheeze, phlegm, dyspnea, and COPD severity based on contingency tables ('unadjusted analysis'). Persistent airflow limitation was defined as post-bronchodilator $FEV_1/FVC <$ lower limit of normal (LLN). Squares represent individual study estimates with the size of the square corresponding to their weight in the pooled estimate (represented with diamonds).

Appendix B

B.1 Symptom assessment questionnaire

Cough
Since your last visit, do you usually cough when you don't have a cold? (Y/N)
Phlegm
Since your last visit, do you usually bring up phlegm from your chest, or do you usually have phlegm in your chest that is difficult to bring up when you don't have a cold? (Y/N)
Wheezing/Whistling
Have you had wheezing or whistling in your chest at any time since your last visit? (Y/N)
Breathlessness
a) Are you unable to walk due to a condition other than shortness of breath? (Y/N)
b) Dyspnea (MRC Dyspnea Scale) Level 1: Not troubled by breathlessness except with strenuous exercise. Level 2: Troubled by shortness of breath when hurrying on level ground or walking up a slight hill. Level 3: Walks slower than people of the same age on level ground because of breathlessness, or has to stop for breath when walking at own pace on level ground. Level 4: Stops for breath after walking about 100 yards (90 m) or after a few minutes on level ground. Level 5: Too breathless to leave the house or breathless when dressing or undressing.

Questionnaire used to measure symptoms at each study visit in CanCOLD.

B.2 Characteristics of study participants in the subset of the data used to assess dyspnea and any symptoms

	Visit 1 (n=347)	**Visit 2** (n=241)	**Visit 3** (n=268)
Age	65.0 (10.2)	66.7 (9.8)	67.9 (9.4)
Male (vs. female)	54.5%	54.4%	54.1%
BMI	27.0 (4.9)	27.1 (4.9)	27.0 (4.9)
Caucasian (vs. non-Caucasian)	97.1%	97.1%	97.8%
Comorbidities*			
0 comorbidities	62.8%	56.4%	57.1%
1 comorbidity	30.5%	33.2%	24.3%
≥2 comorbidities	6.6%	10.4%	18.7%
Anxiety/Depression (vs. no)	18.2%	19.5%	19.4%
Smoking between visits (vs. no)	74.1%	25.7%	24.6%
Lifetime pack-years smoked	26.2 (25.8)	24.7 (25.4)	26.3 (25.6)
Any exacerbations‡ (vs. no)	7.5%	10.0%	14.6%
Medication Possession Ratio§	76.9% (107.6)	75.7% (111.9)	76.5% (107.7)
FEV_1 (L)	2.2 (0.8)	2.1 (0.8)	2.1 (0.7)
% Predicted FEV_1	75.0 (17.8)	76.1 (19.0)	77.1 (18.5)
Diagnosed COPD (vs. undiagnosed)	23.3%	27.0%	32.5%
Asthma (vs. no)	21.0%	26.6%	29.9%
Symptoms (present vs. absent)			
Dyspnea	53.3%	46.5%	44.8%
Any symptoms	83.9%	77.2%	74.6%

Characteristics of study participants in the subset of data that was used to assess dyspnea and any symptoms because 34 participants were unable to walk due to a condition other than shortness of breath. Means (and standard deviations) are reported unless otherwise indicated

* Participants reported whether they had ever been diagnosed with coronary artery disease, hypertension, diabetes, lung cancer, stroke, and tuberculosis at each study visit

‡ COPD exacerbations of any severity (mild, moderate, severe) over the past 12 months

§ 12-month medication possession ratio for all respiratory-related medications

Appendix C

C.1 List of medications classified as other respiratory medications

DIN	Category	DIN	Category
14923	Bronchodilators-Theophylline	1926608	Bronchodilators-Theophylline
156701	Bronchodilators-Theophylline	1926616	Bronchodilators-Theophylline
178497	Bronchodilators-Theophylline	1926640	Bronchodilators-Theophylline
261203	Bronchodilators-Theophylline	1966219	Bronchodilators-Theophylline
346071	Bronchodilators-Theophylline	1966227	Bronchodilators-Theophylline
405310	Bronchodilators-Theophylline	1966235	Bronchodilators-Theophylline
441724	Bronchodilators-Theophylline	1966243	Bronchodilators-Theophylline
441732	Bronchodilators-Theophylline	1966251	Bronchodilators-Theophylline
451282	Bronchodilators-Theophylline	1966278	Bronchodilators-Theophylline
458708	Bronchodilators-Theophylline	1966286	Bronchodilators-Theophylline
458716	Bronchodilators-Theophylline	2014165	Bronchodilators-Theophylline
460982	Bronchodilators-Theophylline	2014181	Bronchodilators-Theophylline
460990	Bronchodilators-Theophylline	2014270	Bronchodilators-Theophylline
461008	Bronchodilators-Theophylline	2014289	Bronchodilators-Theophylline
466409	Bronchodilators-Theophylline	2230085	Bronchodilators-Theophylline
476366	Bronchodilators-Theophylline	2230086	Bronchodilators-Theophylline
476390	Bronchodilators-Theophylline	2230087	Bronchodilators-Theophylline
476412	Bronchodilators-Theophylline	261238	Cromolyn Sodium
488070	Bronchodilators-Theophylline	534609	Cromolyn Sodium
497193	Bronchodilators-Theophylline	555649	Cromolyn Sodium
497207	Bronchodilators-Theophylline	638641	Cromolyn Sodium
503436	Bronchodilators-Theophylline	2046113	Cromolyn Sodium
511692	Bronchodilators-Theophylline	2049082	Cromolyn Sodium
532223	Bronchodilators-Theophylline	2219468	Cromolyn Sodium
536709	Bronchodilators-Theophylline	2231431	Cromolyn Sodium
556742	Bronchodilators-Theophylline	2231671	Cromolyn Sodium
565377	Bronchodilators-Theophylline	605255	Cromolyn Sodium Nasal Solution
575151	Bronchodilators-Theophylline	1950541	Cromolyn Sodium Nasal Solution
582654	Bronchodilators-Theophylline	2231326	Cromolyn Sodium Nasal Solution
582662	Bronchodilators-Theophylline	2231390	Cromolyn Sodium Nasal Solution

DIN	Category	DIN	Category
589942	Bronchodilators-Theophylline	38121	Ephedrine
589950	Bronchodilators-Theophylline	438847	Ephedrine
599905	Bronchodilators-Theophylline	876534	Ephedrine
627410	Bronchodilators-Theophylline	893323	Ephedrine
631698	Bronchodilators-Theophylline	893331	Ephedrine
631701	Bronchodilators-Theophylline	2012111	Ephedrine
692689	Bronchodilators-Theophylline	2100231	Ephedrine
692697	Bronchodilators-Theophylline	2100258	Ephedrine
692700	Bronchodilators-Theophylline	2126400	Ephedrine
722065	Bronchodilators-Theophylline	2126419	Ephedrine
792934	Bronchodilators-Theophylline	2219743	Ephedrine
868450	Bronchodilators-Theophylline	2229678	Ephedrine
1926586	Bronchodilators-Theophylline	2229698	Ephedrine
1926594	Bronchodilators-Theophylline	2229711	Ephedrine
2236722	Ephedrine	30910	Oral Glucocorticoid Steroid
2237085	Ephedrine	30929	Oral Glucocorticoid Steroid
2242639	Ephedrine	30988	Oral Glucocorticoid Steroid
2242961	Ephedrine	36129	Oral Glucocorticoid Steroid
2243148	Ephedrine	36366	Oral Glucocorticoid Steroid
466417	Epinephrine	156876	Oral Glucocorticoid Steroid
525103	Epinephrine	176834	Oral Glucocorticoid Steroid
1927582	Epinephrine	210188	Oral Glucocorticoid Steroid
2017555	Epinephrine	232378	Oral Glucocorticoid Steroid
307548	Guaifenesin/ Theophylline	252417	Oral Glucocorticoid Steroid
317225	Guaifenesin/ Theophylline	271373	Oral Glucocorticoid Steroid
334510	Guaifenesin/ Theophylline	271381	Oral Glucocorticoid Steroid
356123	Guaifenesin/ Theophylline	280437	Oral Glucocorticoid Steroid
476374	Guaifenesin/ Theophylline	285471	Oral Glucocorticoid Steroid
545090	Guaifenesin/ Theophylline	295094	Oral Glucocorticoid Steroid
640093	Guaifenesin/ Theophylline	312770	Oral Glucocorticoid Steroid
721301	Guaifenesin/ Theophylline	354309	Oral Glucocorticoid Steroid
792942	Guaifenesin/ Theophylline	489158	Oral Glucocorticoid Steroid
828718	Guaifenesin/ Theophylline	508586	Oral Glucocorticoid Steroid
828726	Guaifenesin/ Theophylline	550957	Oral Glucocorticoid Steroid
828742	Guaifenesin/ Theophylline	598194	Oral Glucocorticoid Steroid
2449781	Humanised monoclonal antibody	607517	Oral Glucocorticoid Steroid

DIN	Category	DIN	Category
2456419	Humanised monoclonal antibody	610623	Oral Glucocorticoid Steroid
577308	Ketotifen AL	868426	Oral Glucocorticoid Steroid
600784	Ketotifen AL	868434	Oral Glucocorticoid Steroid
2020017	Ketotifen AL	868442	Oral Glucocorticoid Steroid
2176084	Ketotifen AL	1946897	Oral Glucocorticoid Steroid
2218305	Ketotifen AL	1964070	Oral Glucocorticoid Steroid
2221330	Ketotifen AL	1964968	Oral Glucocorticoid Steroid
2230730	Ketotifen AL	1964976	Oral Glucocorticoid Steroid
2231679	Ketotifen AL	2063190	Oral Glucocorticoid Steroid
2231680	Ketotifen AL	2194082	Oral Glucocorticoid Steroid
2236606	Leukotriene receptor antagonist	2194090	Oral Glucocorticoid Steroid
2238216	Leukotriene receptor antagonist	2237044	Oral Glucocorticoid Steroid
2238217	Leukotriene receptor antagonist	2237045	Oral Glucocorticoid Steroid
2243602	Leukotriene receptor antagonist	2237046	Oral Glucocorticoid Steroid
2247997	Leukotriene receptor antagonist	2239534	Oral Glucocorticoid Steroid
2260565	Omalizumab	2240684	Oral Glucocorticoid Steroid
15016	Oral Glucocorticoid Steroid	2240685	Oral Glucocorticoid Steroid
15024	Oral Glucocorticoid Steroid	2240687	Oral Glucocorticoid Steroid
16438	Oral Glucocorticoid Steroid	2250055	Oral Glucocorticoid Steroid
16446	Oral Glucocorticoid Steroid	2260298	Oral Glucocorticoid Steroid
16462	Oral Glucocorticoid Steroid	2260301	Oral Glucocorticoid Steroid
21695	Oral Glucocorticoid Steroid	2261081	Oral Glucocorticoid Steroid
28185	Oral Glucocorticoid Steroid	2279363	Oral Glucocorticoid Steroid
2311267	Oral Glucocorticoid Steroid	2230210	Systemic Glucocorticoid Steroid
3859	Synthetic Derivative of Adrenaline	2230211	Systemic Glucocorticoid Steroid
254134	Synthetic Derivative of Adrenaline	2231893	Systemic Glucocorticoid Steroid
1923870	Synthetic Derivative of Adrenaline	2231894	Systemic Glucocorticoid Steroid
1928449	Synthetic Derivative of Adrenaline	2231895	Systemic Glucocorticoid Steroid
2017652	Synthetic Derivative of Adrenaline	2232748	Systemic Glucocorticoid Steroid
2017660	Synthetic Derivative of Adrenaline	2232750	Systemic Glucocorticoid Steroid

DIN	Category	DIN	Category
16241	Systemic Glucocorticoid Steroid	2237835	Systemic Glucocorticoid Steroid
28096	Systemic Glucocorticoid Steroid	2241229	Systemic Glucocorticoid Steroid
30600	Systemic Glucocorticoid Steroid	2245400	Systemic Glucocorticoid Steroid
30619	Systemic Glucocorticoid Steroid	2245406	Systemic Glucocorticoid Steroid
30627	Systemic Glucocorticoid Steroid	2245407	Systemic Glucocorticoid Steroid
30635	Systemic Glucocorticoid Steroid	2245408	Systemic Glucocorticoid Steroid
30643	Systemic Glucocorticoid Steroid		
30651	Systemic Glucocorticoid Steroid		
30678	Systemic Glucocorticoid Steroid		
30759	Systemic Glucocorticoid Steroid		
30767	Systemic Glucocorticoid Steroid		
36137	Systemic Glucocorticoid Steroid		
213624	Systemic Glucocorticoid Steroid		
664227	Systemic Glucocorticoid Steroid		
716715	Systemic Glucocorticoid Steroid		
732885	Systemic Glucocorticoid Steroid		
732893	Systemic Glucocorticoid Steroid		
751863	Systemic Glucocorticoid Steroid		
783900	Systemic Glucocorticoid Steroid		
872520	Systemic Glucocorticoid Steroid		
872539	Systemic Glucocorticoid Steroid		

DIN	Category	DIN	Category
874582	Systemic Glucocorticoid Steroid		
878618	Systemic Glucocorticoid Steroid		
878626	Systemic Glucocorticoid Steroid		
888206	Systemic Glucocorticoid Steroid		
888214	Systemic Glucocorticoid Steroid		
888222	Systemic Glucocorticoid Steroid		
888230	Systemic Glucocorticoid Steroid		
1934325	Systemic Glucocorticoid Steroid		
1934333	Systemic Glucocorticoid Steroid		
1934341	Systemic Glucocorticoid Steroid		
1977547	Systemic Glucocorticoid Steroid		
2063697	Systemic Glucocorticoid Steroid		
2063700	Systemic Glucocorticoid Steroid		
2063719	Systemic Glucocorticoid Steroid		
2063727	Systemic Glucocorticoid Steroid		
2204266	Systemic Glucocorticoid Steroid		
2204274	Systemic Glucocorticoid Steroid		

C.2 Parameter estimates from the sensitivity analysis of the subset of participants with spirometry-confirmed moderate to severe COPD near the time of diagnosis

	All-cause primary care visits		Respiratory-related primary care visits		Specialist physician visits		Pharmacist visits	
	Rate Ratio	95% CI	Rate Ratio	95% CI	Rate Ratio	95% CI	Rate Ratio	95% CI
COPD (vs. comparator)	1.30	1.27-1.34	2.67	2.57-2.78	1.33	1.29-1.37	1.60	1.54-1.66
Period	1.07	1.06-1.08	1.18	1.17-1.19	1.08	1.08-1.09	1.07	1.06-1.08
Female (vs. male)	1.10	1.07-1.12	1.18	1.14-1.23	1.01	0.98-1.05	1.13	1.08-1.17
Age	1.02	1.02-1.02	1.00	1.00-1.00	1.02	1.02-1.03	1.01	1.01-1.01
SES								
1 (vs. 5)	1.12	1.08-1.17	1.13	1.06-1.20	0.99	0.95-1.04	1.32	1.24-1.41
2 (vs. 5)	1.08	1.04-1.12	1.12	1.06-1.20	0.97	0.93-1.02	1.13	1.07-1.18
3 (vs. 5)	1.04	1.00-1.08	1.10	1.04-1.18	0.97	0.92-1.01	1.08	1.03-1.14
4 (vs. 5)	1.04	1.00-1.08	1.02	0.96-1.09	1.01	0.96-1.07	1.07	1.03-1.13
Calendar year	1.00	0.99-1.00	0.96	0.95-0.96	1.01	1.01-1.02	1.02	1.01-1.02

Parameter estimates and confidence intervals for the rate of outpatient visits among COPD patients who were prescribed long-acting muscarinic antagonist (LAMA) in the year before or after the index date (N=9,079). Patients in this subgroup had spirometry-confirmed moderate to severe COPD (FEV1/FVC<0.7 and FEV1 ≤65%).

C.3 Parameter estimates from the subset of participants with no missing data

	All-cause primary care visits		Respiratory-related primary care visits		Specialist physician visits		Pharmacist visits	
	Rate Ratio	95% CI	Rate Ratio	95% CI	Rate Ratio	95% CI	Rate Ratio	95% CI
COPD (vs. comparator)	1.40	1.39-1.41	2.16	2.14-2.19	1.35	1.34-1.36	1.61	1.60-1.63
Period	1.06	1.06-1.06	1.14	1.14-1.14	1.07	1.07-1.08	1.06	1.06-1.06
Female (vs. male)	1.15	1.15-1.16	1.27	1.25-1.28	1.08	1.07-1.09	1.18	1.17-1.20
Age	1.01	1.01-1.01	1.00	1.00-1.00	1.02	1.02-1.02	1.01	1.01-1.01
SES								
1 (vs. 5)	1.17	1.16-1.19	1.11	1.09-1.13	1.02	1.00-1.03	1.32	1.30-1.35
2 (vs. 5)	1.10	1.09-1.11	1.08	1.06-1.10	0.99	0.98-1.01	1.12	1.10-1.14
3 (vs. 5)	1.06	1.04-1.07	1.05	1.03-1.07	0.99	0.97-1.00	1.06	1.04-1.08
4 (vs. 5)	1.03	1.02-1.05	1.02	1.00-1.04	0.99	0.97-1.00	1.04	1.03-1.06
Calendar year	1.00	1.00-1.00	0.97	0.96-0.97	1.01	1.01-1.01	1.02	1.02-1.02

Parameter estimates and confidence intervals for the rate of outpatient visits in the subset of COPD patients and comparator subjects with no missing data (N=110,556).

C.4 Parameters estimates from a new cohort of participants in which comparator subjects never developed COPD during follow-up

	All-cause primary care visits		Respiratory related primary care visits		Specialist physician visits		Pharmacist visits	
	Rate Ratio	95% CI	Rate Ratio	95% CI	Rate Ratio	95% CI	Rate Ratio	95% CI
COPD (vs. comparator)	1.46	1.45-1.47	2.35	2.32-2.38	1.42	1.40-1.43	1.72	1.70-1.75
Period	1.06	1.06-1.06	1.13	1.13-1.14	1.07	1.07-1.08	1.06	1.05-1.06
Female (vs. male)	1.16	1.15-1.17	1.27	1.26-1.29	1.09	1.08-1.10	1.19	1.18-1.21
Age	1.01	1.01-1.01	1.00	1.00-1.00	1.02	1.02-1.02	1.01	1.01-1.01
SES								
1 (vs. 5)	1.15	1.13-1.16	1.09	1.07-1.11	1.01	1.00-1.02	1.29	1.26-1.31
2 (vs. 5)	1.09	1.07-1.10	1.08	1.06-1.10	0.99	0.97-1.00	1.11	1.09-1.13
3 (vs. 5)	1.04	1.03-1.05	1.04	1.02-1.06	0.99	0.97-1.00	1.06	1.04-1.08
4 (vs. 5)	1.02	1.01-1.04	1.01	0.99-1.03	1.00	0.98-1.01	1.03	1.01-1.05
Calendar year	1.01	1.00-1.01	0.97	0.97-0.97	1.01	1.01-1.01	1.02	1.02-1.03

Parameter estimates and confidence intervals for the rate of outpatient visits in a cohort of 106,439 COPD/comparator pairs in which comparator subjects never developed COPD during follow-up.

Appendix D

D.1 Development and validation of the symptom module in EPIC

D.1.1 Regression coefficients for the log odds of the presence of symptoms.

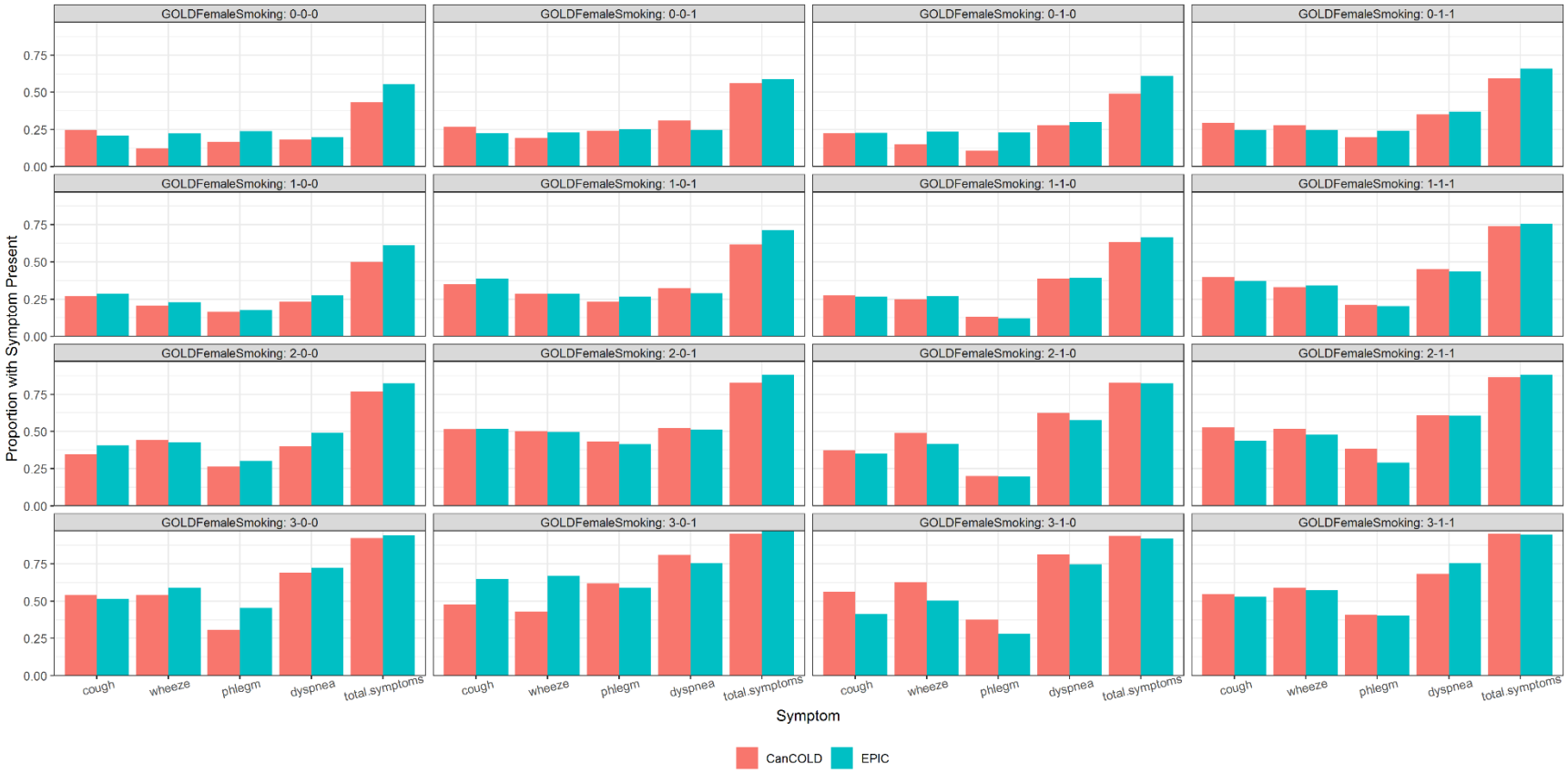
Parameter	Estimate (SE)	p-value	Estimate (SE)	p-value
	Cough		Wheeze	
COPD				
Intercept	4.4006 (1.3129)	<0.01	14.2686 (2.4553)	<0.01
Age	-0.0412 (0.0138)	<0.01	-0.1408 (0.0255)	<0.01
Female	-0.9472 (0.2956)	<0.01	-1.4995 (0.4489)	<0.01
Smoking	0.6036 (0.2089)	<0.01	0.1345 (0.2685)	0.62
FEV_1	-0.9564 (0.2170)	<0.01	-2.3122 (0.3931)	<0.01
Non-COPD				
Intercept	-5.2872 (1.9482)	0.01	-6.6284 (1.5300)	<0.01
Age	0.03429 (0.0158)	0.03	-0.02051 (0.0217)	0.34
Female	0.2178 (0.2743)	0.43	0.4671 (0.4208)	0.27
Smoking	0.3786 (0.2114)	0.07	0.2332 (0.3205)	0.47
	Phlegm		Dyspnea	
COPD				
Intercept	3.5726 (1.845)	0.05	4.8358 (1.4826)	<0.01
Age	-0.02422 (0.0193)	0.21	-0.00891 (0.0150)	0.55
Female	-2.089 (0.4924)	<0.01	-0.6346 (0.3256)	0.05
Smoking	1.0754 (0.2826)	<0.01	0.4177 (0.2281)	0.07
FEV_1	-1.6443 (0.356)	<0.01	-1.9942 (0.2824)	<0.01
Non-COPD				
Intercept	-10.3164 (1.8041)	<0.01	-7.1802 (0.9182)	<0.01
Age	0.02771 (0.0252)	0.27	0.07002 (0.0119)	<0.01
Female	-0.3459 (0.4763)	0.47	0.9343 (0.2204)	<0.01
Smoking	0.5865 (0.3413)	0.08	0.8388 (0.1856)	<0.01

D.1.2 Covariance matrix of random effects.

	Cough	Phlegm	Wheeze	Dyspnea
	COPD			
Cough	2.7934	2.11077	1.1737	0.64573
Phlegm	2.11077	7.0945	1.45258	0.89548
Wheeze	1.1737	1.45258	7.4793	1.48313
Dyspnea	0.64573	0.89548	1.48313	3.6357
	Non-COPD			
Cough	10.4693	17.10328	9.39833	1.04549
Phlegm	17.10328	138.8000	36.8647	4.67073
Wheeze	9.39833	36.86470	107.09	5.78527

	Cough	Phlegm	Wheeze	Dyspnea
Dyspnea	1.04549	4.67073	5.78527	5.1828

D.1.3 Results of internal validation between EPIC and CanCOLD for the prevalence of symptoms.



150,000 individuals were simulated in EPIC, and 1,573 participants were included from CanCOLD.

GOLD 4 is not showing due to the small number of observations in CanCOLD (n=6).

D.2 Development and validation of the primary care visits module in EPIC

D.2.1 Regression coefficients for the rate (log scale) of annual primary care visits.

Parameter	Estimate (SE)	p-value
COPD		
Intercept	0.4472 (0.5578)	0.42
Age	0.012 (0.0055)	0.03
Female	-0.0725 (0.1143)	0.53
Smoking	0.0669 (0.0704)	0.34
Cough	-0.0037 (0.0631)	0.95
Phlegm	-0.0108 (0.0734)	0.88
Wheeze	0.0553 (0.0603)	0.36
Dyspnea	0.0947 (0.0737)	0.20
FEV_1	0.1414 (0.0881)	0.11
Dispersion*	0.4310	
Non-COPD		
Intercept	-0.3596 (0.3337)	0.28
Age	0.0169 (0.0047)	<0.01
Female	0.0095 (0.0668)	0.80
Smoking	0.0722 (0.0615)	0.24
Cough	0.181 (0.1186)	0.13
Phlegm	-0.0275 (0.0763)	0.72
Wheeze	0.2262 (0.0637)	<0.01
Dyspnea	0.0807 (0.0619)	0.19
Dispersion*	0.4093	

* The reciprocal of the dispersion parameter is the alpha parameter in a gamma distribution, which was used to generate a negative binomial distribution.

D.2.2 Results of internal validation between EPIC and CanCOLD for the mean number of annual primary care visits.

150,000 individuals were simulated in EPIC, and 1,572 participants were included from CanCOLD.

GOLD 4 is not showing due to the small number of observations in CanCOLD (n=6).

D.3 Development and validation of the diagnosis module in EPIC

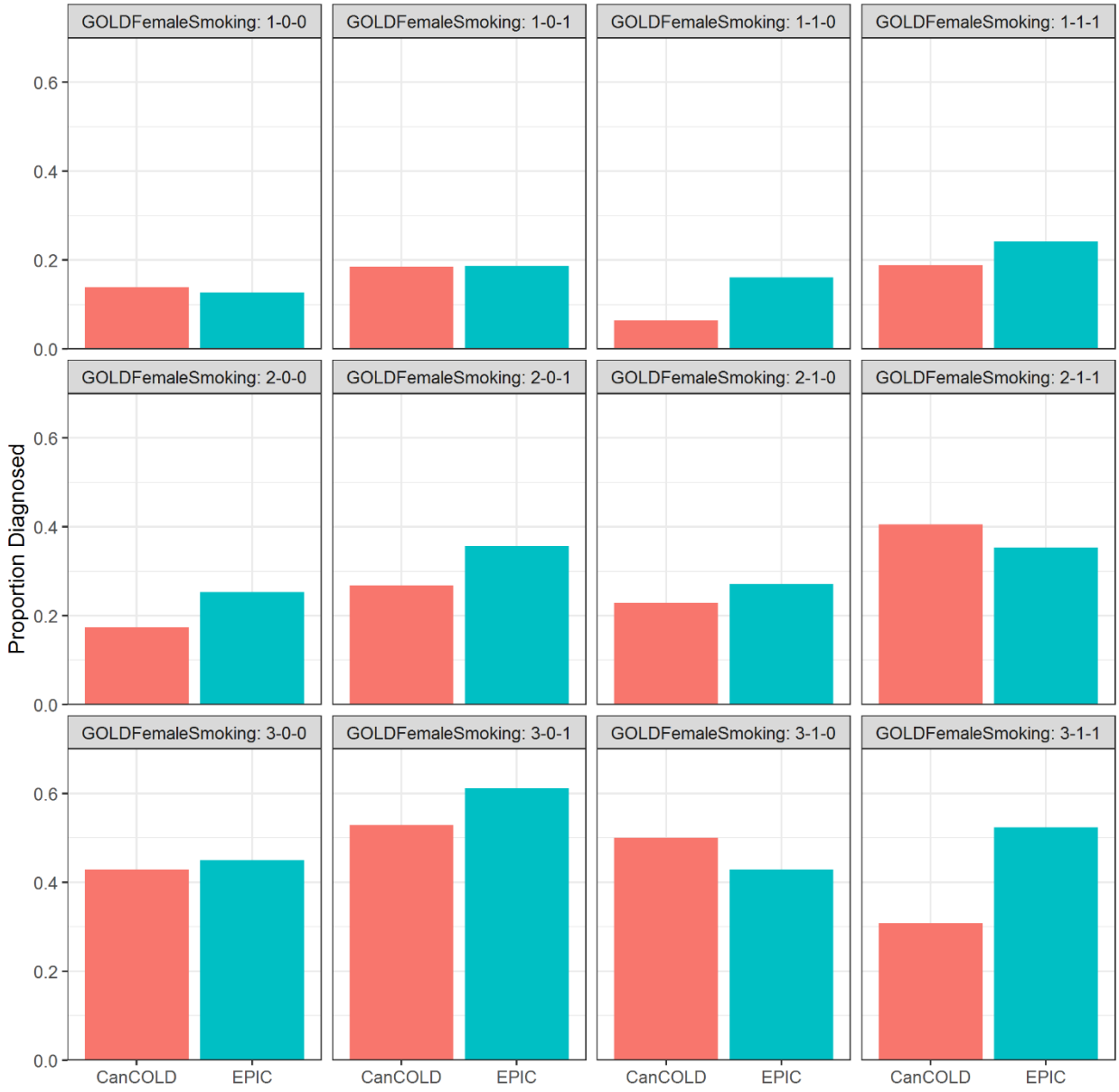
D.3.1 Regression coefficients for the log odds of diagnosis.

Parameter	Estimate (SE)	p-value	Estimate (SE)	p-value
Prevalent Diagnosis			False Positive Diagnosis	
Intercept	1.0543 (1.2144)	0.39	-5.2169 (1.0711)	<0.01
Age	-0.0152 (0.0134)	0.26	0.0025 (0.0153)	0.87
Female	-0.1638 (0.1395)	0.24	0.2597 (0.2906)	0.37
Smoking	0.1068 (0.1255)	0.39	0.6911 (0.2954)	0.02
FEV_1	-0.6146 (0.2263)	0.01		
Cough	0.075 (0.1302)	0.56	0.7264 (0.3722)	0.05
Phlegm	0.283 (0.1337)	0.03	0.7956 (0.375)	0.03
Wheeze	-0.0275 (0.124)	0.82	0.66 (0.3468)	0.06
Dyspnea	0.5414 (0.1302)	<0.01	0.8798 (0.3245)	0.01
Primary care visits*			0.0075 (0.0258)	0.77
Incident Diagnosis				
Intercept	-2†			
Age	-0.0324 (0.0108)	<0.01		
Female	-0.4873 (0.2273)	0.03		
Smoking	0.3711 (0.1946)	0.06		
FEV_1	-0.8032 (0.1957)	<0.01		
Cough	0.208 (0.2164)	0.34		
Phlegm	0.4088 (0.2356)	0.08		
Wheeze	0.0321 (0.2081)	0.88		
Dyspnea	0.722 (0.2048)	<0.01		
Primary care visits	0.0087 (0.0231)	0.71		

* Primary care visits were not simulated at baseline; therefore, this parameter was not included in the regression equation for prevalent diagnosis.

† Coefficient was determined through model calibration. (Original intercept 1.9614)

D.3.2 Results of internal validation between EPIC and CanCOLD for the prevalence of diagnosis among COPD patients.

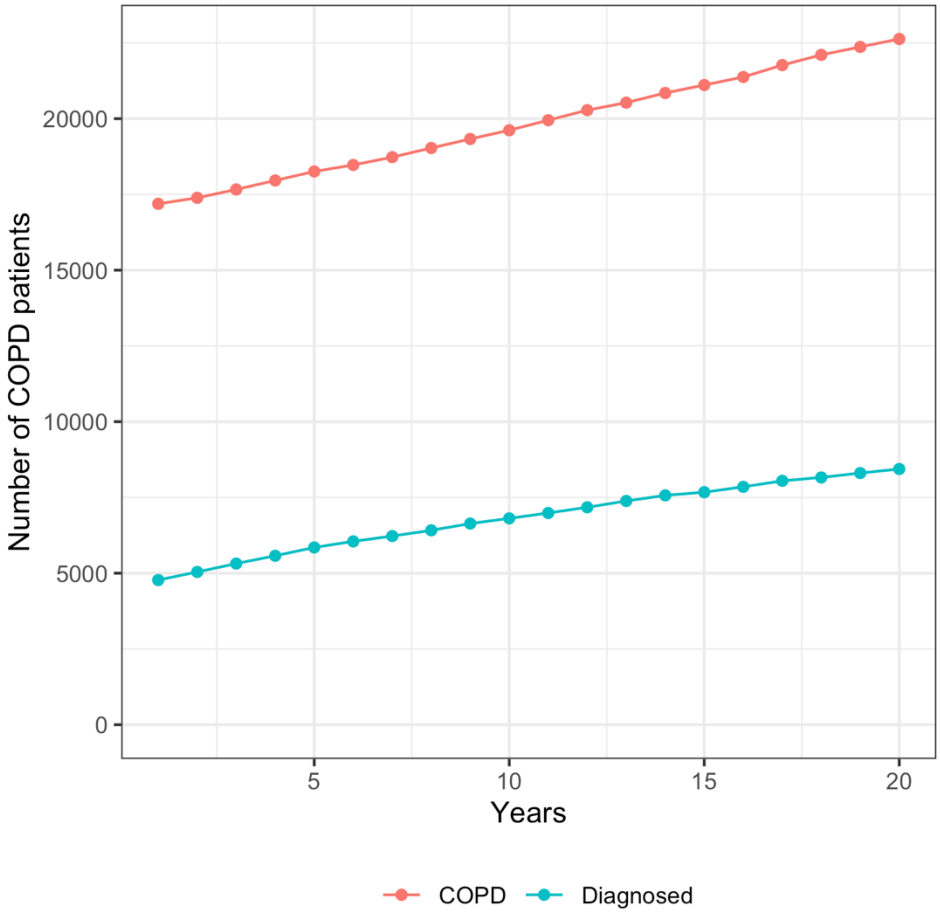


150,000 individuals were simulated in EPIC, and 467 participants were included from CanCOLD.

GOLD 4 is not showing due to the small number of observations in CanCOLD (n=2).

Results from EPIC were generated using the original regression equations for diagnosis that were developed using data from CanCOLD. Following internal validation, the intercept of the regression equation was calibrated to yield a stable prevalence of diagnosed patients at a proportion approximately equal to that observed in CanCOLD (29%[150]).

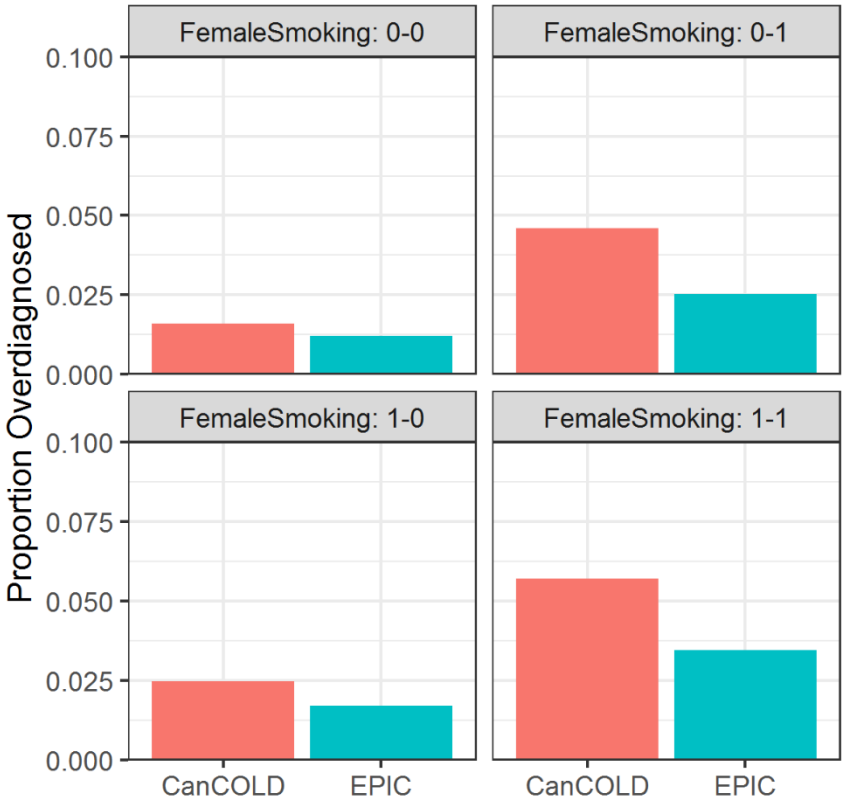
D.3.3 Number of COPD patients diagnosed over model time.



150,000 individuals were simulated in EPIC.

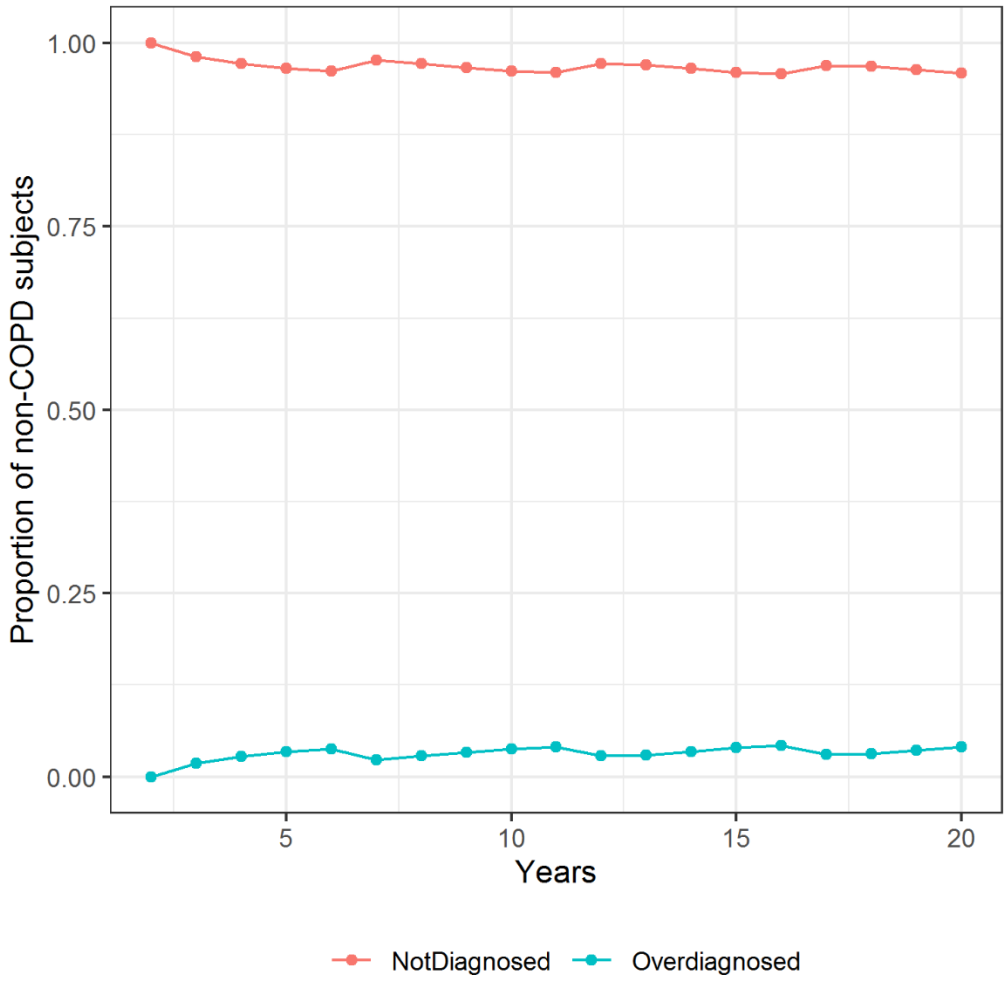
This figure was used during calibration to assess the stability of diagnosis and the proportion of COPD patients diagnosed.

D.3.4 Results of internal validation between EPIC and CanCOLD for the prevalence of false positive diagnosis ('overdiagnosis') among non-COPD individuals.



150,000 individuals were simulated in EPIC. 1,011 non-COPD participants (n=53 overdiagnosed) were included from CanCOLD.

D.3.5 Proportion of non-COPD individuals with a false positive diagnosis ('overdiagnosed') over model time.



Results are shown for 101,579 non-COPD individuals simulated in EPIC at year one.

This figure was used during calibration to assess the stability of overdiagnosis.

D.4 Development and validation of the treatment module in EPIC

D.4.1 Treatment algorithm for individuals diagnosed with COPD.

Exacerbation history*	**Symptoms**	
	No dyspnea	Dyspnea
≥2 moderate exacerbations† or 1 severe‡/very severe§ exacerbation	LAMA/LABA	ICS/LAMA/LABA
No exacerbations or 1 moderate exacerbation	SABA	LAMA
False positive diagnosis	SABA	

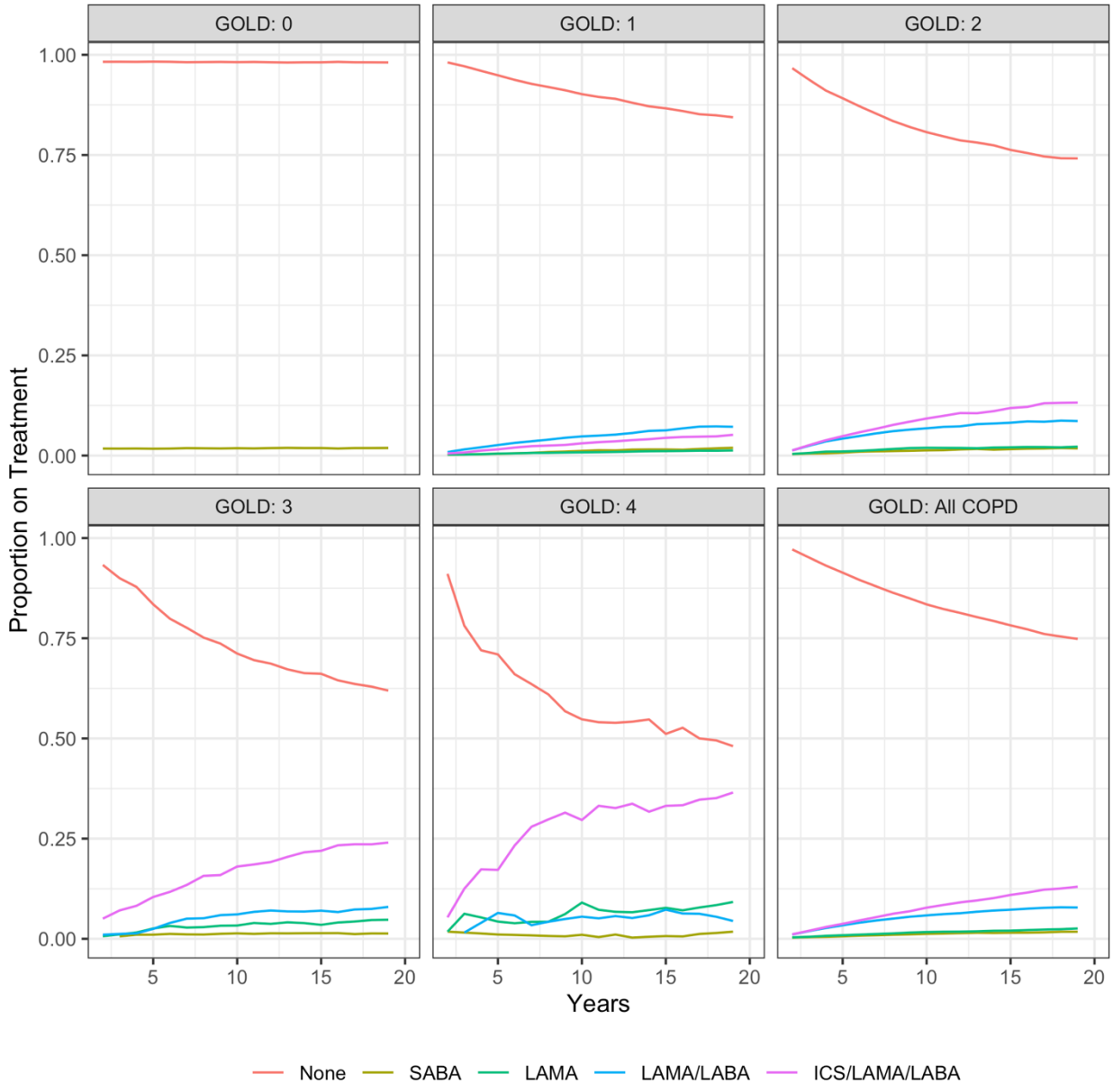
* Exacerbation history in the previous 12 months

† Moderate exacerbations are defined as those requiring a visit to the emergency department

‡ Severe exacerbations require hospital admission

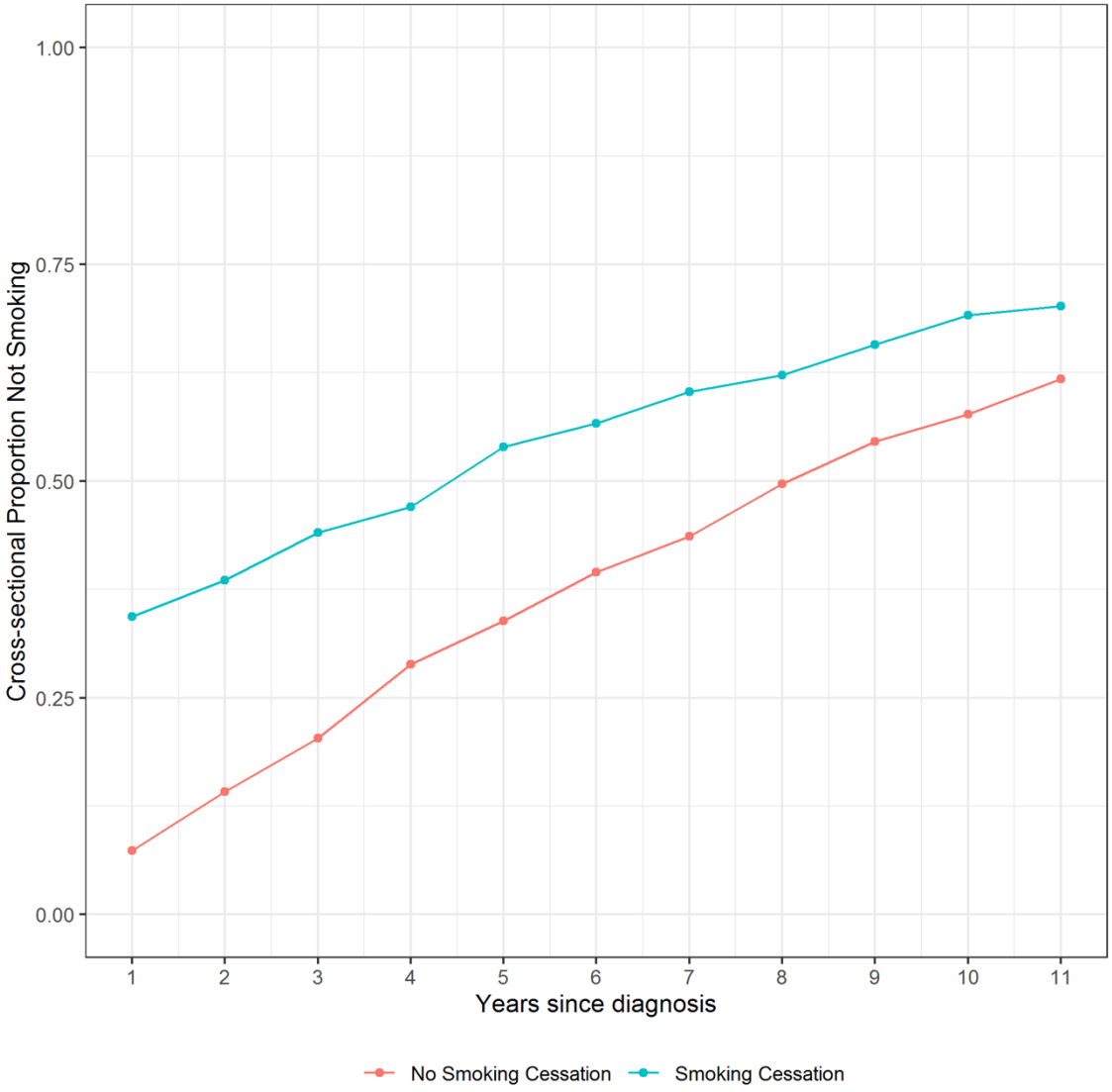
§ Very severe exacerbations require admission to an intensive care unit

D.4.2 Proportion of simulated individuals in EPIC on medications of each class over model time.



210,000 individuals were simulated in EPIC.

D.4.3 Effectiveness of smoking cessation among newly diagnosed patients in EPIC.



Cross-sectional proportion of non-smokers in the years since COPD diagnosis.

150,000 individuals were simulated in EPIC in both the no smoking cessation and smoking cessation scenarios.

This figure was used during calibration to assess the marginal effect of the smoking cessation intervention. In year 1, 34.4% of individuals who received smoking cessation were non-smokers, compared to 7.4% under no smoking cessation. These figures were 70.2% and 61.8% after 11 years, respectively.

D.5 Performance characteristics of case detection methods

D.5.1 Performance characteristics of case detection methods evaluated for each scenario.

Case detection method	Sensitivity	β logit(Diagnosis)*	Specificity	β logit(Overdiagnosis)
(S1) *All patients*				
S1a: CDQ ≥17 points	91	4.1013	49	4.3940
S1b: Screening spirometry (with bronchodilator)	80	3.1740	94	1.6025
S1c: CDQ + Screening spirometry (with bronchodilator)	72	2.7321	97	0.8779
(S2) *Symptomatic patients* (any respiratory symptoms)				
S2a: Screening spirometry (without bronchodilator)	81.5	3.2705	88.9	2.2735
(S3) *Smoking history* (ever smokers ≥ 50 years)				
S3a: CDQ ≥19.5 points	64.5	2.3848	65.2	3.7262
S3b: CDQ ≥16.5 points	87.5	3.7336	38.8	4.8098
S3c: Screening spirometry (without bronchodilator)	79.9	3.1677	84.4	2.6657
S3d: CDQ + Screening spirometry (with bronchodilator)	74.4	2.8545	97	0.8779

* This refers to β_{10} in Equation 5-1

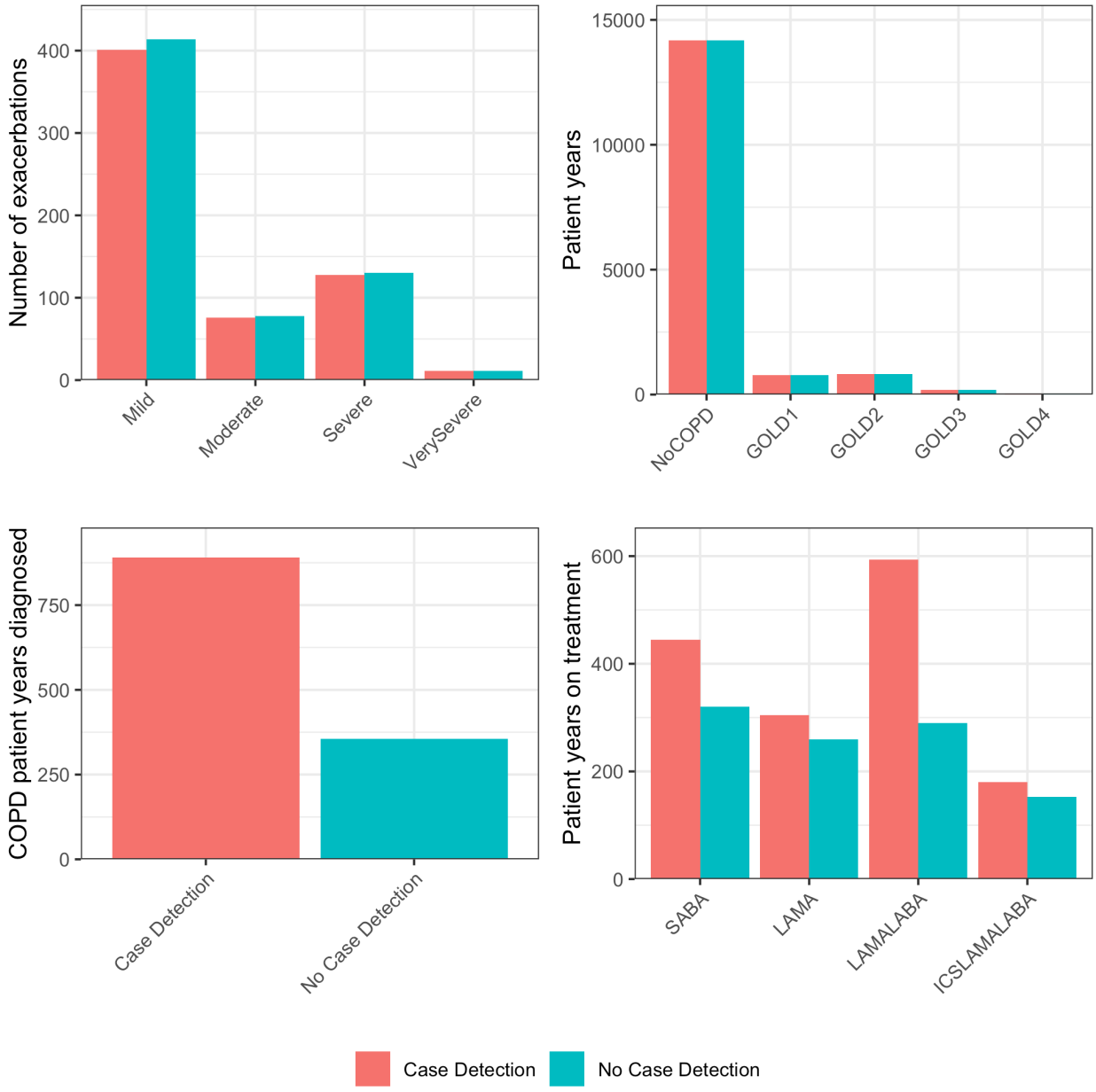
D.5.2 Example calculation of the coefficient for case detection.

The sensitivity of the example case detection method is 75%, therefore the odds of diagnosis among COPD patients is 3.

Subject	Probability of routine diagnosis	Odds of routine diagnosis	Odds ratio for case detection
1	0.13	0.15	3/0.15 = 19.59
2	0.18	0.22	3/0.22 = 13.40
3	0.27	0.37	3/0.37 = 8.13

The average odds ratio for case detection among Subjects 1-3 is 13.71. Therefore, the coefficient for case detection (β_{10}) in the regression equation for the logit of diagnosis (Equation 5-1) would be ln(13.71) = 2.62.

D.6 Results of the preferred case detection scenario



Results of the preferred case detection scenario (*S1a*: CDQ ≥17 points delivered at 3 years intervals to all patients ≥40 years) compared to no case detection. Results are shown for a cohort of 1,000 individuals eligible to receive case detection.