BEYOND AIRFLOW OBSTRUCTION:

MULTICOMPONENT COPD PROGNOSTICATION IN PERSONALISED CARE

Spencer Joseph Keene

BEYOND AIRFLOW OBSTRUCTION:

MULTICOMPONENT COPD PROGNOSTICATION IN PERSONALISED CARE

Spencer Joseph Keene

Cover design Vera van Beek

Printing Proefschrift.nu Printing ProefschriftMaken | www.proefschriftmaken.nl

ISBN 978-94-6469-041-5

BEYOND AIRFLOW OBSTRUCTION:

MULTICOMPONENT COPD PROGNOSTICATION IN PERSONALISED CARE

DISSERTATION

to obtain the degree of Doctor at the Maastricht University,

on the authority of the Rector Magnificus, Prof. dr. Pamela Habibović

in accordance with the decision of the Board of Deans, to be defended in public

on Tuesday 20 September 2022, at 13:00 hours

by

Spencer Joseph Keene

Supervisors:

prof. dr. Frits M.E. Franssen, Maastricht University

prof. dr. Peymane Abab, University of Birmingham, UK

Co-supervisors:

dr. Johanna H.M. Driessen, Maastricht University

dr. Rachel E. Jordan, University of Birmingham

Assessment Committee:

prof. dr. R.P. Koopmans, Professor of General Internal Medicine, in particular, Education and Training in this very discipline, Maastricht University (Chair);

prof. dr. G.J. Wesseling, Professor of Pulmonology, Maastricht University;

dr. N. Adderley, Institute of Applied Health Research, University of Birmingham, United Kingdom;

prof. dr. K. Jolly, Professor of Public Health and Primary Care, University of Birmingham, United Kingdom;

prof. dr. M. Puhan, Professor of Epidemiology and Public Health, University of Zurich, Switzerland;

prof. dr. J. Hurst, Professor of Respiratory Medicine, University College London, United Kingdom.

ABSTRACT

COPD is increasingly recognized as a heterogeneous and multidimensional disease. Multicomponent prognostic scores account for this by measuring components beyond FEV_1. This thesis used data from large cohort studies and routine health data from general practice to answer research questions under four themes: 1) demonstrate the burden of exacerbation occurence; 2) provide evidence on the external validity of prognostic scores in accurately predicting risk in various clinical settings; 3) examine the potential for extending the use of these scores to detect disease worsening; 4) further our understanding of some components that comprise prognostic scores.

Severe COPD exacerbations present a significant burden to patients as they increase hospitalisation and mortality. We found that the incidence rates of severe COPD shows signs of an increase from year-to-year which highlights the importance in accurately predicting these events. We demonstrate the external discriminative validity of the BLISS and ADO scores in predicting exacerbations and mortality, respectively. However, these scores may need to be recalibrated before predicting outcomes in different time horizons or healthcare settings. Serial measurements of the ADO score may help to update prognostic risk in people with COPD. Among people screened for COPD with respiratory symptoms, we found that symptom burden over time and prognosis of persistent moderate-to-severe respiratory symptoms was similar in those with normal FEV_1, compared to those with airway obstruction. Finally, weight loss due to continuous smoking is accelerated if a person has COPD, and quitting results in an accelerated weight gain compared to those without COPD.

Table of Contents

CHAPTER I: GENERAL INTRODUCTION

Background on COPD

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterised by persistent respiratory symptoms and airflow limitation (1). Airflow limitation results from parenchymal and small airways destruction (i.e., emphysema), chronic inflammation and narrowing of the airways (i.e., chronic bronchitis), or both (1). The relative contribution of emphysema and chronic bronchitis to the pathophysiology and symptomology of COPD may vary considerably from patient to patient (1,2). Impaired oxygen uptake and increased accumulation of air in the lungs (i.e., hyperinflation) are other pulmonary abnormalities in COPD that contribute to the clinical presentation of a patient.

Risk factors

COPD is mainly caused by exposure to cigarette smoking and ambient noxious chemicals (3,4). Other risk factors include household air pollution, occupational particulates, and second-hand smoke (3,4). In low socio-economic regions and countries, particulate matter pollution is a major cause of both COPD and deaths related to this condition (5,6). Although these exposures have a large impact on COPD incidence, there is also accumulating evidence that approximately half of COPD patients had impaired lung development as a result of genetic susceptibility and/or early-life events and exposures, resulting in a low maximally attained lung function in early adulthood and an increased risk of COPD later in life (7). Parental asthma, childhood asthma, maternal smoking, and childhood respiratory infections are factors associated with a low maximally attained lung function and an increased COPD risk (8).

Diagnosis

The Global initiative for chronic Obstructive Lung Disease (GOLD) advocates for the combination of respiratory symptoms, family history, and a history of exposure to risk factors as indicators to diagnose COPD via spirometry (1). Spirometry allows assessment of the presence and extent of airflow limitation using the following formula: FEV_1 (forced expiratory volume of air exhaled in one second) as a proportion of their FVC (forced vital capacity). According to GOLD, a post-bronchodilator FEV_1 /FVC <0.70 confirms the presence of airflow limitation (9). There is a second method for diagnosing COPD based on spirometry using the

lower limit of normal (LLN), COPD is diagnosed in a patient if the FEV_1/FVC ratio is below the lower fifth percentile of an aged-matched healthy reference group who are characterised as never smokers (10).

Whether using LLN or the fixed ratio more accurately diagnoses COPD patients is controversial. Among 4,965 participants aged ≥65 years in the Cardiovascular Health Study, those who were classified as “abnormal” by the fixed ratio and ‘‘normal’’ using the LLN had increased mortality and COPD-related hospitalisation during follow-up (11). On the other hand, in a study of 24,207 US adults from 4 US general population-based cohorts, the prognostic accuracy of LLN was not significantly different than that of the fixed ratio when predicting the risk of COPD-related hospitalization or mortality (12). Unlike the previous studies, a third study found that the fixed ratio may miscategorise patients. Among 95,288 participants aged 20 to 100 years from the Copenhagen General Population Study, those with a normal spirometry according to the fixed ratio method but abnormal according to the LLN method had an over two-fold increased risk of pneumonia, heart failure, and mortality after adjusting for age and sex (13). Thus, it is unclear whether the LLN or fixed ratio methods better categorise COPD.

There are also advantages and disadvantages to the use of each method. The LLN may underdiagnose COPD, especially in areas of the world where the “healthy” reference population is exposed to significant air pollution and other non-smoking risk factors (14). If we were ever able to diagnose patients in early adulthood then finding an appropriate reference population may be complicated (15). The fixed ratio method is simple but may overdiagnose COPD, especially in older patients who may be healthy but exhibit low lung function due to their age (14). LLN may underdiagnose COPD in the elderly. Some primary care patients will likely meet the fixed ratio criteria before LLN after further progression of their disease and only using LLN may delay diagnosis and treatment in these patients (16).

This lack of consensus means that it is important to consider symptoms and other indicators that can add to the accuracy of a COPD diagnosis (17). For example, neither LLN nor the fixed ratio may be helpful for primary care patients with mild COPD when the decision to diagnose the disease will be primarily based on clinical grounds, not spirometry (2). Symptomatic individuals with normal spirometry measurements have worse mortality and health-related quality of life than non-symptomatic individuals with normal spirometry, regardless of whether or not the individual is diagnosed with COPD later on (17). Using FEV_1 to diagnose COPD may not be useful since there is little evidence that it can be altered with therapy (18). Emphasising “careful phenotyping using clinical, physiologic, and radiologic

data to elucidate factors that dictate disease heterogeneity and therefore might be relevant to diagnosis, prognosis, or both" may be more beneficial (18).

Symptoms

The most common symptoms of COPD include dyspnoea (defined as difficult or laboured breathing), chronic cough, sputum production, wheezing, chest tightness, and fatigue (4). COPD develops slowly and these symptoms may worsen over time in many patients, especially if exposure to risk factors persists (4). Accordingly, the ability of patients to undertake certain physical tasks decreases, and a medical diagnosis is often only sought after the simplest of routine tasks become difficult (19). The importance of symptoms is reflected in the current GOLD strategy which recommends assessing symptoms (breathlessness is highlighted most of all) and exacerbations for the treatment of COPD (1).

There exist patients who primarily suffer from high symptom burden (i.e., chronic cough, sputum production) but do not have spirometrically defined COPD (17). Among 108,246 randomly chosen individuals aged 20 to 100 from a Danish population-based cohort study, chronic respiratory symptoms were associated with both respiratory hospitalisations and death among individuals with and without normal spirometry (20). The authors state that normal spirometry is not enough to rule out COPD and that those with symptoms should be followed more closely for the persistence of their symptoms and potential development of abnormal spirometry. In one of the early iterations of GOLD strategy, defining patients with symptoms but normal spirometry was presented as an opportunity for early identification and targeted therapy (21). However, subsequent iterations of GOLD have excluded this concept since these individuals do not necessarily progress to stage I and therefore cannot be defined as simply "at risk". The relevance of chronic respiratory symptoms in individuals with normal spirometry is still debated to this day (21). Therefore, it is still unclear how stable symptoms are over time and whether the prognosis of individuals with respiratory symptoms varies by whether they have normal or abnormal spirometry. A better understanding of individuals with respiratory symptoms and normal lung function may allow targeted screening or management of these patients to improve their outcomes.

Acute exacerbations

The clinical course of COPD may be complicated by the occurrence of acute exacerbations of the disease. These are defined as an acute worsening of

symptoms beyond normal day-to-day variations that require additional therapy (1). Exacerbations lead to the deterioration of a patient's stable condition (22) and can increase the rate of COPD progression (23). Also, they are associated with reduced health status and increased risk of respiratory failure, hospital admission, and mortality (24). Exacerbations are usually triggered by bacterial and viral infections (22) but other triggers include eosinophilic inflammation and smoking (25). There is a high variation in the frequency of exacerbations experienced from patient-to-patient but this is often associated with the severity of airflow obstruction and the number of previously treated exacerbations (26). The overall burden of COPD exacerbations and resources necessary to manage them can be examined by tracking the long-term changes in the incidence rates of exacerbations but this has not been shown in the UK general population.

Exacerbation severity is often dichotomised into either moderate exacerbations that require outpatient drug therapy such as antibiotics and/or steroids or severe exacerbations that result in hospitalisation (27). However, these definitions can lead to under-reporting of exacerbation events, are inaccurate, and lack generalisability across various healthcare systems (27). One study of ATTAIN trial participants living in nine European countries and South Africa found that twice as many patients experienced at least one exacerbation event after accounting for unreported exacerbations (28). Unreported exacerbations were defined as symptomatic events that resulted in a persistent increase of ≥9 points for ≥3 days or ≥12 points for ≥2 days on the EXAcerbations of Chronic pulmonary disease Tool (EXACT) total daily patient diary score that was not reported to a physician. Both unreported and reported exacerbations had a similar negative impact on health-related quality of life but patients were less likely to recover from unreported (and therefore untreated) exacerbations 28 days later. A second study of 491 COPD patients in China found that 466 out of 876 (53%) exacerbations were unreported, identified using a monthly questionnaire during follow-up (29). Here, an exacerbation was defined as a worsening of at least one of either the amount of sputum, changed sputum colour or purulence, or increased dyspnoea for ≥2 days reported using a monthly structured questionnaire. An exacerbation was considered unreported if it was not brought to the attention of healthcare providers. Unlike the previous study, patients with unreported exacerbations had a much smaller change in health-related quality of life when compared to patients with reported exacerbations. Differences between studies in how common unreported exacerbations are and their impact on health-related quality of life may be due to what tool was used to detect unreported exacerbations, the threshold used to define an exacerbation, differences in health services and self-management provision, and whether the analysis quantifying the effect of exacerbations was

performed at the level of the event itself (28) or the level of patients grouped according to these events (29). In addition, ATTAIN reduced recall bias by requiring participants to report daily EXACT assessments, which may have captured more unreported exacerbations compared to the study in China. The study in China included patients from respiratory divisions of 10 general hospitals. These individuals may be more likely to seek further healthcare for their exacerbations since they have prior experience with doing this and they already have access to physicians. Therefore, they may be more likely to report milder exacerbations than participants in the ATTAIN trial. Furthermore, patients in the China study had worse health status at baseline than ATTAIN participants, potentially limiting the extent to which quality of life could worsen further.

The overall burden of exacerbations on patients is higher after accounting for unreported exacerbations and patients may receive less than optimal maintenance if some exacerbations go unnoticed. Accurate prediction of these events is essential so that clinical decisions can be well informed, and patients can receive proper therapy. However, accurate and unbiased prediction tools for exacerbations are lacking in COPD.

Prevalence

Data from 2010 shows that 330 to 390 million people are diagnosed with COPD worldwide, corresponding to approximately 10 to 12% of the global population (30,31). The highest prevalence was in North and South America and the lowest in South East Asia (31). COPD prevalence across countries varies with smoking prevalence (32). There is a higher estimated prevalence among men (12%-14%) than women (7-9%) (31,32) but this may be due to women being underdiagnosed relative to men, despite being more susceptible to cigarette exposure (33). In addition, the prevalence of smoking in women is lower than it is in men but, unfortunately, women are closing the gap (34). There are very few recent studies that describe the prevalence of COPD in the Netherlands and England. Using functional respiratory tests, the prevalence of stage II or higher COPD in England ranges from 5 to 8%, depending on whether any respiratory symptom is included in the definition (35,36). Its prevalence is approximately 10% in the Netherlands (37). Country-wide prevalence estimates across studies can vary due to differences in sampling and different COPD definitions and methods used (e.g. COPD defined using lung function, symptoms, physician report, statistical modelling, etc.) (38).

There is also evidence that COPD prevalence is increasing over time. The prevalence of COPD increased by 44% from 1990 to 2015 (3). However, the

prevalence decreased by 15% during this period after accounting for an aging population structure. This reflects that as populations become older, people become more susceptible to respiratory function decline. Increases in the prevalence of COPD were the most rapid in the Eastern Mediterranean and African regions while the lowest increase was in Europe after controlling for mean age and the year of study (31). Increases in COPD prevalence within a country may be due to increases in exposure to risk factors such as smoking behaviour, biomass smoke, and outdoor air pollution due to urbanisation (39). Even though COPD burden is high, it remains an underdiagnosed disease (40). Thus, the prevalence of COPD, especially in low-to-middle income countries where spirometry is underutilised (41), is likely underestimated. The prevalence of previously undiagnosed COPD was 47% among current smokers between 40 and 70 years of age, and a smoking history of at least 15 pack-years in six semi-rural general practices (42) whereas the prevalence was 27% among 138 patients attending a primary health care centre or urgent primary care centre in a suburban area of Sweden with acute respiratory tract infection, positive smoking history and no previously known pulmonary disease (43). This difference in prevalence may reflect less access to healthcare in more rural areas (44). Patients may be more likely to have their COPD diagnosed prior to the case finding if they are older and were more likely to have chronic cough and fatigue whereas wheezing, age, pack-years, and current smoking, cough, dyspnoea, sputum, and body mass index (BMI) seemed to differentiate COPD patients from those who did not end up receiving a diagnosis (42,43,45).

Healthcare costs

COPD is associated with a significant economic burden. The mean annual direct, health-service related (e.g. respiratory treatment, hospitalisation, consultations/visits to a healthcare provider, etc.) cost per patient was the lowest in South Korea (504 dollars (converted to USD currency)), Brazil (555), and Russia (742) and the highest in France (3,406), Spain (3,570), Japan (4,650), and the USA (9,981) (46). Relative to these and other countries, direct costs were high in the UK (3,224) and much lower in the Netherlands (1,690). Indirect costs (e.g. attributable to productivity loss from early-retirement, work absence, etc) made up 40% of the total societal costs (indirect costs + direct costs) in France and a much higher percentage in the UK (83%), and the Netherlands (82%) (46). Variability of direct costs between countries is likely can be explained by different healthcare systems, and the ability of patients to access healthcare, as well as different healthcare practices and guidelines used for COPD care (46). However, indirect

costs tend to increase with higher national per capita incomes and may also vary by culture as well (46). For instance, although both direct and indirect costs increase exponentially with increasing COPD severity and in those with comorbidities (47), more patients with low symptom burden are admitted into specialised care in Japan than similar patients from other countries (46). An individual's social support and available working days off after a COPD diagnosis may be dependent on cultural values pertaining to the importance of independence and self-sufficiency and maintaining a work-life balance.

Mortality

COPD is the third leading cause of death, accounting for nearly 6% of the total worldwide deaths (48). In 2017, the age-standardised mortality rate for males and females with COPD was approximately 55 and 32 deaths per 100,000 people (5). Compared to age, sex, and smoking history matched controls, COPD patients have a three-fold increased rate of death after adjusting for comorbidities (49). Among patients diagnosed with COPD, 40 to 60% of deaths are attributable to their disease (50–52) while the remaining top underlying causes of death are diseases of the circulatory system (most common were acute myocardial infarction), neoplasms (mostly lung cancer), and other respiratory diseases (51). The top causes of death in patients hospitalised for acute exacerbations were cardiac failure, pneumonia, and pulmonary thromboembolism, while respiratory failure due to COPD only accounted for 14% of deaths (53). From 1990 to 2015, the global age-standardised death rate for COPD patients decreased by 42% (3) and an average of 2.4% per year (5). This decline may be due to improved care of comorbidities and the worldwide decline in poverty. If the death rate in 1990 was maintained into 2010, then over 5 million deaths would have occurred worldwide due to COPD (54). However, despite decreases in death rates across the globe (55), 3.2 million people still died from COPD in 2015, an increase of nearly 12% since 1990, largely driven by population growth (3). COPD is expected to be the leading cause of death within 15 years (30).

A complex and heterogeneous disease

Disease staging uses objective medical criteria to produce groups of clinically homogeneous patients based on the severity and progression of their disease (56). COPD staging used to be based on the severity of airflow limitation which grouped

patients into the following four distinct spirometric stages: FEV_1 as a percentage of predicted value: GOLD 1 - mild: $FEV_1 \geq 80\%$ predicted, GOLD 2 - moderate: $50\% \leq FEV_1 < 80\%$ predicted, GOLD 3 - severe: $30\% \leq FEV_1 < 50\%$ predicted, GOLD 4 - very severe: $FEV_1 < 30\%$ predicted (57). These stages guided what treatment a patient received. However, it is now well-recognized that COPD severity and the burden of disease for individual patients are not adequately captured by FEV_1 alone (1). The primary reason is that FEV_1 is not a reliable marker of the severity of symptoms such as breathlessness and, therefore, has limited influence over individualised patient care decisions. Some COPD patients primarily suffer from cough and sputum production due to chronic airway inflammation (2). Other patients have breathlessness caused by air trapping and hyperinflation of the lungs (2) which can be more successfully treated with bronchodilators (58). Still other patients may have a reduced ability to perform physical functions (59). COPD is also influenced by many intra- and extra-pulmonary components which vary in whether and at what time they present themselves (60). Thus, only accounting for FEV_1 represents a reductionist approach to define severity, and subsequently, the management of COPD (60,61).

Although most COPD is mainly related to smoking, particulate matter exposure, passive smoking, and tuberculosis also predispose to lung function decline and a COPD diagnosis (3,4). It is hypothesised that tuberculosis-related lung parenchymal inflammation may facilitate the destruction of the pulmonary extra-cellular matrix (62). Next, exposure to particulate matter 2.5 micrometres in diameter or less ($PM_{2.5}$) resulted in oxidative stress, emphysematous lesions, small airway remodelling, mucus metaplasia, and pulmonary and systemic inflammation that altogether impaired lung function in mouse models (63,64). Cigarette smoke and $PM_{2.5}$ may also have a synergistic effect on both COPD development and its progression over time (63). Furthermore, the presence of certain COPD clinical phenotypes, defined as “a single or combination of disease attributes that describe differences between individuals with the disease as they relate to clinically meaningful outcomes” (65), could be dependent on the type of adverse exposure that caused an individual to develop COPD in the first place. The lungs of rats exposed to motor vehicle exhaust $PM_{2.5}$ had earlier and more severe neutrophilic airway inflammation, less emphysema, greater numbers of goblet epithelial cells, and thicker small airway walls with collagen deposition compared to rats exposed to biomass fuel $PM_{2.5}$ (64). In addition, COPD patients exposed to tobacco smoke had lower lung function and higher levels of fibrinogen, circulating leukocytes, and monocytes whereas patients exposed to biomass had higher levels of blood Immunoglobulin E (66). These differences may result in distinct

phenotypes of COPD that can potentially be targeted with different therapies in the future.

The ‘treatable traits’ concept for disease management was proposed in 2016 (67) to account for the heterogeneity of COPD (58). Patients may exhibit a broad variety of disease-specific and non-disease-specific traits that can be treated in a more personalised and effective manner (67). Although this concept represents a precision medicine approach to patient care, targeting a diverse set of treatable traits per patient can be resource-intensive and difficult to apply in clinical practice due to fragmented treatment plans (60). To address these concerns, treatable traits can be grouped into subtypes of COPD, called COPD phenotypes (i.e., clusters of disease traits). Unfortunately, the reproducibility of many COPD clusters across cohorts has not been adequately shown (68). Thus, only three clusters are reproducible across cohorts, associated with prognosis, and responsive to therapy: the frequent exacerbator, the COPD/asthma patient, and the emphysema-hyperinflation patient (69). The COPD/asthma phenotype, defined as airflow obstruction that is not completely reversible and accompanied by clinical characteristics associated with increased reversibility, responds relatively well to corticosteroids due to a higher-than-average concentration of eosinophils. The frequent exacerbator phenotype is characterised by patients with two or more exacerbations per year and these individuals should be given long-acting bronchodilators followed by anti-inflammatories and antibiotics as step-up treatments. Emphysema-hyperinflation patients have breathlessness, low exercise tolerance, may have low BMI, and are preferentially treated with bronchodilators and lung-volume reduction interventions in very advanced cases (69). These individuals may also benefit from nutritional support.

Certain patients may still belong to more than one cluster and there is variability in how well a certain cluster characterises each patient that has been grouped into it. Thus, while COPD clusters can account for the heterogeneity of COPD, they are limited because clinical practice deals with individuals and not with groups of patients classified according to a particular clinical phenotype (70). Rather than mutually exclusive subtypes, multiple coexisting disease traits present to varying degrees in each patient. Represented as continuous characteristics, these traits have been shown to be more reproducible (68). But this, again, adds complexity as treatment plans can be more easily established using clusters. Thus, treating each patient as a separate COPD case is likely too complex to apply to clinical practice, however, oversimplifying the disease will be detrimental to many patients who suffer from components of COPD that do not fit neatly into the particular group that they have been labelled into.

A systemic disease

COPD is also a systemic disease that often affects a patient's health outside of the lungs. Many patients suffer from co-occurring chronic conditions. These comorbidities constitute the combined effect of multiple conditions with reference to an index disease (71). They contribute substantially to the burden of disease and mortality and some are more likely to co-exist in COPD patients when compared to age-matched controls (72,73).

There exist patterns of diseases that co-occur with COPD more often than what would be expected by chance because these comorbid conditions either share a common exposure (such as smoking) or some diseases may be a consequence of COPD itself (74). For instance, lung cancer has a strong association with emphysema and is one of the main causes of death in COPD patients (1). Lung cancer and COPD share smoking as a risk factor but chronic inflammation in COPD may contribute to the pathogenesis of lung cancer as well (75). Next, airflow obstruction can increase the risk of adverse cardiac function and result in hypoxemia (59). Third, inflammatory markers from lung inflammation and common risk factors may account for increased risk of comorbidities such as osteoporosis and ischemic heart disease (59). Inhaled corticosteroids are used to reduce exacerbations and improve quality of life in COPD patients but may increase the risk of fractures from osteoporosis (76). Fourth, depression and anxiety are often underdiagnosed in COPD patients and contribute to worse health-related quality of life and prognosis (77). Feelings of depression and anxiety in COPD patients may be the result of patients worrying about their disease, a lack of social interaction due to respiratory symptoms (78), and decreased frequency and quality of emotional support from loved ones (79). Finally, oxidative stress, inflammation, as well as inactivity as a result of COPD symptoms contribute to skeletal muscle wasting and cachexia (59). A reduction in known risk factors and treatment of COPD may reduce the risk and burden of these comorbidities.

Several conditions may complicate or worsen COPD. Gastroesophageal reflux disease may increase the risk of exacerbations in COPD (80). The presence of heart failure may make differential diagnosis difficult due to its sharing of clinical symptoms and signs with COPD (81). Despite this, heart failure is common in COPD as 10 to 30% of COPD patients are diagnosed with it (82). Compared with patients with sleep apnoea and without airflow limitation, COPD patients with sleep

apnoea have more frequent episodes of oxygen desaturation and spend more sleep time in a hypoxemic and hypercapnic state (83). This can lead to cardiac arrhythmias and pulmonary hypertension (1). COPD patients with sleep apnoea (i.e., overlap syndrome) have a worse prognosis than patients diagnosed with either disease alone. Finally, arterial stiffness becomes more pronounced during COPD exacerbations, particularly in those with airway infection, and this, in turn, is associated with inflammation (84). Myocardial damage can accumulate in COPD patients with ischemic heart disease after an acute exacerbation occurs (84).

Similar to its intra-pulmonary components, extra-pulmonary components vary in presentation and severity from patient to patient (60). It is clear that patients with COPD have an increased risk of comorbidities and that these comorbidities may worsen and complicate their disease and its management. Despite these relationships, there is no evidence to support alternative management of COPD due to the presence of comorbidities and *vice versa* (1).

COPD progression

A rapid decline in FEV_1 is not a fixed characteristic of COPD. It is estimated that approximately half of all people who are eventually diagnosed with COPD had a normal maximally attained FEV_1 in early adulthood followed by a rapid decline in lung function (85). The other half had a low maximally attained FEV_1 and a less rapid, age-related decline. In Figure 1.1 below, patients in panels A and C (N= 2207) had normal maximally attained FEV_1 earlier in life. However, the distribution of FEV_1 decline for patients who were subsequently diagnosed with COPD (N= 158 (7%) in panel C) was shifted toward higher rates of decline. Similarly, among patients with low maximally attained COPD (657 patients shown in panels B and D), most patients still had a less rapid decline and were not diagnosed with COPD (Panel B) while 174 patients (26%) tended to have a more rapid decline in lung function (Panel D) leading up to a COPD diagnosis. Patients in Panel C tended to have a more rapid decline than patients in Panel D because lung function deteriorated from a higher peak in early adulthood.

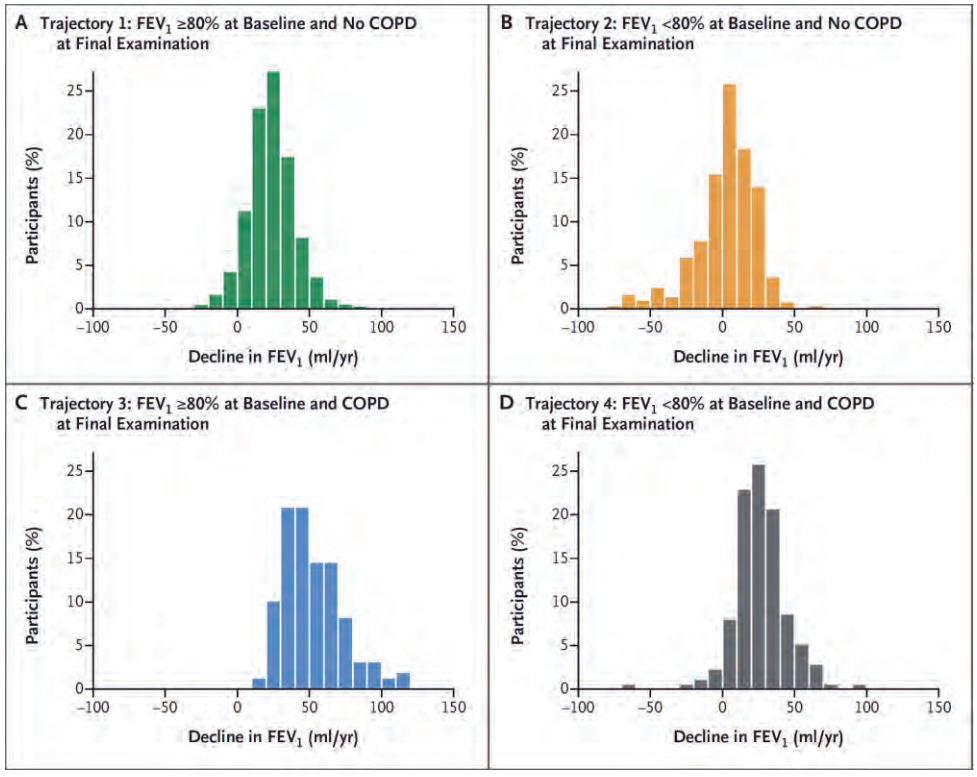


Figure 1.1: The mean decline in FEV1 was 24 ml per year in trajectory 1 (Panel A), 2 ml per year in trajectory 2 (Panel B), 53 ml per year in trajectory 3 (Panel C), and 27 ml per year in trajectory 4 (Panel D). Reproduced with permission from Lange et al. (85)*, Copyright Massachusetts Medical Society.*

Trajectories leading to COPD may represent a stable characteristic associated with prognosis. Indeed, it was also recently shown that patients that followed different lung function trajectories leading up to the diagnosis of COPD have a different risk of mortality (86). COPD developed through normal maximally attained lung function but rapid decline thereafter was associated with an increased risk of respiratory and all-cause mortality compared to COPD developed through low maximally attained lung function and less rapid decline (86).

Although patients can be grouped into certain trajectories to better describe their disease, progression is still highly variable after diagnosis (87). Some patients show stable disease over time while others rapidly progress to more advanced disease (88). In the latter case, patients are more likely to have a worse prognosis such as developing severe breathlessness and exacerbations as well as an

increased incidence of hospitalisations and death (88). Emphysema, worse health-related quality of life (89), and exacerbations can increase the rate of progression (90,91). Lifestyle behaviours such as smoking, diet, and exercise; respiratory insults; exposures such as biomass fuel, air pollution, occupation, respiratory infection; markers of general wellbeing such as socioeconomic status or health-related quality of life; and clinical markers such as BMI and comorbidities may also influence the rate of progression (88,90,92). Most studies have used lung function (typically FEV_1 or FEV_1 % predicted) to objectively measure progression over time (93,94). However, since COPD affects multiple systemic domains, some patients may show stable lung function over time but a worsening of symptoms such as breathlessness (95). Part of the aims of COPD management is to reduce the rate of deterioration. This is difficult if patients are deteriorating from components of COPD that are not being measured. To account for the diversity of COPD, combining multiple domains of the disease into a single overall score and measuring that score serially with patients may be the best approach for monitoring the worsening of COPD over time.

Management and Treatment of COPD – risk versus reward

COPD is treatable but not curable (96). Extra-pulmonary characteristics found in COPD patients contribute to adverse outcomes and are sometimes more treatable than COPD itself (12). The goals of management (including pharmacotherapy) are focused on improving symptoms (e.g. dyspnoea), functional capacity, and quality of life and reducing the frequency and impact of exacerbations (1).

In terms of non-pharmacological treatment, smoking cessation is the single most effective approach for altering the course of COPD and slowing lung function decline. Therefore, all those with COPD who smoke should receive smoking cessation advice (1). Pulmonary rehabilitation can improve many aspects of COPD patient's lives and is an important therapy to consider for any patient willing to participate. For patients with severe breathlessness, pulmonary rehabilitation improves breathlessness symptoms, health status, and exercise tolerance (1,97,98). Previous randomised controlled trials have shown that it also reduces hospitalised exacerbations but observational studies have more mixed results (99). This may reflect either residual confounding within cohort studies or broader patient inclusion criteria in these studies which may result in pulmonary rehabilitation having no impact for some patients. Physical activity, which is a component of

pulmonary rehabilitation, may be severely limited in patients with moderate-to-severe COPD (100) and lack of physical activity predicts decreased quality of life and increased incidence of hospitalisation and mortality (1). The problem is that it is unclear how to best motivate patients to initiate and sustain increased physical activity levels on their own. The other component of pulmonary rehabilitation involves educating individuals on COPD and self-management advice, which initially included information on medications, symptom control, relaxation, and energy conservation but topics on the early recognition and treatment of exacerbations as well as the promotion of physical activity and long-term adherence to regular exercise have been added (101). Malnourished COPD patients may require nutritional supplementation (102) since low body mass and cachexia are associated with mortality (103). Low body weight is common in COPD patients, especially in those with more severe disease (104) and these changes in body weight have been attributed to COPD itself. However, it is known that smoking status also affects body weight in patients without COPD (105,106). Unless the effect of smoking status on body weight is examined in COPD patients, the mechanisms by which weight changes in COPD may remain unknown. Also, non-invasive mechanical ventilation may reduce re-hospitalisation and mortality in stable COPD patients with severe chronic hypercapnia and a history of hospitalisation for acute respiratory failure as well as in patients with an exacerbation (1). Influenza vaccination is recommended for all patients because it can reduce the incidence of lower-respiratory tract infections (107), the number of exacerbations (108), and mortality (1) whereas pneumococcal vaccinations may help patients around 65 years of age or older and younger patients with comorbid heart and lung diseases (109). Long-term oxygen therapy may also benefit many patients with severe resting hypoxemia (1) as it can improve their survival (110).

Effective pharmacologic treatments for COPD patients include long-acting beta2 agonists (LABA) (111,112), long-acting antimuscarinic antagonists (LAMA) (113–116), and LABA/LAMA (117–120), inhaled corticosteroid (ICS)/LABA (121,122) and ICS/LAMA/LABA (123) combinations. A recent Cochrane network meta-analysis of 99 studies and 101,311 participants with advanced COPD showed that LABA/LAMA combination was the best in reducing COPD exacerbations (mostly due to LAMA) and that symptoms and quality-of-life were improved more by combination rather than monotherapies (124). When pharmacological treatment response is less than optimal, the cause may be inhaler technique and/or poor adherence to medication (1). In addition, macrolides (125) and PDE4-inhibitors (126–128) may reduce the burden of exacerbations when combined with inhaled therapies. According to the GOLD 2022 strategy, preferred pharmacotherapy for COPD is based on the classification of patients according to the degree of

symptoms and the frequency of exacerbations of the disease: A (low symptom, low exacerbation risk), B (high symptom, low exacerbation risk), C (low symptom, high exacerbation risk), and D (high symptom and high exacerbation risk) (1). These groups were paired with their associated treatments by matching the burden of COPD with the level of treatment.

Treatments should provide more benefit than harm to a patient's well-being. All treatments come with both financial and time obligations. Unfortunately, treatments for COPD also have very real health side effects. For instance, azithromycin may lead to hearing loss and microbial resistance (125) while ICS-containing therapies may increase the risk of nontuberculous mycobacteria lung infection (129), fractures (130), and pneumonia (124). However, studies have found that eosinophil counts also predict pneumonia risk in COPD patients (131,132) and blood eosinophils may be used as an indicator for positive ICS treatment response (133). Among 643 individuals with COPD from the Copenhagen General Population Study, ICS increased pneumonia risk in both COPD patients with high blood eosinophils ($\geq 0.34 \times 10^9$ cells·L^{-1}) and in a separate stratum consisting of patients with low eosinophils ($<0.34 \times 10^9$ cells·L^{-1}), however, neither estimate was statistically significant (IRR = 2.25; 95% CI: 0.76 to 6.69, and IRR = 1.53; 95% CI: 0.90 to 2.59, respectively) (132). In individuals with clinical COPD (N = 202 with a recent exacerbation, ≥10 pack-years and FEV_1 <70% predicted), the association between ICS and pneumonia was weaker in the low eosinophil group (HR = 1.09; 95% CI: 0.48 to 2.47) and stronger in the high eosinophil group (HR = 6.73; 95% CI: 1.89 to 23.93) probably reflecting that these individuals may be given more rounds and/or higher doses of ICS. Given that some of these estimates are fairly strong (notably in the high eosinophil count group), the low number of patients (and events) means that statistically insignificant findings should not be over-interpreted to mean the lack of an association. Thus, it is still unclear if a higher incidence of pneumonia is caused by higher eosinophil levels or ICS treatment guided by eosinophil levels. Further complicating this issue, a patient meta-analysis of randomised controlled trials found that lower eosinophil counts predict pneumonia (134), and this contrasting conclusion may be due to differences in treatment.

In conclusion, medications may only provide more benefit than harm in a subset of COPD patients with certain characteristics, symptoms, and severities. Each patient needs to be characterised with just enough precision so that treatments can be better tailored on a case-by-case basis without complicating clinical practice. It is important to account for the diversity of COPD in measuring a patient's risk of adverse outcomes so that the risks of treatments can properly be weighed against their benefits.

Multicomponent COPD prognostication – beyond airway obstruction

Prognostic research aims to establish potential associations between future health outcomes and baseline health in patients with certain diseases or conditions in order to influence clinical decision-making, healthcare policy, and patient management (135). The aim is to translate findings from the laboratory and clinical research to clinical practice so that outcomes in patients can be improved. There are four pillars of prognostic research: fundamental prognosis, prognostic factor, prognostic model, and stratified medicine research (135). Prognostic factor research attempts to determine specific factors or biomarkers that are associated with prognosis so that interventions can then modify these targets to improve outcomes (136). Although there is little evidence that FEV_1 can be modified with existing medications (1), it is still a factor that is associated with mortality in COPD patients (137). However, accurate prediction of outcomes often requires multiple prognostic factors in combination (138).

It is well recognized that other factors in combination with FEV_1 may add prognostic information and better reflect disease severity than FEV_1 alone. Multicomponent prognostic models convert baseline values for a combination of factors into estimates of risk of an outcome within a specific period of time for each patient (138). Prognostic models for COPD are tools developed to predict outcomes, such as the risk of death or exacerbations (139). These scores are typically developed using a selection process to combine the most prognostically relevant components that independently add accuracy to risk predictions in one particular patient population (138). Although rare in COPD research, the score is then validated in another population with different characteristics (e.g. separate country, different patient severity group, younger/older patients, etc.) to test its transportability (i.e., generalisability or accuracy in unrelated populations) (140,141). Lastly, the score is tested to show whether or not it influences the behaviour of clinicians (i.e., decision-making) which in turn can affect patient outcomes (140,141).

Since COPD prediction models use multiple components - often including FEV_1 - to predict future outcomes, they are well suited to capture the heterogeneity found in COPD (60,142). Figure 1.2 shows the 10 most common components that are included in COPD prognostic models, with age being the most common regardless of the clinical setting (139). All of these predictors are easily collected in various settings and prognostic scores that include easily measured predictors are more

likely to get used in clinical practice. Several prognostic scores have been developed for COPD to predict mortality including the BODE (BMI, obstruction, dyspnoea, and exercise capacity) (137), the DOSE (dyspnoea, obstruction, smoking, and exacerbation) (143), the COTE (COmorbidity TEst) (52), and the ADO (age, dyspnoea, and obstruction) (144) scores. A large network meta-analysis that included 15,762 patients with COPD from 24 cohorts from the COPD Cohorts Collaborative International Assessment consortium found that the ADO score had the best discriminative performance when compared to the BODE score (difference $AUC_{ADO} – AUC_{BODE}$ =0.015 (95% confidence interval = −0.002 to 0.032); p = 0.08) for predicting 3-year mortality out of 9 other scores. However similar methods should also be used to compare calibration statistics (slope and calibration-in-the-large) across multiple prognostic scores (145,146)**.** The ADO score has been shown to be accurate and simple to use and requires very little space and advanced equipment, making it suitable for use in primary care settings. However, the ADO score has not been sufficiently tested in primary care, where most COPD management takes place (147). It is unclear if the score is transportable to this setting. Multicomponent prediction of exacerbations in COPD has been less successful due to a lack of scores developed using high-quality statistical methods that are practical and easy to use across various clinical settings (148). The Bertens' score (149) is the only COPD prognostic score used to predict exacerbations that has a low risk of bias in its development methodology (139). Recently, another score, the BLISS score, was developed using low risk of bias methodology at the Institute of Applied Health Research, University of Birmingham. This is one of the few prediction models for COPD exacerbations that was developed in primary care. It would be of interest to determine how the two scores compare in predicting exacerbations in patients with more advanced disease than the patients in both score's development cohorts. Once transportability has been shown then the most suitable exacerbation prediction score can be tested for impact on clinical practice decisions and patient outcomes.

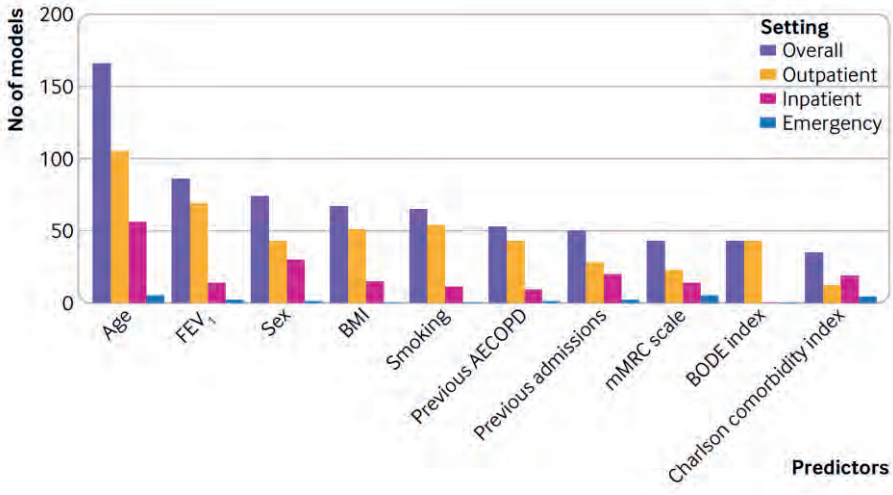


Figure 1.2: The 10 most common components of COPD prognostic scores. Reproduced with permission from Bellou et al. 2019 (139)*, British Medical Association.*

Decisions regarding treatment choices can be informed by risk estimates given by prognostic models (138). Since respiratory treatments come with non-response, side effects, costs, and other inconveniences, treatments may only be beneficial if the predicted risk of mortality (or exacerbation) is high without treatment (138). This risk estimate, given by the prediction model, is then weighed against the risks involved in adhering to certain treatments. Conversely, if treatment is already being taken and the risk of an outcome is low, then it might be better to withhold further treatment. These risk estimates are meant "to assist (not replace) clinicians with their prediction of a patient's future outcome and to enhance informed decision making with the patient" (138). But even before prognostic scores are used in the real world, they should be ready for clinical practice. Some characteristics that improve readiness for clinical practice are the following (138,148):

- validation of the score in a setting outside of the one it was developed in (i.e., external validation);
- that the score is accurate and was developed in an unbiased way;
- the model is supported by leading professionals in the field of COPD;
- a relatively small number of components that are needed to be measured as well as the availability, ease, cost, and known clinical effectiveness of the measurement of components included in the score;
- ease in deriving individual patient risks of the outcome being predicted;

- ability to stratify final scores into treatment groups (i.e., stratified care);
- evidence that the prognostic model makes an impact on treatment decisions and, subsequently, patient outcomes (i.e., an impact study);
- that the score was validated and/or updated recently to reflect the current effects of components on the outcomes.

Although many scores have been developed in COPD, most were developed using a biased methodology (139), some contain too many components or are too difficult to measure, too few have been externally validated or updated, and only the DECAF (Dyspnoea, Eosinopenia, Consolidation, Acidaemia, and Atrial Fibrillation) score (139,150) has received an impact study (151). The latter step is important because "a prognostic model can influence patient outcome or the cost-effectiveness of care only when changes in clinical management are made based on the prognostic information provided" (138). The use of prognostic models (e.g., measuring the components included in each) has costs, especially if the risk of an outcome for an individual has been overestimated (leading to overtreatment and potentially more side effects) or underestimated (clinicians may withhold or stop beneficial treatment). So, quantifying the impact of a prognostic score is needed. Impact studies use (cluster) randomised or before-and-after designs to quantify the effect that risk estimates derived from prognostic models have on clinical practice (140,141) but are very underutilised in COPD research. An impact study using a cluster randomised trial design randomises clinic(s) (as an example) to provide usual care *plus* a prognostic model or usual care alone and the costs of care, and outcomes are ascertainment after a period of time. However, studies that examine these outcomes before and after the introduction of a prognostic model to a single clinic can also be performed (138). This is more cost-effective and can also better facilitate a detailed qualitative examination of any potential changes in the decision-making of clinicians before and after they used the score but is more vulnerable to individual and group-level confounders.

In conclusion, treating COPD as a heterogeneous disease with multiple components may enable a more accurate prediction of mortality and exacerbations as well as tracking of changes in progression on a more personalised level that can then be used to inform treatment decisions.

Aims of the thesis

Although all patients have respiratory symptoms and chronic airflow limitation, COPD is made up of multiple components and is a heterogeneous disease. Many pulmonary and extra-pulmonary features contribute to disease burden and trajectory and may warrant differential treatment and follow-up. COPD research has shifted away from an obstruction-centric focus and is now examining these other features more closely. There is still room to describe components such as symptoms and health behaviours in more detail. In addition, by assessing multiple

components at once in each patient, the variability in COPD severity and progression is accounted for in a more personalised manner. Healthcare providers can then more accurately predict prognosis, and this can then be used for more informed treatment decisions. Although multicomponent scores have been introduced in COPD management, many have not been adequately tested and described. Therefore, this thesis aimed to highlight components beyond FEV_1 and explore how they affect COPD patients as well as validate and expand the role of new and existing multicomponent COPD prognostic scores that include these same components. The specific aims of this thesis are:

- To test if the ADO score is valid in predicting 3-year mortality in incident and prevalent primary care patients, a healthcare setting where the score can reliably assess prognostic outlook.
- To determine if it is potentially beneficial to measure the ADO score serially in primary care patients.
- To answer whether there is a difference in the effects of smoking behaviour and cessation from smoking on body weight between those with COPD compared to those without COPD.
- To examine the long-term trends in severe and moderate-to-severe exacerbations in UK primary care patients by age and sex.
- To test the validity of the BLISS and Bertens' scores in predicting moderate-to-severe and severe exacerbations in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort patients.
- To study and compare prognosis and stability of symptoms among people with normal versus abnormal spirometry.

Outline of the thesis

>>> CHAPTER II: External validation of the updated ADO score in COPD patients from the Birmingham COPD cohort.

Conclusion: The ADO score showed promising discrimination in predicting 3-year mortality in a primary care population including screen-detected patients. It may need to be recalibrated if it is used to provide risk predictions for 1- or 2-year mortality since, in these time-periods, patients with higher predicted mortality risks showed more pronounced overprediction.

>>> CHAPTER III: The stability in the ADO score among UK COPD patients from The Health Improvement Network.

Conclusion: Serial assessment of the ADO score can identify patients with worsening disease and update their prognosis, especially for patients who smoke, are depressed, or have lower BMI.

>>> CHAPTER IV: Evaluating the independent and combined effects of COPD and smoking on BMI trajectory: longitudinal findings from the THIN Primary Care Database

Conclusion: Regardless of COPD status, baseline BMI was highest in former smokers followed by never smokers. Both smoking groups had a similar rate of decline. Among continuous smokers, those with COPD had a more rapid decline. Conversely, quitters with COPD had a more rapid improvement in BMI. Weight loss was not an important mediator in the association between smoking, COPD status, and mortality.

>>> CHAPTER V: Trends in moderate and severe exacerbations among COPD patients in the UK from 2005 to 2013

Conclusion: Women showed a substantially higher incidence rate of any COPD exacerbations, and their rate increased across calendar years. The incidence rates of exacerbations increased during the study period, especially severe exacerbations. Furthermore, incidence rates varied substantially by age group.

>>> CHAPTER VI: External validation of two prognostic scores predicting exacerbations in ECLIPSE COPD patients.

Conclusion: The BLISS score more accurately predicted severe exacerbations but neither model should be used to predict moderate-to-severe exacerbations without first updating their intercepts. Future work should test if the BLISS score can effectively guide patient management.

>>> CHAPTER VII: Persistent respiratory symptoms in individuals with and without normal lung function − a Birmingham COPD cohort study.

Conclusion: Normal spirometry may not rule out the need for further clinical investigation of airway disease and people with pre-COPD may have unmet needs consistent with people with newly identified COPD.

>>> CHAPTER VIII: Summarizes previous chapters, discusses the value and overall direction the thesis is promoting, and details future directions for research and clinical practice.

CHAPTER II: EXTERNAL VALIDATION OF THE UPDATED ADO SCORE IN COPD PATIENTS FROM THE BIRMINGHAM COPD COHORT.

Spencer J Keene[1,2,3], Rachel Jordan[1], Frits M.E. Franssen[3,4], Frank de Vries[2,5], James Martin[1], Alice Sitch[1,6], Alice Turner[1], Andrew P Dickens[1], David Fitzmaurice[7], and Peymane Adab[1]

Affiliations

[1] Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, UK.

[2] Department of Clinical Pharmacy & Toxicology, Maastricht University Medical Center+, Maastricht, the Netherlands.

[3] CIRO, Horn, the Netherlands.

[4] Department of Respiratory Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, the Netherlands.

[5] Utrecht Institute for Pharmaceutical Sciences Utrecht University Utrecht the Netherlands.

[6] NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust, and University of Birmingham, UK.

[7]Clinical Trials Unit, Warwick Medical School, University of Warwick

ABSTRACT

Background: Reviews suggest that the ADO score is the most discriminatory prognostic score for predicting mortality among chronic obstructive pulmonary disease (COPD) patients but a full evaluation and external validation within primary care settings is critical before implementation.

Objectives: To validate the ADO score in prevalent and case-found primary care COPD patients at 3-years and shorter time horizons.

Patients and Methods: 1,892 COPD patients were recruited between 2012 and 2014 from 71 United Kingdom general practices as part of the Birmingham COPD Cohort study. Participants were either on the practice COPD register or screen-detected cases. We validated the ADO score for predicting 3-year mortality with 1-year and 2-year mortality as secondary endpoints using discrimination (area-under-the-curve (AUC)) and calibration plots.

Results: 154 deaths occurred within three years. The ADO score was discriminatory for predicting 3-year mortality (AUC = 0.74; 95% CI: 0.69 to 0.79), and similar for 1- and 2-year mortality (AUC = 0.73; 95% CI: 0.66 to 0.80 and 0.72; 95% CI: 0.67 to 0.76 respectively). The ADO score showed reasonable calibration for predicting 3-year mortality (calibration slope 0.95; 95% CI: 0.70 to 1.19) but overpredicted in patients with higher predicted risks of mortality at 1- (slope = 0.79; 95% CI: 0.45 to 1.13) and 2-year (slope = 0.79; 95% CI: 0.57 to 1.01) mortality.

Discussion: The ADO score showed promising discrimination in predicting 3-year mortality in a primary care population including screen-detected patients. It may need to be recalibrated if it is used to provide risk predictions for 1- or 2-year mortality since, in these time horizons, patients with higher predicted mortality risks showed more pronounced overprediction.

The Chapter was published as:

Keene SJ, Jordan RE, Franssen FME, Vries F de, Martin J, Sitch A, Turner AM, Dickens AP, Fitzmaurice D, Adab P. External validation of the updated ADO score in COPD patients from the Birmingham COPD cohort. Int J COPD 2019; 14:2395–2407.

Results presented as an oral presentation at the European Respiratory Society conference (Madrid 2019)

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality worldwide and is predicted to be the third leading cause by 2030 (4,152). Prognostic scores to predict mortality risk in people with COPD are useful in order to assess disease severity, define intervention options, and facilitate consultations with patients about their prognosis (153). Knowledge of the risk of mortality also allows the benefits of treatments for COPD to be weighed against potential harms, such as side effects, costs, and inconvenience (4) in order to enable informed clinical decision-making. The extent of airflow obstruction, usually assessed by forced expiratory volume in the first second (FEV_1), has long been recognised as an important measure of prognosis and is used for disease staging (4). However, the complex and multifaceted nature of COPD (154,155) has led to the identification of other important predictors of mortality and recognition that combining these in multicomponent indices (52,137,143,156,157) improves prognostic ability. However, before implementation in clinical practice, it is important to evaluate the predictive ability of the prognostic index in different populations. There are two important aspects to such evaluation, including assessment of how well the index can differentiate between those who die and those who remain alive (i.e., discrimination) and the extent of agreement between predicted and observed mortality (i.e., calibration). The latter is particularly important for prognostication (158).

Amongst prognostic indices, the ADO (age, dyspnoea, airflow obstruction) score has wide applicability as it is made up of only three easily measured components (157), overcoming the limitation of many other indices (146). The original ADO score was developed in 2009 (157) to predict 3-year mortality in patients with moderate-to-severe COPD from secondary care and was updated in 2012 in an international cohort from a variety of healthcare settings to improve its generalisability (144). The updated ADO has been externally validated several times (144,145,159,160). However, only two validation studies were in primary care populations (159,160), where most people with COPD are cared for (147). In one of these studies calibration was not assessed (159). The other study only considered 2-year mortality as the outcome and adjusted the intercept of the ADO score (160). A further two studies used populations across primary, secondary, and tertiary settings (144,145). However, no analyses were undertaken to assess the differential performance of the ADO score in each setting.

Our aim was to validate the updated ADO score in COPD patients from a large primary care research cohort (the Birmingham COPD cohort) which included both

previously and newly diagnosed patients and where dyspnoea and lung function were measured under standardized conditions.

METHODS

This paper was written in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis statement (161).

Design

External validation study of a published prognostic score.

Source and Study Population

The characteristics of the Birmingham COPD cohort, which is part of the Birmingham Lung Improvement Studies (BLISS), have been summarized in a previous publication (162). Briefly, COPD patients were recruited from 71 UK general practices across the West Midlands, United Kingdom. For this analysis, cohort patients with diagnosed COPD (aged 40 and over) on practice Quality and Outcomes Framework COPD registers (i.e., prevalent cases) and those with newly detected COPD identified through a case-finding trial (i.e., incident cases),(163) were included. The definition of COPD in incident cases was based on reporting of relevant symptoms in those with airflow obstruction (forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC) <0.7 according to recommendations in the UK guidelines). Baseline assessments took place at cohort entry from 31 May 2012 to 25 June 2014.

Exposure and Outcome Measurements

The ADO score (0-14) was computed from three variables taken at baseline: age, dyspnoea (modified MRC score), and obstruction (FEV_1% predicted). Age was calculated from the patient-reported date of birth, and dyspnoea was assessed by questionnaire using the British Medical Research Council guidelines (164). The nddEasy One Spirometer (ndd, Switzerland) was administered by a researcher trained to international standards to measure FEV_1 before (max eight blows) and after (max six blows) 400µg salbutamol, aiming for three blows within 100 mLs. FEV_1 and FVC recordings were considered useable if they met ATS acceptability criteria and were within 200 mL. The highest recording was then taken (162).

Quality assurance was maintained using real-time quality assessment, with over-reading of spirometry measurements. FEV_1% predicted was estimated using the Global Lung Function Initiative equations (165).

Linked mortality data was obtained through the Office of National Statistics for the period of recruitment until 31 March 2016 through NHS Digital (166). Other patient characteristics including ethnicity, level of deprivation (using Index of Multiple Deprivation derived from home postcode), smoking status, quality of life, and medical history (including self-reported comorbidities and previous exacerbations), were obtained by patient self-report through standardized questionnaires. Body-mass index (BMI derived from height and weight measurements) and exercise capacity (using sit-to-stand test) were obtained by trained researchers using standard protocols at the baseline visit (162).

Patient selection criteria

The ADO score was developed for participants 40 years old and over. Missing baseline mMRC scores or FEV_1% predicted observations were imputed using multiple imputation by chained equations so that all remaining incident and prevalent patients (N= 1,892) could be included in the final analyses (baseline tables show data prior to imputation). Additional auxiliary variables (cardiovascular disease history, cardiovascular disease medication, chronic cough, chronic phlegm, ethnicity, and gender) were used to aid the imputation. The number of imputed datasets used was based on the fraction of missing data for all variables (11%, so 11 MI datasets were used) (167). Death data were complete for all participants under the assumption that patients without a date of death remained alive.

Analysis

Baseline characteristics were compared between prevalent and incident cases as well as between those who died within 3-years of study entry compared to those who did not. Chi-square and Student's t-tests were used for categorical and continuous variables, respectively.

The updated ADO score regression coefficients and intercept (144) were used to compute the predicted probability of 3-year mortality for each eligible cohort participant (Supplementary table 2.1). To assess discrimination, area-under-the-curve (AUC) was estimated with a 95% confidence interval (95% CI) and plotted using AUC-ROC plots (168). Calibration was assessed by comparing the predicted probability to the observed probability of mortality and examined with a calibration plot and calibration slope with 95% CI. Calibration plots (STATA function: *pmcalplot*) displayed observed risk by deciles of the predicted risk and also examined risk at the individual level using Locally Weighted Scatterplot Smoothing

algorithms (169). An estimate of the Calibration-in-the-large (CITL) was used to indicate whether the predictions were systematically too high or too low (169). As MI datasets were used, estimates of the AUC and calibration slope were estimated in each individual dataset, before Rubin's rule was used to combine estimates (170).

Supplementary Table 2.1: Updated ADO regression coefficients and assignment of points for the score

Points	Regression Coefficients	0	2	3	4	5	7
Age (in years)	0.0703	40 - 49	50 - 59		60 - 69	70 - 79	≥80
Dyspnoea (mMRC)	0.2585	0	3	4			
FEV1% predicted	−0.0288	≥81	51 - 64	36 - 50	≤35		

A Kaplan-Meier plot was created according to the ADO score group (0 to 5, 6 and 7, 8 and 9, and 10 to 14). Scores were grouped based on the number of patients. The separation of Kaplan-Meier curves for ADO score groups indicates better discriminative performance.

In secondary analyses (using the same discrimination and calibration methods as above), we evaluated the ability of the ADO index to predict mortality at 1 and 2 years. The period end dates were 1, 2, and 3 years after study entry (i.e., for each mortality endpoint), and these defined the time horizons of interest. If the end date for the time horizon fell on a day after the 31st of March 2016, then the patient was excluded from that time horizon, regardless of whether and at what time they died. Two separate sensitivity analyses were conducted: 1) We estimated the discrimination and calibration estimates for prevalent patients alone and 2) for complete cases (non-missing obstruction and dyspnoea). Prevalent cases were studied alone because the accuracy of the ADO score may be affected by the inclusion of screen-detected patients (which might not reflect usual primary care populations). All analyses were undertaken using STATA (StataCorp, College Station TX, USA).

RESULTS

Out of 1,894 patients in the cohort, two were younger than 40 years of age at baseline, 111 (5.9%) had missing mMRC score, and 102 (5.4%) had missing FEV_1% predicted values (22 (1.2%) were missing both) (Figure 2.1). Before imputing missing mMRC and FEV_1% predicted, there were 1,392 prevalent and 309 incident patients (total 1,701). The median observation time was 2.78 years (minimum 1.52 and maximum 3.58 years). The average age was 68.4 years old and 651 (38.3%) of the patients were female. The majority (79.5%) had mild to moderate airflow obstruction (50.6% with GOLD stage II) and the mean ADO score at baseline was 7.0 (SD 2.4). 124 (7.3%) deaths occurred within 3-years of observation time, 116 (94%) of which occurred in the prevalent cases.

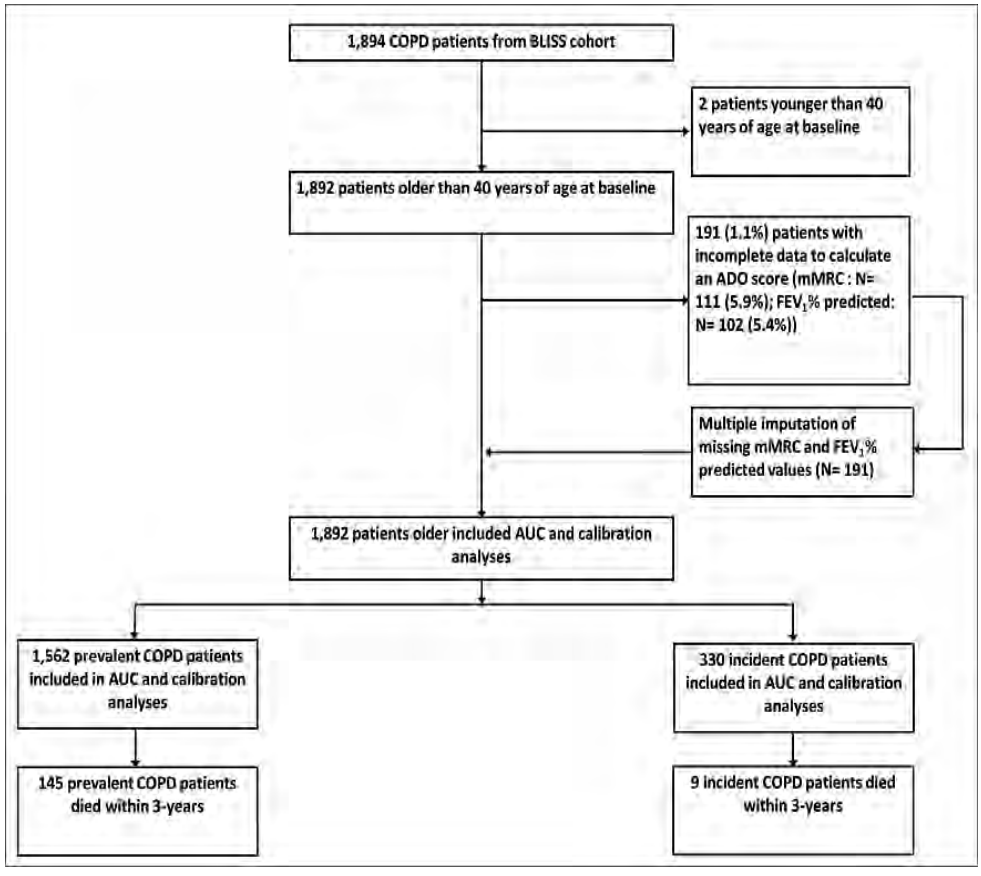


Figure 2.1: Flow of BLISS patients into the final analysis sample.

When compared to incident patients, prevalent patients tended to have a worse baseline ADO score (older age, more severe obstruction, and worse breathlessness), lower exercise capacity scores, more comorbidities, were more likely to report a worse health-related quality of life score, had more former smokers, and were more likely to report a respiratory hospitalisation and at least one exacerbation in the previous 12 months (Table 2.1).

Table 2.1: Comparison of baseline characteristics of existing COPD cases with those who were screen-detected (N=1,892).

	Prevalent Cases	Incident Cases
	N= 1,562	N= 330
Female- N (%)	600 (38.4)	129 (39.1)
Age in years- N (%)		
40 - 49	49 (3.1)	19 (5.8)
50 - 59	185 (11.8)	69 (20.9)
60 - 69	587 (37.6)	127 (38.5)
70 - 79	532 (34.1)	114 (34.6)
80+	209 (13.4)	≤5
GOLD[b] – N(%)		
Mild (FEV_1>= 80% of normal)	330 (21.1)	181 (54.9)
Moderate (FEV_1 >= 50 & <80% of normal)	779 (49.9)	131 (39.7)
Severe (FEV_1 >= 30 & <50% of normal)	303 (19.4)	6 (1.8)
Very Severe (FEV_1 >= 0 & <30% of normal)	59 (3.8)	≤5
Missing	91 (5.8)	11 (3.3)
FEV_1 % Predicted – Mean (SD)	64.6 (20.3)	82.5 (16.6)
FEV_1/FVC ratio – Mean (SD)	0.55 (0.13)	0.63 (0.08)
mMRC dyspnea – N (%)		
0	238 (15.2)	108 (32.7)
1	314 (20.1)	98 (29.7)
2	320 (20.5)	65 (19.7)
3	261 (16.7)	22 (6.7)
4	331 (21.2)	24 (7.3)

	Missing	98 (6.3)	13 (3.9)
Baseline ADO – Mean (SD)		7.41 (2.35)	5.20 (1.93)
Baseline ADO groups – N (%)			
	0 to 5	265 (17.0)	170 (51.5)
	6 to 7	471 (30.2)	101 (30.6)
	8 to 9	392 (25.1)	37 (11.2)
	10 to 14	264 (16.9)	≤5
	Missing	170 (10.9)	21 (6.4)
White British/Mixed British – N (%)		1,311 (83.9)	278 (84.2)
Other – N (%)		126 (8.1)	27 (8.2)
	Missing	125 (8.0)	25 (7.6)
IMD[c] Deprivation Score – N (%)			
	most deprived - Quintile 1	317 (20.3)	51 (15.5)
	Quintile 2	293 (18.8)	75 (22.7)
	Quintile 3	282 (18.1)	78 (23.6)
	Quintile 4	332 (21.3)	62 (18.8)
	least deprived - Quintile 5	329 (21.1)	53 (16.1)
	Missing	9 (0.6)	11 (3.3)
Exercise capacity[d] – N (%)			
	worst - 0 to 9	82 (5.3)	12 (3.6)
	10 to 19	654 (41.9)	86 (26.1)
	20 to 29	437 (28.0)	139 (42.1)
	30 to 39	34 (2.2)	26 (7.9)
	best - 40 to 50	≤5	≤5
	Missing	350 (22.4)	64 (19.4)
BMI groups – N (%)			
	0 - 18.49	33 (2.1)	≤5
	18.50 - 24.99	391 (25.0)	67 (20.3)
	25.00 - 29.99	571 (36.6)	111 (33.6)
	30.00 +	501 (32.1)	109 (33.0)
	Missing	66 (4.2)	40 (12.1)
Smoking group – N (%)			
	Never Smoker	148 (9.5)	45 (13.6)
	Current Smoker	404 (25.9)	102 (30.9)
	Former Smoker	879 (56.3)	159 (48.2)

	Missing	131 (8.4)	24 (7.3)
HRQL [e] Category – N (%)			
	Low Impact - 0 to 9	149 (9.5)	75 (22.7)
	10 to 19	399 (25.5)	112 (33.9)
	20 to 29	420 (26.9)	55 (16.7)
	Severe Impact - 30 to 40	179 (11.5)	9 (2.7)
	Missing	415 (26.6)	79 (23.9)
Exacerbation in last 12 months – N (%)		887 (56.8)	80 (24.2)
	Missing	100 (6.4)	17 (5.2)
Cardiovascular Disease History – N (%)		875 (56.0)	140 (42.4)
Any Cancer – N (%)		187 (11.9)	40 (12.1)
	Missing	224 (14.3)	24 (7.3)
Asthma – N (%)		618 (39.6)	86 (26.1)
	Missing	216 (13.8)	29 (8.8)
Osteoporosis – N (%)		113 (7.2)	24 (7.3)
	Missing	308 (19.7)	34 (10.3)
Depression – N (%)		282 (18.1)	71 (21.5)
	Missing	255 (16.3)	30 (9.1)
Respiratory Hospital Admission in previous 12 Months – N (%)		97 (6.2)	≤5

Missing rows were added only for variables with missing data.

Bold denotes statistical significance

[a] P-value describes differences in characteristics between cohorts without accounting for missing as a separate category. Chi-square test for categorical data and Student's T-test for continuous data.

[b] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) categories of airflow limitation

abbreviations: FEV_1, forced expiratory volume in one second; MRC, medical research council; HRQL, health-related quality of life.

[c] Based on the Index of Multiple Deprivation (IMD) 2010. Lower quintiles indicate more deprivation

[d] assessed using the sit-to-stand test

[e] Based on the COPD Assessment Test (CAT)

Table 2.2 shows a comparison of characteristics of patients according to whether or not they were alive within 3-years of observation time. Patients who died were older and had a more severe obstruction and dyspnoea (all P<0.001) which resulted in a higher baseline ADO score (mean (SD) score 8.98 (2.14)) compared to those who remained alive (6.85 (2.39)). Patients who died were also less likely to be female, had poorer exercise capacity, lower BMI, were more likely to have a severe impact of COPD on health-related quality of life, were more likely to have cardiovascular comorbidity, and were more likely to report respiratory hospitalisation in the 12 months before baseline compared to those who remained alive.

Table 2.2: Baseline Characteristics of participants (N=1,892) by whether or not they had an event at 3-years.

	Alive at 3-years (N=1,738)	Dead at 3-years (N=154)
Female-N(%)	684 (39.4)	45 (29.2)
Age in years-N(%)		
40 - 49	66 (3.8)	≤5
50 - 59	248 (14.3)	6 (3.9)
60 - 69	671 (38.6)	43 (27.9)
70 - 79	589 (33.9)	57 (37.0)
80+	164 (9.4)	46 (29.9)
GOLD - N(%)		
Mild (FEV1>= 80% of normal)	497 (28.6)	14 (9.1)
Moderate (FEV1 >= 50 & <80% of normal)	844 (48.6)	66 (42.9)
Severe (FEV1 >= 30 & <50% of normal)	267 (15.4)	42 (27.3)
Very Severe (FEV1 >= 0 & <30% of normal)	46 (2.7)	14 (9.1)
Missing	84 (4.8)	18 (11.7)
FEV1 % Predicted – Mean (SD)	68.8 (20.6)	55.3 (20.1)
FEV1/FVC ratio - Mean (SD)	0.57 (0.13)	0.52 (0.14)
mMRC Dyspnoea – N (%)		
0	327 (18.8)	19 (12.3)
1	396 (22.8)	16 (10.4)
2	357 (20.5)	28 (18.2)
3	258 (14.8)	25 (16.2)

4	308 (17.7)	47 (30.5)
Missing	92 (5.3)	19 (12.3)
Baseline ADO - Mean (SD)	6.85 (2.39)	8.98 (2.14)
Baseline ADO groups – N (%)		
low risk - 0 to 5	428 (24.6)	7 (4.6)
6 to 7	548 (31.5)	24 (15.6)
8 to 9	390 (22.4)	39 (25.3)
high risk - 10 to 14	211 (12.1)	54 (35.1)
Missing	161 (9.3)	30 (19.5)
White British/Mixed British – N (%)	1,455 (83.7)	134 (87.0)
Other – N (%)	142 (8.1)	11 (7.1)
Missing	141 (8.1)	9 (5.8)
IMD** Deprivation Score – N (%)		
more deprived - Quintile 1	340 (19.6)	28 (18.2)
Quintile 2	327 (18.8)	41 (26.6)
Quintile 3	340 (19.6)	20 (13.0)
Quintile 4	359 (20.7)	35 (22.7)
less deprived - Quintile 5	354 (20.4)	28 (18.2)
Missing	18 (1.04)	≤5
Sit-to-Stand Test - N (%)		
0 to 9	83 (4.8)	11 (7.1)
10 to 19	674 (38.8)	66 (42.9)
20 to 29	555 (31.9)	21 (13.6)
30 to 39	59 (3.4)	≤5
40 to 50	8 (0.5)	0
Missing	359 (20.7)	55 (35.7)
Body-Mass Index (BMI) groups – N (%)		
Underweight - 0 - 18.49 kg/m2	28 (1.6)	8 (5.2)
Normal - 18.50 - 24.99 kg/m2	415 (23.9)	43 (27.9)
Overweight - 25.00 - 29.99 kg/m2	624 (35.9)	58 (37.7)
Obese - 30.00 + kg/m2	576 (33.1)	34 (22.1)
Missing	95 (5.5)	11 (7.1)
Smoking group – N (%)		
Never Smoker	184 (10.6)	9 (5.8)
Current Smoker	465 (26.8)	41 (26.6)
Former Smoker	948 (54.6)	90 (58.4)

	Missing	141 (8.1)	14 (9.1)
CAT score Δ (HRQL) Category – N (%)			
	Low - 0 to 9	204 (11.7)	20 (13.0)
	10 to 19	479 (27.6)	32 (20.8)
	20 to 29	437 (25.1)	38 (24.7)
	High - 30 to 40	158 (9.1)	30 (19.5)
	Missing	460 (26.5)	34 (22.1)
Exacerbation in last 12 months – N (%)		888 (51.1)	79 (51.3)
	Missing	99 (5.7)	18 (11.7)
Cardiovascular Disease History – N (%)		908 (52.2)	107 (69.5)
Any Cancer – N (%)		203 (11.7)	24 (15.6)
	Missing	222 (12.8)	26 (16.9)
Asthma – N (%)		653 (37.6)	51 (33.1)
	Missing	216 (12.4)	29 (18.8)
Osteoporosis – N (%)		128 (7.4)	9 (5.8)
	Missing	307 (17.6)	35 (22.7)
Depression – N (%)		328 (18.9)	25 (16.2)
	Missing	256 (14.7)	29 (18.8)
Respiratory Hospital Admission in previous 12 Months – N (%)		77 (4.4)	23 (14.9)

Missing rows were added only for variables with missingness.
**Based on the Index of Multiple Deprivation (IMD) 2010. Lower quintiles indicate more deprivation
Δ Based on the COPD Assessment Test (CAT)
abbreviations: FEV1, forced expiratory volume in one second; MRC, medical research council; HRQL, health-related quality of life.

Figure 2.2 shows a Kaplan-Meier plot of the survival of patients according to their ADO score at baseline. The survival curves are well separated which indicates good discrimination. Patients with an ADO score of 10 or higher had nearly twelve times the rate of death when compared to patients with an ADO of 0 to 5.

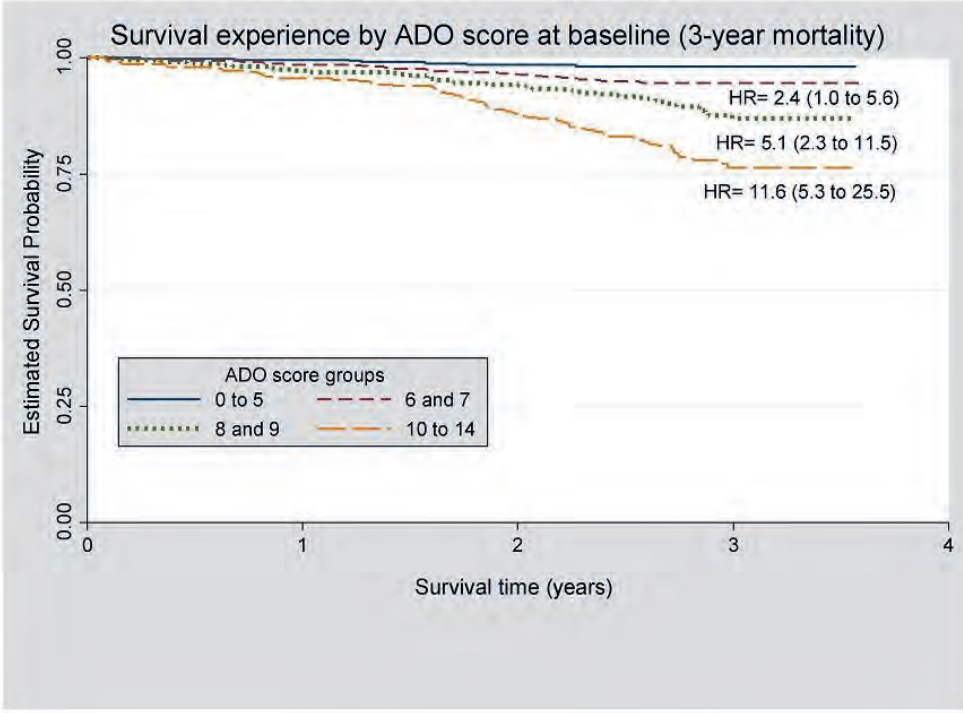


Figure 2.2: Association between ADO score groups and mortality. ADO score 0 to 5 was used as the reference group (N= 1,701).

Figure 2.3 shows AUC and calibration plots for prevalent and incident cases. 1,892 patients were available after imputing missing mMRC and FEV_1% predicted observations which added 30 more deaths (total equal to 154 deaths) within 3-years of observation time. For 3-year mortality (N= 980), the ADO score was able to discriminate fairly well between patients who died (N= 98) and those who remained alive (AUC= 0.74; 95% CI: 0.69- 0.79). Discriminative ability remained consistent for 1-year (N= 1,892, 37 died; AUC=0.73; 95% CI: 0.66 – 0.80) and 2-year (N= 1,876, 93 died; AUC= 0.72; 95% CI: 0.67 – 0.77) mortality. Calibration plots showed that the ADO score accurately predicted 3-year mortality (calibration slope= 0.95; 95% CI: 0.70 to 1.19) but overprediction was evident in those with higher predicted risks of mortality at 1 (0.79; 95% CI: 0.45 to 1.13) and 2-years (0.79; 95% CI: 0.57 to 1.01) time horizons. Predictions were too high (i.e., CITL< 0) at all time horizons, however, these improved as the time horizons lengthened.

Re-introducing cases that died within a period but with period end dates after the 31 March 2016 only affected the 3-year mortality outcome (N=1,036) and resulted in worse discrimination (AUC= 0.712; 95% CI: 0.670 to 0.755) and calibration (slope= 0.820; 95% CI: 0.620 to 1.020) but a more accurate intercept (CITL = -0.281; 95% CI: -0.640 to 0.079). This post-hoc analysis was performed to ensure that patients who died within a time horizon were not excluded since, despite having a reduced follow-up time compared to the time-horizon for 3-year mortality, the outcome was still ascertained and not unknown.

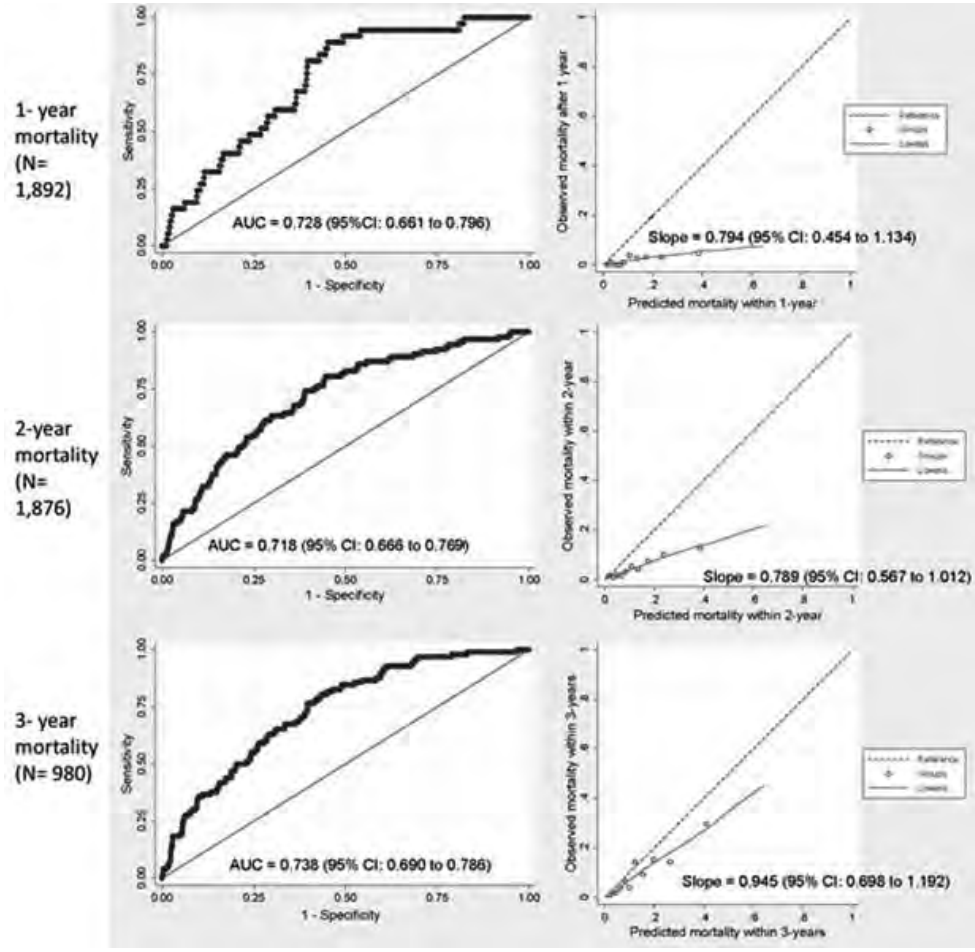


Figure 2.3: AUC plots (left) and calibration slopes (right) for ADO score validation at 1-, 2-, and 3-year time horizons (going top to bottom) comparing observed and predicted mortality for incident and prevalent cases.

Sensitivity analysis with only prevalent patients showed similar results for discriminative performance, calibration slopes, and CITL (Supplementary Table 2.2). After re-introducing prevalent patients who died within 3-years but had less than 3-years of follow-up (N = 1,027), the discriminative power (AUC = 0.74; 95%CI 0.69 to 0.78) and calibration slope were similar (0.92; 95% CI: 0.71 to 1.14) but the CITL (-0.192; 95% CI: -0.558 to 0.175) was more accurate when compared to the prevalent cases. In complete cases, the calibration slope was decreased to 0.73 at 1-year mortality when compared to the analysis that included all cases. At

3-year mortality, calibration slope increased to 1.08 while discrimination also showed an increase, to 0.77. However, after reintroducing complete cases who died within 3-years but had less than 3-years of follow-up (N = 917), the accuracy decreased for discrimination (AUC = 0.73; 95% CI: 0.68 to 0.77) and calibration slope (slope = 0.857; 95% CI: 0.638 to 1.076) but improved for the intercept (CITL = - 0.333; 95% CI: -0.721 to 0.055) when compared to the complete cases from Supplementary Table 2.2.

Supplementary Table 2.2: Sensitivity analysis of accuracy measures in complete cases and prevalent cases.

	Prevalent Cases (N= 1,562)	Whole sample (N= 1892) ^	Complete Cases (1,701) *
1-year mortality			
No. of events	34	37	28
AUC (95% CI)	0.721 (0.657 to 0.786)	0.728 (0.661 to 0.796)	0.717 (0.639 to 0.795)
Calibration slope (95% CI)	0.808 (0.434 to 1.182)	0.794 (0.454 to 1.134)	0.727 (0.349 to 1.105)
CITL (95% CI)	(-)2.40 (-3.03 to -1.78)	(-)2.43 (-3.03 to -1.82)	(-)2.69 (-3.39 to -1.99)
2-year mortality			
No. of events	86	93	76
AUC (95% CI)	0.712 (0.660 to 0.764)	0.718 (0.666 to 0.769)	0.727 (0.669 to 0.784)
Calibration slope (95% CI)	0.803 (0.559 to 1.046)	0.789 (0.567 to 1.012)	0.807 (0.566 tot 1.048)
CITL (95% CI)	(-)1.43 (-1.85 to -1.01)	(-)1.45 (-1.86 to -1.05)	(-)1.52 (-1.96 to -1.07)
3-year mortality			
No. of events	98	98	124
AUC (95% CI)	0.738 (0.690 to 0.786)	0.738 (0.690 to 0.786)	0.773 (0.723 to 0.822)
Calibration slope (95% CI)	0.945 (0.698 to 1.192)	0.945 (0.698 to 1.192)	1.08 (0.801 to 1.361)

CITL (95% CI)	(-)0.558 (-0.975 to -0.141)	(-)0.558 (-0.975 to -0.141)	(-)0.498 (-0.948 to -0.049)

*Only cases with complete dyspnoea and obstruction measurements.
^Results also presented in Figure 2.3 (but CITL also included)

DISCUSSION

In this external validation study in a primary care COPD population which included screen-detected and prevalent cases, we found that the updated ADO score (144) was discriminatory with an AUC of 0.74 for predicting 3-year mortality. Discrimination remained stable when predicting 1- and 2-year mortality. However, we found that the ADO score tended to overpredict mortality among the few patients with higher predicted risks of mortality at 1- and 2-year time horizons.

Our findings of an AUC of 0.74 is lower than the development model (AUC= 0.85) (144) but consistent with estimates from two other studies that validated the ADO score for predicting 3-year mortality, one in primary care (AUC= 0.724, 95% CI: 0.719–0.730; mean FEV_1% predicted of participants: 59.5) (159) and the other across multiple healthcare settings (AUC= 0.73, 95% CI: 0.70-0.76; FEV_1% predicted 65.9) (144). However, a third study used a network meta-analysis to pool data on patients across many healthcare settings and found that the discriminative performance of the ADO score was below 0.70 but still better than nine other prognostic scores (145). At 1 and 2-years mortality, our validation findings are consistent with the results of one primary care study (1-year AUC= 0.720; 95% CI: 0.710 – 0.729); 2-year AUC= 0.725; 95% CI: 0.718 – 0.731)) (159), but slightly less accurate than a second study (2-year AUC= 0.78; 95% CI: 0.71–0.84) (160) since the upper CI of our 2-year AUC estimate is slightly lower than 0.78.

Accurate calibration is particularly important for evaluating prognostic models because predicted and observed risks need to closely match for predictions to be clinically useful (158). This is the first study that reports the calibration slope of the ADO score when predicting 3-year mortality. In addition to 3-year mortality, prediction using shorter time frames are important for end-of-life care because clinicians rely on multicomponent prediction models to identify patients nearing the end of life who may benefit from palliative care (171). No other studies have assessed calibration for shorter time horizons without adjusting the model. We have shown that overprediction was more pronounced in patients with higher predicted risks of mortality for these time horizons. Thus, our findings suggest that

recalibration, for example by using statistical shrinkage techniques (172) is needed, for the ADO score to better predict mortality over a short time horizon.

Our study overcomes several limitations found in previous validation studies. For example, we used recommended statistical approaches for predicting mortality in a validation study. Using a research dataset, such as the Birmingham COPD cohort, has the advantage of more accurate and higher quality measurements at prescribed time points, particularly for spirometry. On the other hand, the Birmingham COPD cohort is not completely representative of all primary care patients with COPD. Ethnic diversity was limited. Additionally, patients needed to be mobile to take part in the cohort study, and therefore, patients with more severe disease who were housebound were more likely to be excluded. Since we used a fixed ratio (based on UK guideline recommendations) instead of a lower limit of normal of FEV1/FVC to define COPD, overdiagnosis may have occurred in older patients (10). However, the ADO score was developed in a population where COPD was defined using the fixed ratio (157), and using the lower limit of normal could lead to underdiagnosis compared to expert opinion (14). Furthermore, in a study of 24,207 US adults from 4 cohorts, COPD-related hospitalization and mortality were not significantly different when using the fixed ratio of FEV1/FVC < 0.70 compared to the lower limit of normal to define COPD (12). This indicates that our results would not be very different if we had used the lower limit of normal to define our cohort. Ideally, COPD prognostic scores should be used in patients with COPD and borderline COPD. We included screen-detected COPD patients who had very few deaths because they were a smaller group than the prevalent cases, tended to be younger, were more likely to have either exacerbation and/or cardiovascular disease history, and had decreased severity of symptoms such as obstruction. However, other studies have not included screen-detected patients despite at least fifty percent of the COPD population remaining undiagnosed worldwide (173). It is important to assess the validity of prognostic indices to predict mortality in this population to inform treatment decisions. Finally, a very small number of deceased patients may have had delayed death registration due to a variety of reasons such as suspicious, unexpected, or accidental deaths (174). In addition to the loss of power (i.e., fewer deaths), if patients were considered alive when they were truly dead then this would result in weaker prognostic accuracy.

Conclusion

It is well-known that prognostic scores are rarely used in clinical practice for managing COPD patients, especially in primary care (153). Although the ADO

score is attractive because of its ease of measurement and calculation in a primary care setting and has relatively good discriminative ability, recalibration is needed to improve risk prediction for shorter time frames. Currently, when predicting 1 and 2-year mortality, the ADO score may not be accurate in primary care populations because overprediction was evident in those with higher predicted risks of mortality and COPD patients may be given treatment that is not needed as a result.

CHAPTER III: THE STABILITY OF THE ADO SCORE AMONG UK COPD PATIENTS FROM THE HEALTH IMPROVEMENT NETWORK

Spencer J. Keene[1,2,4], Peymane Adab*[1], Frank de Vries[2,3], Frits M.E. Franssen[4,5,6],

Alice Sitch[1], James Martin[1], Tom Marshall[1], Rachel Jordan[1]

Affiliations

[1] Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom.

[2] Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+, Maastricht, the Netherlands

[3] Utrecht Institute for Pharmaceutical Sciences Utrecht University, Utrecht the Netherlands.

[4] CIRO+, Horn, the Netherlands

[5] Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands

[6] NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands.

ABSTRACT

Background: The ADO score (age, dyspnoea, airflow obstruction) predicts 3-year overall mortality among chronic obstructive pulmonary disease (COPD) patients. Information on the changes in COPD prognostic scores is sparse and it is unclear if the ADO score should be measured serially.

Methods: We followed 4,804 UK COPD patients with ≥3 ADO measurements from The Health Improvement Network (2005 to 2014) in a retrospective open cohort design. Patient's ADO scores were calculated once per year unless an obstruction or dyspnoea measurement was missing. Cox regression models assessed the independent role of serial ADO scores on mortality. The association between baseline patient characteristics and long-term change in ADO scores was assessed using linear mixed effect models.

Results: Fewer than 7% of patients had worsened (i.e., increased) by ≥1 point per year after a median follow-up of 4.4 years. There was strong evidence that patients with more rapid worsening in ADO scores had increased mortality (hazard ratio= 2.00 per one unit increase in ADO per year; 95% CI: 1.59 to 2.52). More rapid ADO score worsening was seen among current (rate difference= 0.059; 95% CI: 0.031 to 0.087; P=0.001) and former smokers (0.028; 0.003 to 0.054; P=0.032) and patients with depression (0.038; 0.005 to 0.071; P=0.022) while overweight (-0.0347; -0.0544 to -0.0150; P=0.001) and obese (-0.0412; -0.0625 to -0.0198; P<0.001) patients had a less rapid ADO score worsening.

Discussion: Serial assessment of the ADO score can identify patients with worsening disease and update their prognosis, especially for patients who smoke, are depressed, or have lower BMI.

The Chapter was published as:

Keene SJ, Adab P, de Vries F, et al. The stability of the ADO score among UK COPD patients from The Health Improvement Network. ERJ Open Res 2020; 6: 00196-2019 [https://doi.org/10.1183/23120541.00196-2019].

Results presented as an oral presentation at the European Respiratory Society conference (Madrid 2019)

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disease confirmed by the presence of respiratory symptoms in combination with non-reversible airflow limitation (175). Disease progression is not uniform for all patients, and 'rapid decliners' have been defined as those with an accelerated decrease in forced expiratory volume in 1 second (FEV_1) (93,95,176,177). However, it is now recognized that other components of COPD contribute to its worsening (2,95,178,179). Multicomponent prognostic scores can better evaluate the risk of deterioration or death compared to FEV_1 alone as they combine multiple domains of COPD. The ADO score (144) combines three easily accessible components (age, dyspnoea, airflow obstruction) and accurately predicts 3-year mortality (145).

However, it is unclear whether or not the ADO score should only be measured at a single point in time (180). The ADO score may change differently with certain patient characteristics. Deterioration or treatment response may also alter its rate of change and these changes may be predictive of survival. Therefore, it may be important to review and revise mortality predictions in order to better guide management. Information on the changes in prognostic scores for COPD is sparse and no studies have examined the serial measurement of prognostic scores in primary care.

We sought to determine if it is useful to measure the ADO score serially in primary care COPD patients. Our objectives were to examine 1) how serial ADO scores change over time, 2) whether this change was prognostically relevant, and 3) which characteristics are related to the rate of change in ADO scores.

METHODS

Study Design

A register-based retrospective open cohort study was conducted according to the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data Statement (181).

Data Source

The Health Improvement Network (THIN) is a longitudinal, clinical primary care database that contains anonymized and validated data on diagnoses, symptoms, hospital referrals, discharge summaries, lifestyle, mortality, prescribing, and clinical

and laboratory tests. THIN covers about 6% of the United Kingdom population (182).

Study Population

Patients from THIN were included in the study population if they had a current recorded COPD diagnosis Read code (183) assigned by the general practitioner, on (i.e., previously diagnosed patients) or after 1 April 2005 (i.e., newly diagnosed patients). In addition, patients were only included if they had been registered with the practice by 1 April 2004 (i.e., patients moving into the practice at later time-points were excluded) and were alive and contributing data for at least one day after 1 April 2005. This date was chosen because it represents one year after the introduction of the Quality and Outcomes Framework (183). In order to accurately estimate the change in ADO score over time, patients were only included in the sample if a minimum of three ADO scores were available (either consecutive or non-consecutive years). Patients younger than 40 years of age in the year of their COPD diagnosis were also excluded as they comprise a minority of the COPD population and are more likely to have a different disease trajectory due to primary asthma or a genetic predisposition such as alpha1-antitrypsin deficiency. Their end date was the earliest of the date of death, the date the patient left the practice, the last practice collection date, or 1 April 2014.

Patient characteristics

We obtained sociodemographic data for each participant including sex and Townsend deprivation quintile based on their home postcode (0 to 5 [most deprived] - last value recorded). The latest recorded status at any time before study entry was used to define body-mass index categories (underweight (<18.5), normal (18.5 to <25), overweight (25 to <30), obese (30+)) (184), and smoking status (never, former, current). Comorbidities such as ischaemic heart disease, asthma (185), diabetes, heart failure, and vascular disease (including transient ischaemic attack, stroke, or peripheral arterial disease (TIA-PAD)) were noted as present if there was a relevant clinical code at any time before study entry. Similar to previous studies (173,186), a clinical code within the previous 3 years of study entry was used to determine the presence of anxiety and depression. Treatments for COPD were reported present if there was a relevant record of prescription one year before study entry. Data on the following treatments was available: referral to pulmonary rehabilitation (PR), long-acting antimuscarinic agent (LAMA) prescription (tiotropium), short-acting antimuscarinic agent (SAMA) prescription (ipratropium), long-acting beta-2 antagonists (LABA) prescription (consisting of salmeterol, formoterol, or indacaterol), short-acting beta-2 antagonists (SABA) prescription (salbutamol or terbutaline), and inhaled corticosteroids (ICS) (consisting of budesonide, fluticasone, and beclomethasone) containing prescription (ICS only, ICS + LAMA, ICS + LABA, or ICS + LAMA + LABA).

Outcomes

Serial ADO scores

The overall ADO score is comprised of scores assigned to levels for each of its three components: age, mMRC, and FEV_1% predicted. Points were assigned according to the updated ADO publication (144) and is also shown in Supplementary Table 2.1. The study period (2005-2014) was broken up into intervals lasting from 1st April to 31st March to reflect years of data capture from routine primary care records. In routine practice, ADO score components are recorded sporadically. Therefore, we calculated the score once per interval, choosing the latest available values for each component in each interval. If either FEV_1 or mMRC was not recorded in a certain interval, the score was missing for that interval. The date of each calculable ADO score was designated as the latest date of the mMRC or FEV_1 components in each interval. Supplementary Box 3.1 provides the rules used to convert raw FEV_1 measurements into FEV_1% predicted.

Mortality

All-cause mortality was also a dependent variable for our time-to-first event analyses. Mortality information was derived from General Practitioners who recorded the deaths of their patients after receiving this information from a variety of sources, mainly hospital discharge summaries and patient relatives (187).

Follow-up

For our investigation of factors associated with serial ADO scores, the start of follow-up was designated as the date of the baseline ADO score. However, for the time-to-event analysis of the association between change in ADO score and mortality, follow-up time began with the last ADO score taken from each patient since the change in ADO score was our main exposure variable.

Supplementary Box 3.1: Rules used to convert raw FEV1 into FEV1% predicted

FEV1% predicted: For certain observations, it was necessary to convert raw FEV1 values to FEV1% predicted. FEV1 units were extracted from THIN and showed that raw FEV1 may be in litres, % predicted, or with a missing unit. The FEV1 unit variable had substantially more missingness than the raw FEV1 and was thus found to be unreliable. We used four assumptions to translate raw FEV1 into % predicted.

1. If raw FEV1 was greater than or equal to 0.1 and less than 0.3 then these values were multiplied by 100 to obtain FEV1% predicted. This was done because, based on clinical advice, it is unlikely that a patient would have an FEV1 that is below 0.3 litres unless the measurement was erroneously taken.
2. If the FEV1 raw value was greater than or equal to 10 and less than or equal to 160 then it was assumed that this was already FEV1% predicted.
3. If raw FEV1 was less than 10 and greater than or equal to 0.3, this represented a litre value. In these instances, we had to calculate expected FEV1 values for each patient for each year using that patient's age, height, and gender. The equation (called HSE) to calculate expected FEV1 values was developed specifically for the English population (359) and gives very similar results to the GLI equations (165) , the latter of which seemed more suitable for more diverse populations and for international cohorts. The HSE equation is given below.

$$expectedFEV1 = e^{(intercept+b1[age]+b2[age^2]+b3(\ln[height]))}$$

4. If after 1 through 3, the converted FEV1% predicted remained greater than 160 or less than 10, then we assumed that these were errors and we converted these measurements to missing observations.

Statistical Analysis

Simple linear regression was used to assign rates of change in ADO scores over time to patients. We defined a stable ADO score as a change between ≥ -0.5 and ≤ +0.5 points per year. Patients with ADO score changes above and below this range were defined as worsening (i.e., increasing) and improving (i.e., decreasing) ADO score patients, respectively. We then compared baseline characteristics across

these groups. Multivariable Cox regression models were used to calculate the hazard ratio (HR) for mortality. Here, we used each individual's change in ADO score over time as a continuous exposure variable and adjusted for the following baseline covariates: ADO score, age, dyspnoea, obstruction, number of ADO measurements, sex, BMI, smoking, and selected comorbidities. These covariates were agreed upon by the research team, supported by clinical evidence from the literature. Secondary analyses examined the same association using the ADO score change groups (from above) as well as separately examing the last ADO score as the variables of interest. Finally, using all ADO scores for each participant as the outcome, we built linear mixed-effect models to investigate the effect of each baseline characteristic on the change in ADO scores over time. Each model was fitted with a random intercept and a random time slope for each patient to account for clustering due to repeated measurements and contained the following independent variables: time, the characteristic of interest, and an interaction term of the characteristic of interest and time (characteristic*time), adjusted for baseline covariates listed above for the Cox model. Multiple imputation was not used to impute missing ADO scores because mixed effect models are unaffected by complete-case bias (188). STATA 14 was used for all analyses.

Ethics

The NHS South East Multi-centre Research Ethics Committee (MREC) approved THIN data collection for research in 2003 subject to independent scientific review which we obtained (Reference number: 16THIN039) on May 23rd, 2016.

RESULTS

THIN patients

We identified 67,066 COPD patients, 1,542 were excluded because they were diagnosed prior to 40 years of age. Of the remaining 65,524, a further 60,720 did not have at least three calculable ADO scores leaving 4,804 patients with a median of 4.38 years (IQR: 3.75 to 5.55 years) of follow-up in our analytical cohort. Over half of all those identified with COPD did not have data to derive an ADO score at any time but around one-third of all calculable ADO measurements were included in the final analysis (Table 3.1).

Table 3.1: Frequency of calculable ADO Measurements in the overall population of THIN patients

No. of measurements per subject	No. of individuals (%)	Total no. of measurements (%)
0*	34,706 (53)	0 (0)
1*	17,396 (27)	17,396 (34)
2*	8,618 (13)	17,236 (34)
3	3,393 (5)	10,179 (20)
4	1,073 (2)	4,292 (8)
5	263 (0)	1,315 (3)
6	59 (0)	354 (1)
7	13 (0)	91 (0)
8	3 (0)	24 (0)
Total	65,524	50,877

*Individuals were excluded from analysis Right column calculated by multiplying the number of measurements by the number of individuals.

Differences between those with and without three or more ADO score measurements

Supplementary Table 3.1 shows that patients with ≥3 total ADO measurements who were included in the analysis and patients with <3 ADO measurements who were excluded from the analysis had relatively similar baseline characteristics. The exception was that patients with ≥3 total ADO measurements were more likely to be prescribed respiratory treatment in the year prior to baseline. For instance, 34% of patients with ≥3 ADO measurements were prescribed ICS-containing treatment compared to 22% in those with <3 measurements.

Supplementary Table 3.1: Baseline characteristics of patients included and excluded in the ADO change analysis based upon enough ADO measurements (≥3).

Characteristics	≥ 3 ADO Measurements (N= 4,804)	< 3 ADO Measurements (N= 60,720)	Total (N= 65,524)
Age – Mean (SD)	68.9 (9.3)	72.6 (11.3)	72.3 (11.2)
Dyspnoea (mMRC Score) – N (%)			
0	859 (17.9)	5,686 (16.2)	6,545 (16.4)
1	1,883 (39.2)	12,827 (36.5)	14,710 (36.8)
2	1,323 (27.5)	9,285 (26.4)	10,608 (26.6)
3	666 (13.9)	5,873 (16.7)	6,539 (16.4)
4	73 (1.5)	1,453 (4.1)	1,526 (3.8)
missing	0	25596	25596
FEV1% predicted – Mean (SD)	59.3 (19.7)	59.8 (21.7)	59.7 (21.5)
First ADO score – Mean (SD)	7.4 (2.1)	7.6 (2.3)	7.6 (2.3)

No. of Females – N (%)	2,151 (44.8)	28,361 (46.7)	30,512 (46.6)
Country – N (%)			
England	3,577 (74.5)	44,984 (74.1)	48,561 (74.1)
Northern Ireland	275 (5.7)	2,940 (4.8)	3,215 (4.9)
Scotland	382 (8.0)	5,514 (9.1)	5,896 (9.0)
Wales	570 (11.9)	7,282 (12.0)	7,852 (12.0)
Townsend deprivation quintile - N (%)			
1 – least deprived	815 (17.3)	9,955 (16.7)	10,770 (16.8)
2	880 (18.7)	10,727 (18.0)	11,607 (18.1)
3	1,032 (21.9)	12,648 (21.2)	13,680 (21.3)
4	1,058 (22.5)	14,174 (23.8)	15,232 (23.7)
5 – most deprived	924 (19.6)	12,101 (20.3)	13,025 (20.3)
missing	95	1115	1210
Cigarette smoking – N (%)			
Current	1,301 (28.7)	17,479 (32.3)	18,780 (32.1)
Former	2,638 (58.3)	29,116 (53.9)	31,754 (54.2)
Never	588 (13.0)	7,449 (13.8)	8,037 (13.7)
missing	277	6676	6953
BMI category – N (%)			
Underweight (<18.5 kg/m^2)	124 (2.7)	3,396 (6.5)	3,520 (6.2)
Normal (18.5 - < 25 kg/m^2)	1,480 (32.6)	19,604 (37.4)	21,084 (37.0)
Overweight (25 - < 30 kg/m^2)	1,675 (36.9)	16,669 (31.8)	18,344 (32.2)
Obese (≥30 kg/m^2)	1,263 (27.8)	12,813 (24.4)	14,076 (24.7)
missing	262	8238	8500
LAMA prescription ⁻ N (%)	1,332 (27.7)	12,519 (20.6)	13,851 (21.1)
LABA prescription ⁻ N (%)	1,477 (30.8)	12,097 (19.9)	13,574 (20.7)
SAMA prescription ⁻ N (%)	777 (16.2)	5,521 (9.1)	6,298 (9.6)
SABA prescription ⁻ N (%)	2,848 (59.3)	26,231 (43.2)	29,079 (44.4)
ICS containing prescription – N (%)	1,645 (34.2)	13,472 (22.2)	15,117 (23.1)
PR referral - N (%)	211 (4.4)	1,416 (2.3)	1,627 (2.5)
Heart Failure – N (%)	245 (5.1)	5,985 (9.9)	6,230 (9.5)
Ischemic Heart Disease – N (%)	934 (19.4)	13,753 (22.7)	14,687 (22.4)
Anxiety – N (%)	109 (2.3)	1,378 (2.3)	1,487 (2.3)
Depression – N (%)	305 (6.4)	3,080 (5.1)	3,385 (5.2)
Diabetes – N (%)	593 (12.3)	8,135 (13.4)	8,728 (13.3)
TIA, stroke, PAD – N (%)	589 (12.3)	10,264 (16.9)	10,853 (16.6)
Asthma – N (%)	1,730 (36.0)	19,362 (31.9)	21,092 (32.2)

For patients without a single calculable ADO score, a random pseudo study entry date was assigned based on the distribution of the study entry dates among included patients. Age, mMRC score, and FEV1% predicted were used to calculate the first ADO score in the table.
Abbreviations: BMI= body-mass index, LAMA= long-acting muscarinic antagonist, LABA= long-acting beta2 Agonists, mMRC= modified Medical Research Council, FEV= forced expiratory volume, ICS= inhaled corticosteroids, PR= Pulmonary Rehabilitation, TIA= transient Ischemic attack, PAD= Peripheral artery disease

Description of the rate of change in ADO score
The mean baseline ADO score was 7.4 (SD: 2.1), range 0 to 14. The ADO score increased by an average of 0.187 points per year (95% CI: 0.174 to 0.200; the average number of measurements per patient was 3.4). The age component increased by 0.152 points (95%CI: 0.149 to 0.155), the dyspnoea score by 0.055 points (95%C: 0.050 to 0.060; the average number of measurements per patient was 5.2), and the obstruction score decreased by 0.009 points (95%CI: 0.001 to 0.016; the average number of measurements per patient was 4.3) per year (data not shown). The rate of change per patient was approximately normally distributed and 323 (6.7%) patients had an increase of at least 1 point per year (Figure 3.1).

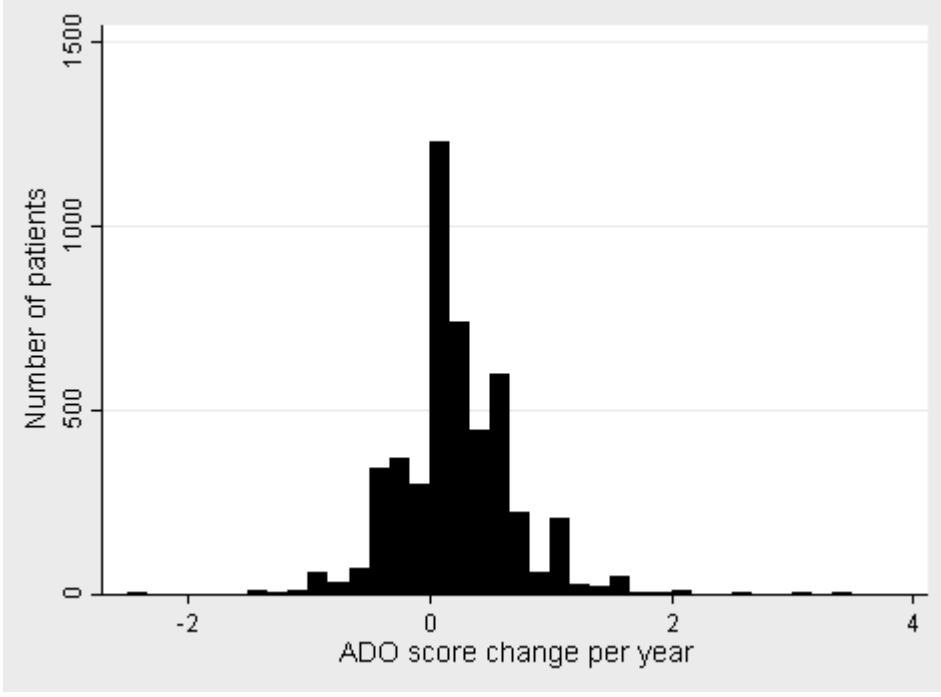


Figure 3.1: Histogram of distribution of change in ADO score per year in 4804 included patients.

Differences between ADO score change categories

Using +/- 0.5 to indicate worsening/improvement, 3,766 (78%) of included patients had a stable ADO score whereas 850 (18%) had a worsening and 188 (4%) had improving ADO score over time. Those with improving ADO scores had fewer ADO measurements (17% with ≥4 ADO measurements) than the worsening (27%) and stable (30%) groups (Table 3.2). Patients with a worsening ADO score had the lowest baseline ADO score (6.6; SD: 2.0) and least severe obstruction (FEV_1% predicted 64.9; SD: 21.3) and dyspnoea (mMRC 1.23; SD: 0.97). From improving to worsening groups there was a trend toward more current smokers and normal-weight patients and fewer never smokers and obese patients.

Table 3.2 Baseline characteristics by categories of change ADO score change over time groups among included patients with ≥3 ADO measurements (N=4,804).

Characteristics -	Improving ADO Change (N= 188)	Stable ADO Change (N= 3,766)	Worsening ADO Change (N= 850)
Age	69.6 (9.5)	68.8 (9.2)	69.2 (9.5)
Dyspnoea (mMRC Score) – N (%)	1.44 (0.97)	1.94 (1.04)	1.23 (0.97)
0	9 (4.8)	613 (16.3)	237 (27.9)
1	71 (37.8)	1,547 (41.1)	265 (31.2)
2	40 (21.3)	1,016 (27.0)	267 (31.4)
3	58 (30.9)	533 (14.2)	75 (8.8)
4	10 (5.3)	57 (1.5)	6 (0.7)
FEV1% predicted	47.6 (15.0)	58.6 (19.1)	64.9 (21.3)
First ADO score	8.9 (1.9)	7.6 (2.0))	6.6 (2.0)
0 to 5	7 (3.7)	543 (14.4)	239 (28.1)
6 and 7	33 (17.6)	1,262 (33.5)	333 (39.2)
8 and 9	77 (41.0)	1,355 (36.0)	230 (27.1)
10 to 14	71 (37.8)	606 (16.1)	48 (5.7)
≥4 ADO measurements	32 (17.0)	1,146 (30.4)	233 (27.4)
Female – N (%)	96 (51.1)	1,676 (44.5)	379 (44.6)
White Ethnicity – N (%)	99 (100.0)	1,848 (98.4)	426 (98.2)
Townsend deprivation quintile – N (%)			
1 – least deprived	27 (14.6)	643 (17.4)	145 (17.3)
2	37 (20.0)	692 (18.8)	151 (18.0)
3	41 (22.2)	805 (21.8)	186 (22.2)
4	43 (23.2)	820 (22.3)	195 (23.3)
5 – most deprived	37 (20.0)	726 (19.7)	161 (19.2)
Cigarette smoking – N (%)			
Current	49 (26.9)	994 (28.1)	258 (32.0)
Former	104 (57.1)	2,066 (58.4)	468 (58.0)
Never	29 (15.9)	478 (13.5)	81 (10.0)
Body-Mass Index	28.3 (6.3)	27.5 (5.5)	26.9 (5.6)

Underweight (<18.5 kg/m^2)	7 (3.9)	90 (2.5)	27 (3.3)
Normal (18.5 - < 25 kg/m^2)	50 (27.9)	1,130 (31.8)	300 (36.9)
Overweight (25 - < 30 kg/m^2)	70 (39.1)	1,324 (37.3)	281 (34.5)
Obese (≥30 kg/m^2)	52 (29.1)	1,005 (28.3)	206 (25.3)
LAMA prescription – N (%)	66 (35.1)	1,000 (26.6)	266 (31.3)
LABA prescription – N (%)	53 (28.2)	1,165 (30.9)	259 (30.5)
SAMA prescription – N (%)	31 (16.5)	603 (16.0)	143 (16.8)
SABA prescription – N (%)	118 (62.8)	2,212 (58.7)	518 (60.9)
ICS containing prescription – N (%)	52 (27.7)	1,306 (34.7)	287 (33.8)
PR referral – N (%)	6 (3.2)	176 (4.7)	29 (3.4)
Heart Failure – N (%)	11 (5.9)	192 (5.1)	42 (4.9)
Ischemic Heart Disease – N (%)	37 (19.7)	716 (19.0)	181 (21.3)
Anxiety – N (%)	7 (3.7)	86 (2.3)	16 (1.9)
Depression – N (%)	12 (6.4)	238 (6.3)	55 (6.5)
Diabetes – N (%)	28 (14.9)	469 (12.5)	96 (11.3)
TIA, stroke, PAD – N (%)	25 (13.3)	443 (11.8)	121 (14.2)
Asthma – N (%)	68 (36.2)	1,351 (35.9)	311 (36.6)

Results are shown as mean + standard deviation (SD) unless otherwise specified
*Chi-squared test and Student's t-test used where appropriate to calculate p-values comparing worsening
group to both stable and improving groups. Abbreviations: LAMA= long-acting muscarinic antagonist, LABA= long-acting beta2 Agonists, mMRC= modified Medical Research Council, FEV= forced expiratory volume, ICS= inhaled corticosteroids, PR= Pulmonary Rehabilitation, TIA= transient ischemic attack, PAD= Peripheral artery disease

Prognostic role of the change in ADO scores over time

There were 388 (8.1%) deaths in the follow-up period. There was strong evidence (P<0.001) of a 2.00-fold (95% CI: 1.59 to 2.52) increase in the rate of mortality per unit increase in individual ADO score per year, after adjusting for covariates (Table 3.3). Similarly, the association with mortality was stronger in patients grouped in worsening (HR= 2.08; 95% CI: 1.61 to 2.69) and improving (HR= 0.49; 95% CI: 0.27 to 0.91) categories compared to those with stable scores after adjustment for the same covariates (data not shown).

Table 3.3: Multivariable Cox regression model showing the adjusted hazard ratio (95% CI) for time to mortality for the change in ADO scores over time (calculated within each individual) compared to the baseline ADO score.

Characteristics	HR (95% CI)	P-value
Change in ADO score over time (per 1 point increase/year)	2.00 (1.59 to 2.52)	<0.001
Baseline ADO Score (per 1 point increase)	1.28 (1.10 to 1.50)	0.002
Age at baseline (per 1 year increase)	1.03 (1.00 to 1.05)	0.074
mMRC at baseline (per 1 point increase)	1.18 (1.03 to 1.36)	0.017
FEV1% predicted (per 1 percentage point increase)	0.99 (0.98 to 1.01)	0.277
No. of ADO measurements (per measurement)	0.79 (0.65 to 0.95)	0.010
Female Sex	0.88 (0.71 to 1.10)	0.262
Body-mass index category*		
<18.5	1.71 (1.16 to 2.51)	0.006
18.5 to <25	(reference)	(reference)
25 to <30	0.63 (0.49 to 0.80)	<0.001
≥30	0.62 (0.47 to 0.83)	<0.001
Smoking behavior*		
Never Smokers	(reference)	(reference)
Former Smokers	1.08 (0.79 to 1.48)	0.626
Current Smokers	1.27 (0.87 to 1.83)	0.148
Present of Heart Failure*	1.60 (1.19 to 2.14)	0.002
Presence of Ischemic Heart disease*	1.26 (1.00 to 1.58)	0.054
Presence of Diabetes Mellitus*	0.98 (0.74 to 1.30)	0.873
Presence of TIA-PAD*	1.24 (0.97 to 1.58)	0.092
Presence of Asthma*	1.01 (0.82 to 1.26)	0.898

Abbreviations: TIA-PAD= transient ischaemic attack, stroke, or peripheral arterial disease
*Most recent status prior to the last ADO score measurement.
The proportional-hazards assumption for serial ADO scores was not violated (P= 0.7214).
The median time between the first and final ADO score was 3.54 years (interquartile range 2.71 to 4.45).

In a similar analysis, the last ADO score within each patient showed a stronger association with mortality (HR= 1.25 per one point increase; 95% CI: 1.16 to 1.35) compared to the baseline ADO score (HR = 1.06 per one point increase; 95% CI: 0.93 to 1.22) which no longer showed statistical significance (Table 3.4).

Table 3.4: Multivariable Cox regression model showing the adjusted hazard ratio (95% CI) for time to mortality for the last ADO score compared to the baseline ADO score.

Characteristics	HR (95% CI)	P-value
Last ADO score (per 1 point increase)	1.25 (1.16 to 1.35)	<0.001
Baseline ADO Score (per 1 point increase)	1.06 (0.92 to 1.22)	0.405
Age at baseline (per 1 year increase)	1.01 (0.99 to 1.04)	0.324
mMRC at baseline (per 1 point increase)	1.18 (1.03 to 1.35)	0.020
FEV1% predicted (per 1 percentage point increase)	1.00 (0.99 to 1.01)	0.555
No. of ADO measurements (per measurement)	0.80 (0.65 to 0.96)	0.012
Female Sex	0.89 (0.72 to 1.10)	0.291
Body-mass index category*		
<18.5	1.68 (1.14 to 2.45)	0.008
18.5 to <25	(reference)	(reference)
25 to <30	0.59 (0.46 to 0.76)	<0.001
≥30	0.58 (0.43 to 0.77)	<0.001
Smoking behavior*		
Never Smokers	(reference)	
Former Smokers	1.22 (0.89 to 1.67)	0.222
Current Smokers	1.29 (0.90 to 1.88)	0.164
Present of Heart Failure*	1.61 (1.20 to 2.15)	0.001
Presence of Ischemic Heart disease*	1.25 (1.00 to 1.58)	0.052
Presence of Diabetes Mellitus*	1.06 (0.80 to 1.41)	0.676
Presence of TIA-PAD*	1.32 (1.03 to 1.69)	0.027
Presence of Asthma*	1.05 (0.85 to 1.30)	0.672

Characteristics associated with the change in ADO score over time

Table 3.5 shows multivariable mixed effect models of the characteristics associated with the change in ADO scores over time. After adjustment for baseline covariates, greater deprivation, recent depression, and prior LABA, LAMA, and ICS-containing prescription were all associated with a statistically significant worsening (P<0.05) of ADO scores over time. Compared to never smokers, current smokers had a 0.059 (95% CI: 0.031 to 0.087) point per year worsening of ADO scores. Finally, compared to those with a normal BMI between 18.5 and 25 kg/m^2, overweight (β= -0.035; 95% CI: -0.0544 to -0.0150; P=0.001) and obese (β= -0.041; 95% CI: -0.0625 to -0.0198; P<0.001) patients showed improvement over time and underweight patients had a worsening ADO score of 0.041 ADO points per year (95% CI: -0.018 to 0.100).

Table 3.5: Multivariable linear mixed effect models of the interaction between baseline characteristics and time on the change in the ADO score.

Characteristics interacting with time	Baseline Adjustment (N= 4,363)		
		β (95% CI)	P-value
Baseline ADO score	-0.0397	(-0.0437 to -0.0357)	<0.001
No. of ADO measurements	0.0178	(0.0080 to 0.0276)	<0.001
Age at baseline (years)	-0.0001	(-0.0010 to 0.0008)	0.885
mMRC score at baseline	-0.0446	(-0.0530 to -0.0362)	<0.001
FEV1% predicted at baseline	0.0026	(0.0022 to 0.0031)	<0.001
Townsend Quintile	0.0062	(0.0001 to 0.0123)	0.045
Female sex	0.0001	(-0.0164 to 0.0168)	0.982
Heart Failure – any time	-0.0044	(-0.0413 to 0.0327)	0.817
Ischemic Heart Disease – any time	-0.0001	(-0.0211 to 0.0208)	0.989
Asthma – any time	-0.0035	(-0.0206 to 0.0136)	0.688
Anxiety – 3 years prior	-0.0191	(-0.0770 to 0.0389)	0.519
Depression – 3 years prior	0.0384	(0.0054 to 0.0713)	0.022
Diabetes – any time	-0.0084	(-0.0346 to 0.0178)	0.531
TIA, stroke, PAD – any time	-0.0035	(-0.0288 to 0.0217)	0.783
LAMA prescription* – 1 year prior	0.0236	(0.0045 to 0.0427)	0.016
LABA prescription** – 1 year prior	0.0186	(0.0008 to 0.0365)	0.041
SAMA prescription ‡ – 1 year prior	0.0195	(-0.0019 to 0.0409)	0.075
SABA prescription § – 1 year prior	0.0137	(-0.0031 to 0.0306)	0.111
ICS containing ∆ prescription – 1 year prior	0.0189	(0.0017 to 0.0361)	0.031
PR referral – 1 year prior	0.0029	(-0.0372 to 0.0430)	0.886
Body-mass index group – most recent status			
<18.5	0.0411	(-0.0175 to 0.0996)	0.169
18.5 to <25	(reference)	(reference)	(reference)
25 to <30	-0.0347	(-0.0544 to -0.0150)	0.001
≥30	-0.0412	(-0.0625 to -0.0198)	<0.001
Smoking behaviour – most recent status			
Never Smokers	(reference)	(reference)	(reference)
Former Smokers	0.0282	(0.0025 to 0.0539)	0.032
Current Smokers	0.0588	(0.0311 to 0.0866)	<0.001

Abbreviations: BMI= body-mass index, LAMA= long-acting muscarinic antagonist, LABA= long-acting beta2 Agonists, mMRC= modified Medical Research Council, FEV= forced expiratory volume, ICS= inhaled corticosteroids, PR= Pulmonary Rehabilitation, TIA= transient ischemic attack, PAD= Peripheral artery disease

DISCUSSION

This retrospective longitudinal study showed that most COPD primary care patients had stable disease over a median follow-up of over four years. However, serial

ADO scores had prognostic value beyond the initial measurement. Thus, serial assessment of the ADO score may be needed to update the predicted risk of death. We found that this may be particularly important for patients with lower BMI, depression, and those who are current or former smokers.

In contrast to our study, a prospective study of COPD patients followed for 3 years after their hospital admission with an acute exacerbation, found that baseline BODE (body-mass index, obstruction, dyspnoea, and exercise capacity) score, but not changes in BODE, predicted survival (189). They concluded that a single measurement, rather than serial measurements, of BODE would be sufficient for prognostication (189). Two other studies showed that before and after lung volume reduction surgery, changes in the BODE score and the final BODE score were independently associated with mortality in severe emphysema patients [21, 22]. Similarly, pulmonary rehabilitation improved the BODE score, and its change added prognostic information for 246 COPD outpatients in the US. (190). Combined, serial BODE measurements may be more helpful in assessing treatment response rather than disease worsening.

It is well known the low BMI is associated with an increased risk of mortality in COPD patients (104). We found that lower BMI was associated with worsening disease. Similarly, COPD secondary care patients in the BODE (BMI, obstruction, dyspnoea, exercise capacity) cohort were more likely to have worsening obstruction with low BMI than with normal BMI at baseline (95). While BMI may be associated with disease worsening, obese patients may have trouble breathing due to their weight, resulting in overdiagnosis of COPD (191) and more stable ADO scores over time in our study. Second, the effect of smoking on longitudinal lung function deterioration has long been documented (93). A secondary analysis of the Lung Health Study randomised controlled trial showed that there was a greater decline in lung function over 11 years if participants were continuous smokers (60 ml/year) compared to intermittent quitters (48 ml/year) and sustained quitters (27 ml/year) (192). Although, reducing smoking can improve the decline in FEV_1 (193,194), nearly complete cessation may be necessary for demonstrable benefit (195). Next, it may be difficult to diagnose depression in COPD patients because of overlapping symptoms (196). Patients in our study with worsening COPD may be more likely to be depressed if respiratory symptoms are limiting their social lives (79). We also found that disease worsening was greater in those who had received respiratory pharmacotherapy. Similar to depression, these findings may be due to reverse causation, reflecting that those on a worsening disease trajectory had been started on pharmacotherapy.

The current study has several strengths and limitations. First, previous studies have used longitudinal lung function measurements alone to describe COPD progression. However, COPD is a heterogeneous disease and patients may worsen despite stable lung function (95). A multicomponent prognostic score more accurately accounts for disease heterogeneity. It also allows changes in the score to be placed into the context of changes in individual risk of death. Next, unlike previous studies that examined serial measurements of prognostic scores (95,189,197–199), we included primary care patients, where COPD is mainly

managed (147). However, despite a large sample size, we excluded many patients due to the limited availability of data. These patients were different in only a few characteristics compared to the whole population and may have had more stable disease, requiring fewer dyspnoea and obstruction measurements. Although THIN is generalisable to the UK for demographics, disease prevalence, and mortality rates (182), urban areas may be overrepresented because Vision software use is clustered in these areas (200). Next, unmeasured confounding and unstandardised measurements were unavoidable. The latter may partly explain the improvement in average FEV_1% predicted over time in our sample. Additionally, FEV_1% predicted may be flawed when examining its change over time. FEV_1% predicted would increase as patients age (and/or become shorter) despite relatively stable FEV_1 (in litres). Longitudinal ADO score trends were assumed to be linear to ease interpretation but this was not true for some patients. Visual assessment of ADO trends showed non-linearity for some patients but often overall ADO score changes could still be generalised using a linear estimate without losing too much information. Finally, the ADO score provides an estimate of risk that can be used to support clinical discussions with patients and joint decision-making. However, the lack of impact studies to examine the effect of stratified management based on risk score categories on patient outcomes limits its use. Serial measurement may refine risk estimates and identify those who have a worsening disease trajectory, but we do not yet have evidence of whether differential management would modify outcomes.

CONCLUSION

Given the wide range of clinical courses in patients with COPD, it is important to understand whether and how prognostic scores change over time to identify patients with worsening disease. If this change has prognostic relevance or is related to patient characteristics, then serial assessment may be useful. One-time use of the ADO score could help define treatment options that could be weighed against the current risk of mortality (144). However, serial assessment of the ADO score can identify patients with worsening disease and update their prognosis, especially for patients who smoke, are depressed, or have lower BMI.

CHAPTER IV: BMI TRAJECTORIES IN PEOPLE WITH AND WITHOUT COPD ACCORDING TO SMOKING STATUS: LONGITUDINAL FINDINGS FROM THE THIN PRIMARY CARE DATABASE

Spencer J Keene[1,2,4], Johanna H.M. Driessen[2,3,7], Rachel E Jordan[1], Frank de Vries[2,3,7], Alice Sitch[1,5], Peymane Adab[1], Frits M.E. Franssen [4,6*]

Affiliations

[1] Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom.

[2] Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center+, Maastricht, the Netherlands

[3] Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht the Netherlands.

[4] CIRO+, Horn, the Netherlands

[5] NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, UK

[6] Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands

[7] Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+, Maastricht, the Netherlands

ABSTRACT

Rationale: Low body mass index (BMI) is a feature of severe chronic obstructive pulmonary disease (COPD) but in the general population, cigarette smoking is also associated with low body weight. Many people with COPD remain smokers after diagnosis, and it is unclear whether low BMI is due to the effects of the disease itself or its most common risk factor.

Objectives: To assess the independent and combined effects of smoking and COPD on BMI trajectories and determine if the association between COPD, smoking status, and mortality is mediated by BMI.

Methods: 1,638 people with and 1,100 without COPD from 10 practices in The Health Improvement Network (2005-2019) who had ≥2 BMI measurements, were grouped into: never smokers, former smokers, sustained quitters, intermittent smokers, and continuous smokers (ten total COPD-smoking status groups). BMI trajectories were modeled by these status groups using multivariable mixed effect models. Also, it was investigated whether BMI mediated the association between these status groups and mortality using time-varying Cox regression.

Results: Regardless of COPD status, former smokers had the highest baseline BMI (≈29.5 kg/m^2; SD: 6.5 kg/m^2), followed by never smokers. Both had a similar decline in BMI(≈-0.12kg/m^2/year). The remaining six groups had a lower baseline BMI (26-27kg/m^2). Sustained quitters showed a greater BMI increase and the rate (0.12 kg/m^2/year; 95% CI: -0.02 to 0.26) was four times larger among those with COPD than those without (0.03 kg/m^2 /year; 95% CI: -0.23 to 0.29). Continuous smokers with COPD had the steepest decline in BMI; more than twice as steep as those without COPD (-0.30 kg/m2 /year; 95% CI: -0.40 to -0.19 vs -0.13 kg/m2 /year; 95% CI: -0.33 to 0.07). Although time-varying BMI values (HR= 0.99; 95% CI: 0.97 to 1.00) showed a marginally significant association with mortality, after adjustment, former smokers, continuous smokers, COPD sustained quitters, and non-COPD intermittent smokers had significantly increased risks of mortality which were not affected by BMI.

Conclusion: Regardless of COPD status, baseline BMI was highest in former smokers followed by never smokers. Both smoking groups had a similar rate of decline. Among continuous smokers, those with COPD had a more rapid decline. Conversely, quitters with COPD had a more rapid increase in BMI. Weight loss was not an important mediator in the association between smoking, COPD status, and mortality.

INTRODUCTION

Low body mass index (BMI) was one of the earliest recognized extrapulmonary features in patients with chronic obstructive pulmonary disease (COPD) (201). It is associated with more severe stages of COPD (202) and is identified as an independent contributor to COPD mortality (137). Low BMI in COPD patients is known to result from a variable combination of poor nutritional intake (203), increased work of breathing (204), increased resting energy expenditure (205,206), and mechanical inefficiency (207). Furthermore, reversal of low BMI by nutritional supplementation is associated with improved survival among COPD patients (208). Thus, prior evidence has suggested that the disease process primarily influences weight loss in COPD patients. On the other hand, in the general population, cigarette smoking is also associated with loss of weight, while quitting smoking often results in weight gain (105,209). In smokers, weight loss is attributed to the effects of nicotine on increasing metabolic rate, decreasing metabolic efficiency, or appetite suppression (105).

Cigarette consumption is a main cause of COPD (177), and many patients remain smokers after diagnosis (210). Therefore, it is difficult to disentangle to what extent low BMI in people with COPD is due to the effects of the disease itself and/or its most common risk factor. In addition, although there is evidence that weight loss is associated with increased mortality in COPD (211,212), it is less clear whether this increased risk of mortality is a direct effect of the disease process/effects of smoking or an association mediated by weight loss.

Several studies have investigated the effect of smoking on body composition in COPD (213–217). However, results are inconsistent as to whether smoking or the disease process plays a primary role, or if both have a joint effect on body composition changes over time. A better understanding of the mechanisms contributing to weight change could help inform potential new targets for disease modification beyond the promotion of smoking cessation. The objectives of this study were to answer the questions: 1) What are the differences in BMI trajectories between people with and without COPD according to smoking status? and 2) do longitudinal BMI changes mediate the association between COPD, smoking, and mortality?

METHODS

Study design

A longitudinal open cohort study using primary care data.

Data source

The Health Improvement Network (THIN) is a longitudinal, clinical primary care database of over 11 million patients from over 600 practices in the United Kingdom (~6% of the population). The database contains anonymised data on diagnoses,

symptoms, hospital referrals, discharge summaries, lifestyle, mortality, prescribing, and clinical and laboratory tests captured by General Practitioners using Vision medical software (Vision, London, UK).

Patients

People with and without COPD were included from 10 randomly selected UK primary care practices contributing to the THIN database. People with COPD were included if they were diagnosed at the age of 40 years or older (to reduce the likelihood of including those with alpha-1 antitrypsin deficiency). People with COPD were matched by age (+/- one year), sex, and practice at a 1:1 ratio to those without COPD (defined as no COPD Read codes in their records. We applied several inclusion criteria to both groups separately:

- The date of the first recorded BMI measurement was within one year of the baseline smoking status assessment.
- To allow estimation of body mass index (BMI) trajectory, at least two plausible BMI measurements (>=10 and <=60 kg/m^2) were recorded for each individual.
- We also performed the analysis restricting to those with ≥3 BMI measurements since the slope of BMI over time within patients may be more accurately estimated with a greater number of measurements.

Patients with a COPD diagnosis prior to (i.e., those with prevalent disease) or subsequent (i.e., incident disease) to the cohort start date (1st January 2005) were included. The practice start date was defined as the latest of either 12 months after the acceptable mortality reporting (AMR) date or 12 months after the practice began using the Vision system, to reduce the under-recording of events. We defined the patient start date as the latest of the practice start date or 12 months after the patient's registration date. The index date for COPD patients was defined as the latest of either the patient start date or the diagnosis date after adding 15 months (latency period) to both dates. For people with incident COPD, the index date was 15 months after the date of diagnosis whereas, for people with prevalent COPD, the index date was 15 months after the date the patient became eligible for inclusion. As used by other authors (218,219), a 15-month latency period was introduced to ensure that all baseline covariates were recorded, as the Quality and Outcomes Framework (QOF) incentivizes these are captured within 15 months. It also ensures that any inaccuracies in capturing the true smoking status of a patient are not due to contemporaneous changes in smoking behaviour during the timeframe in which the individual was given news of their COPD diagnosis. People without COPD were assigned the index date of their matched COPD patient. Patients were followed from their index date until the earliest of their date of death, the date the patient transferred out of the practice, the last practice collection date, or 31st July 2019.

Outcomes

The primary outcome was longitudinal BMI (*BMI = weight (kilograms) / height^2 (meters))* measurements over time. BMI was derived from BMI value codes. We also examined all-cause mortality as a dependent variable in secondary analyses. Mortality information was derived from General Practitioners who recorded the deaths of their patients after receiving this information from a variety of sources, mainly hospital discharge summaries and patient relatives (187).

Exposures: smoking and COPD status

The main exposure of interest was smoking behaviour in people with or without COPD. The closest recorded smoking status within one year of the patient's index date was used to group patients into never and former smokers at baseline while current smokers were split into further subcategories based on the individual's pattern of smoking behaviour during follow-up. Similar to the Lung Health Study (193), these sub-groups were defined as sustained quitters (current smokers at baseline who quit smoking and remained former smokers throughout follow-up), intermittent smokers (patients who had at least one transition from current to former smoking as well as a transition from former to current smoking), and continuous smokers (current smokers at baseline who remained current smokers during follow-up). Thus, a total of ten COPD-smoking status groups were developed:

People without COPD	**People with COPD**
1) Never smoker (reference)	2) Never smoker
3) Former smoker	4) Former smoker
5) Sustained quitter	6) Sustained quitter
7) Intermittent smoker	8) Intermittent smoker
9) Continuous smoker	10) Continuous smoker

Adjustment variables

Baseline covariates included age (years), sex, Townsend score (quintiles) (220), and any history of the following comorbidities: ischemic heart disease, any cancer, asthma, tuberculosis, heart failure, stroke/transient ischemic attack (TIA), diabetes, chronic kidney disease (or evidence of renal replacement therapy), and chronic liver disease. Forced expiratory volume in 1 second (FEV_1) in litres and the ratio of FEV_1 / forced vital capacity (FVC) was obtained and shown in baseline tables but were not adjusted for in regression models due to substantial incompleteness. Whilst lung function values such as FEV_1 and FVC are important for defining the severity of COPD and could predict outcomes, these values are not routinely recorded for all patients and seldom for people without COPD. Multiple imputation was not used because incompleteness for FEV_1 and FVC was high, dependent on COPD status, and would have required sufficient auxiliary variable information to account for this (221).

Analysis

Baseline characteristics were compared between those with and without COPD. Next, we built linear mixed effect models to investigate the trajectory of BMI measurements over time in each status group. Each model was fitted with a random intercept and a random time slope for each patient to account for clustering due to repeated BMI measurements and contained the following independent variables: time, status group, and an interaction term between the status group and time (status group × time), age, sex, Townsend score, and comorbidities. Multiple imputation for missing BMI values was not required because mixed effect models are unaffected by complete-case bias (222).

Finally, in secondary analyses, we evaluated the association between status groups with mortality using multivariable Cox regression analyses. We also performed mediation analysis to evaluate whether BMI change mediated the effect of smoking and COPD on mortality. To test for mediation effects, we sought to determine if three criteria were met (223):

1. There must be a significant relationship between the status group (COPD and smoking exposure) and mortality,
2. There must be a significant relationship between the status group variable and the BMI trajectories, and
3. BMI trajectory must be a) significant predictor of the mortality in an equation including both longitudinal BMI measurements and the status group variable and b) push the association between status group and mortality toward the null value of 1.0.

Points 1 and 2 were met after performing the Cox and mixed effect models as discussed above. Point 3 was accomplished by including BMI change over time into the Cox regression analysis evaluating the effect of status group on mortality.

We performed these analyses using Stata version 16 (StataCorp, College Station, TX, USA).

Sensitivity analysis: Including prevalent COPD patients may introduce survivor bias since patients are more likely to be included in a cohort the longer they survive with a disease (224). Patients who die quickly after diagnosis are excluded so a prevalent patient cohort tends to have less severe disease and better prognosis. Therefore, we also excluded prevalent COPD patients from the mixed effect and Cox models to observe whether the associations were different in incident patients alone.

RESULTS

Of 6,796 patients, 5,470 patients had complete baseline smoking status. Of these, 3,386 patients had an initial BMI measurement within one year and 2,738 patients (1,638 with COPD and 1,100 without COPD) had at least one additional BMI measurement during a median follow-up time of 5.45 (IQR: 2.96 to 8.49) years. People with COPD were just over 1 year younger and were much more likely to have ever smoked compared to those without COPD (46% vs 30% former and 39% vs 11%, current/recent smokers (includes sustained quitters, intermittent smokers, and continuous smokers)) (Table 4.1). There were only 9 intermittent smokers among those without COPD. People with COPD were more likely to belong to the two most deprived Townsend quintile groups. Baseline BMI was lower in people with COPD than those without (27.4 kg/m^2; SD: 6.6 vs 28.2 kg/m^2; SD: 5.8). There was strong evidence (P= 0.001) that heart failure was more common among COPD patients (8.1% versus 4.8%), however, diabetes was more common among people without COPD (26% versus 19%).

Table 4.1: Baseline characteristics of THIN patients (N= 2738) by COPD status.

	COPD patients (N= 1,638)	Non-COPD patients (N= 1,100)
age (y) - mean (SD)	67.9	69.2
male sex- n (%)	849 (51.8)	581 (52.8)
Townsend quintile n (%)		
1 (most affluent)	256 (15.6)	301 (27.4)
2	272 (16.6)	249 (22.6)
3	327 (20.0)	210 (19.1)
4	412 (25.2)	181 (16.5)
5 (most deprived)	334 (20.4)	138 (12.6)
missing	*37 (2.3)*	*21 (1.9)*

BMI (kg/m^2) - mean (SD)	27.4 (6.6)	28.2 (5.8)
missing N (%)	14 (1.3)	14 (0.85)
FEV_1 in litres - mean (SD)	4.93 (34.9)	5.29 (17.4)
missing N (%)	154 (9.4)	1000 (90.9)
FEV_1 /FVC ratio - mean (SD)	60.8 (18.1)	72.3 (15.9)
missing N (%)	291 (17.7)	1013 (92.1)
smoking status n (%)		
never	234 (14.3)	642 (58.4)
former	760 (46.4)	333 (30.3)
sustained quitter*	144 (8.8)	31 (2.8)
intermittent smoker*	88 (5.4)	9 (0.8)
continuous smoker*	412 (25.2)	85 (7.7)
Comorbidities n (%)		
heart failure	132 (8.1)	53 (4.8)
coronary heart	388 (23.7)	227 (20.6)
stroke/TIA	143 (8.7)	106 (9.6)
diabetes	314 (19.2)	282 (25.6)
liver	22 (1.3)	15 (1.4)
kidney/renal	141 (8.6)	118 (10.7)

* group defined using smoking status changes during follow-up as well.

BMI trajectories

Figure 4.1 shows the longitudinal BMI measurements by status group. The top panel shows the trajectories in patients with ≥3 BMI measurements (N=2223). Regardless of COPD status, former smokers had the highest baseline BMI with an approx. 0.70 kg/m^2 higher BMI (mean= 29.6 kg/m^2; SD: 6.5) than the reference group, followed by never smokers (Table 4.2). As evidenced by parallel slopes, both former and never-smoking groups with and without COPD had a statistically significant decline (P<0.001) in BMI, which was of similar magnitude (≈-0.12 kg/m^2/year). The remaining six groups (i.e., COPD and non-COPD intermittent smokers, continuous smokers, and sustained quitters) had a lower baseline BMI (26 to 27 kg/m^2). COPD sustained quitters showed an increasing BMI trajectory and the rate of increase (0.12 kg/m^2/year; 95% CI: -0.02 to 0.26) was four times larger than in non-COPD sustained quitters (0.03 kg/m^2/year; 95% CI: -0.23 to

0.29). Continuous smokers with COPD had an over two times steeper decline in BMI (-0.30 kg/m^2/year; 95% CI: -0.40 to -0.19) than continuous smokers without COPD (-0.13 kg/m^2/year; 95% CI: -0.33 to 0.07). Overall, the only groups to show a significant difference in slope of BMI over time from the reference group were the COPD-continuous smokers – who had an average BMI loss over time - and the COPD sustained quitters – who have an average BMI gain (both P = 0.001). In the bottom panel, where patients only needed ≥2 BMI measurements (N= 2,719), the results were similar, although continuous smoking people without COPD had a 1.16 kg/m^2 higher baseline BMI (Table 4.2).

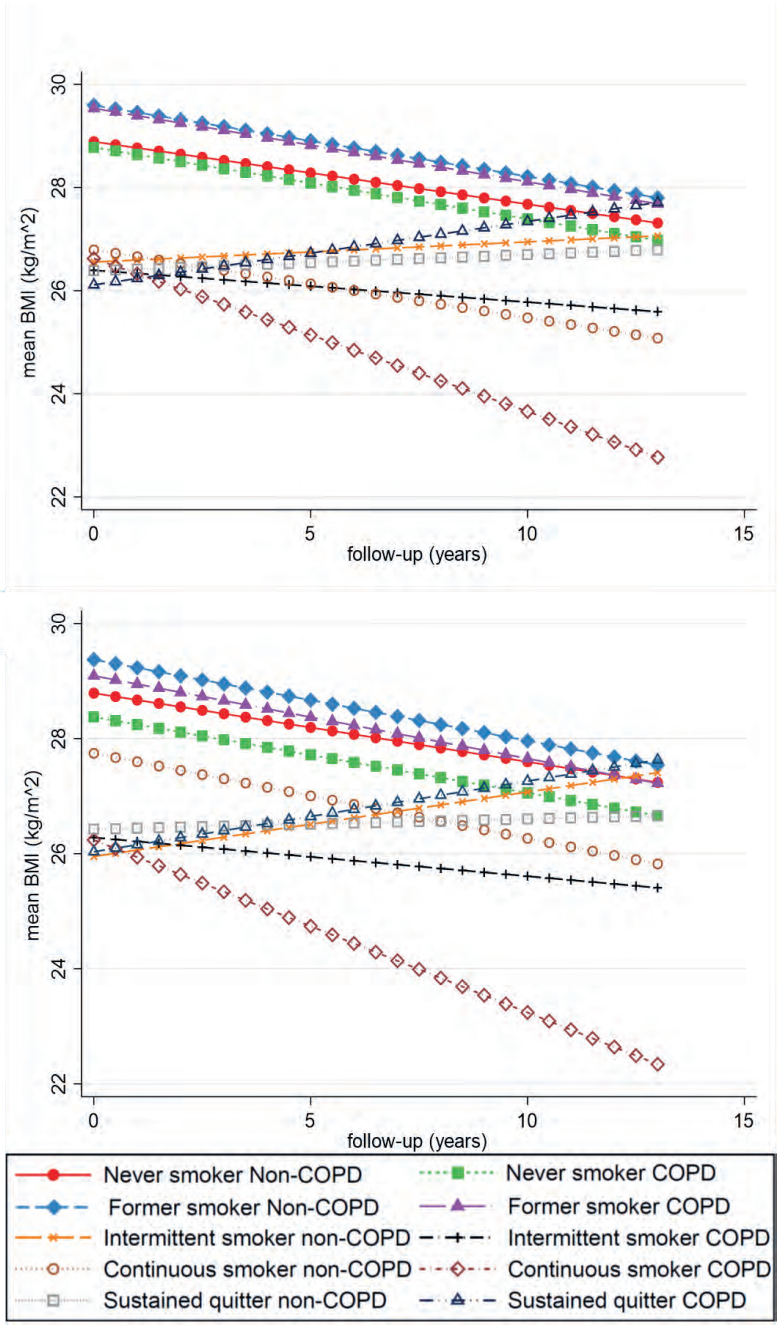


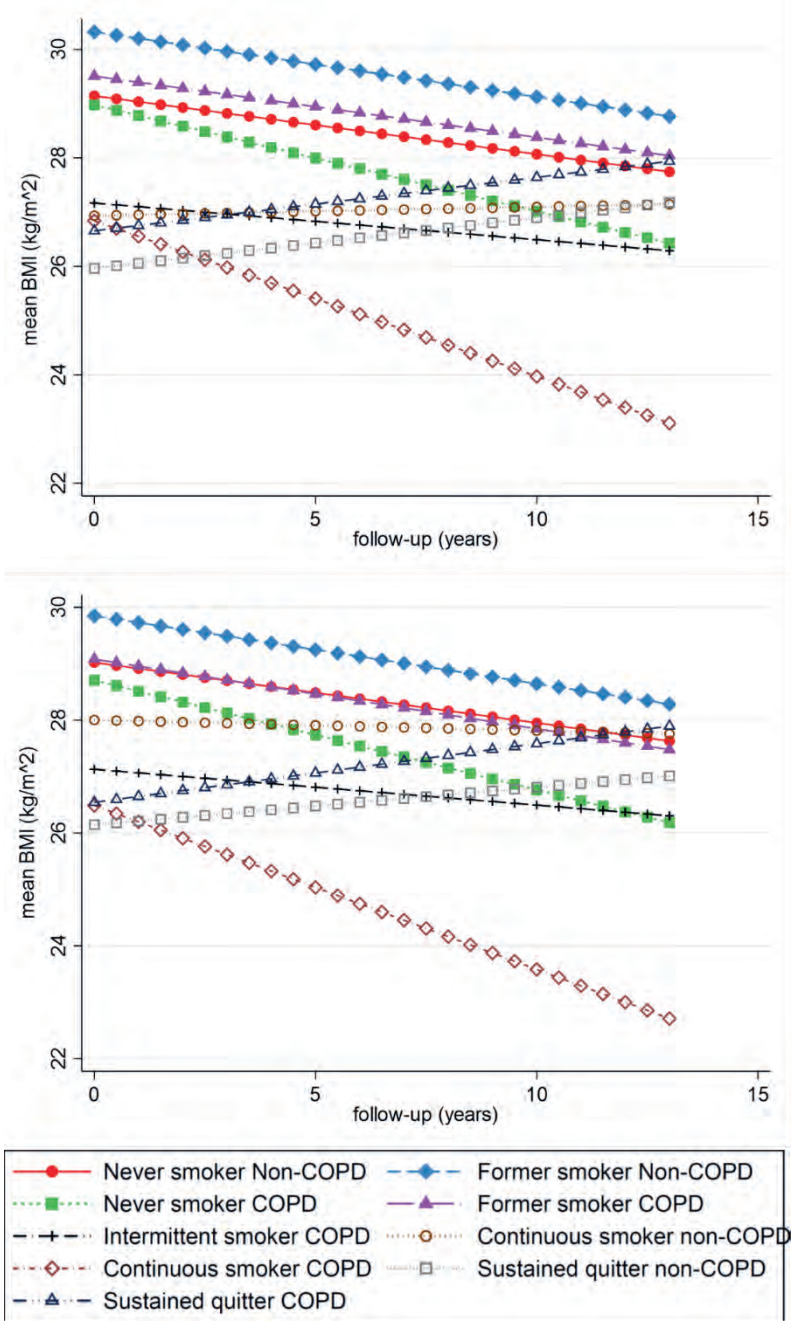
Figure 4.1: The effect of status group on BMI trajectories in incident and prevalent patients with≥3 BMI measurements (Top panel, N= 2,223) and ≥2 BMI measurements (Bottom panel, N= 2,719).

Table 4.2: The effect of COPD-smoking status group on BMI baseline (i.e., intercept) and BMI trajectories in incident and prevalent patients and non-COPD patients from THIN.

	≥3 BMI measurements (N = 2,223)	≥2 BMI measurements (N=2,719)
	B (95% CI)	B (95% CI)
Baseline BMI		
Never smoking non-COPD (kg/m^2)	28.9 (27.1 to 30.8) (reference group)	28.8 (27.1 to 30.5) (reference group)
Never smoking COPD	-0.110 (-1.05 to 0.830)	-0.412 (-1.26 to 0.439)
Former smoking non-COPD	0.704 (-0.147 to 1.55)	0.582 (-0.170 to 1.34)
Former smoking COPD	0.647 (-0.033 to 1.33)	0.301 (-0.304 to 0.907)
Sustained quitter-non-COPD	-2.50 (-4.72 to -0.283)	-2.37 (-4.43 to -0.297)
Sustained quitter COPD	-2.77 (-3.93 to -1.62)	-2.75 (-3.80 to -1.72)
Intermittent smoker non-COPD	-2.33 (-6.34 to 1.67)	-2.84 (-6.55 to 0.877)
Intermittent smoker COPD	-2.49 (-3.85 to -1.13)	-2.50 (-3.78 to -1.23)
Continuous smoker non-COPD	-2.10 (-3.69 to -0.510)	-1.04 (-2.35 to 0.258)
Continuous smoker COPD	-2.27 (-3.10 to -1.43)	-2.55 (-3.28 to -1.82)
BMI Trajectory		
Never smoking non-COPD ($kg/m^2/yr$)	-0.121 (-0.181 to -0.062) (reference group)	-0.119 (-0.176 to -0.063) (reference group)
Never smoking COPD	-0.017 (-0.132 to 0.097)	-0.013 (-0.124 to 0.099)
Former smoking non-COPD	-0.017 (-0.121 to 0.087)	-0.022 (-0.122 to 0.078)
Former smoking COPD	-0.021 (-0.104 to 0.061)	-0.024 (-0.104 to 0.055)
Sustained quitter-non-COPD	0.152 (-0.109 to 0.414)	0.137 (-0.118 to 0.393)
Sustained quitter COPD	0.244 (0.104 to 0.384)	0.242 (0.105 to 0.379)
Intermittent smoker non-COPD	0.160 (-0.320 to 0.640)	0.231 (-0.223 to 0.686)
Intermittent smoker COPD	0.059 (-0.100 to 0.219)	0.052 (-0.104 to 0.207
Continuous smoker non-COPD	-0.010 (-0.209 to 0.188)	-0.029 (-0.214 to 0.157)
Continuous smoker COPD	-0.175 (-0.277 to -0.073)	-0.180 (-0.279 to -0.082)

Adjusted for age, sex, Townsend score, and all comorbidities. The table shows the actual slope and intercept of BMI over time for the reference group as well as the differences in slope and intercept between each subgroup and the reference group.

After restricting to incident COPD patients (Supplementary figure 4.1), former smokers without COPD tended to have a higher baseline BMI than the same subgroup in the main results, especially in the results restricting to patients with ≥3 BMI measurements (BMI = 30.3 kg/m^2) (Supplementary table 4.1). COPD never smokers had an increased rate of decline in BMI (-0.088 kg/m^2/year relative to the reference group) whereas non-COPD continuous smokers now had almost no change in BMI over time. Otherwise, the sensitivity results were comparable with our main findings.



Supplementary Figure 4.1: The effect of status group on BMI trajectories in incident COPD patients and matched people without COPD with ≥3 BMI measurements (Top panel, N= 1,497) and ≥2 BMI measurements (Bottom panel; N= 1,866). Note: Intermittent smoker non-

COPD patients were collapsed into continuous smoking non-COPD patients because there were too few numbers to properly estimate effect size.

Supplementary Table 4.1: The effect of status group on BMI intercepts and BMI trajectories in incident patients and non-COPD patients from THIN

	≥3 BMI measurements (N = 1,497)	≥2 BMI measurements (N=1,866)
	B (95% CI)	B (95% CI)
Intercept		
Never smoking non-COPD (kg/m^2)	29.1 (26.9 to 31.3) (reference group)	29.0 (27.0 to 31.0) (reference group)
Never smoking COPD	-0.168 (-1.37 to 1.04)	-0.314 (-1.41 to 0.776)
Former smoking non-COPD	1.18 (0.074 to 2.28)	0.827 (-0.132 to 1.79)
Former smoking COPD	0.365 (-0.467 to 1.20)	0.059 (-0.675 to 0.793)
Sustained quitter-non-COPD	-3.18 (-5.84 to -0.518)	-2.88 (-5.35 to -0.406)
Sustained quitter COPD	-2.49 (-3.90 to -1.07)	-2.48 (-3.73 to -1.22)
Intermittent smoker COPD	-1.97 (-3.62 to -0.331)	-1.89 (-3.42 to -0.365)
Continuous smoker non-COPD	-2.21 (-4.06 to -0.355)	-1.02 (-2.50 to 0.457)
Continuous smoker COPD	-2.30 (-3.27 to -1.33)	-2.53 (-3.38 to -1.69)
Trajectory		
Never smoking non-COPD ($kg/m^2/yr$)	-0.108 (-0.188 to -0.027) (reference group)	-0.107 (-0.194 to -0.031) (reference group)
Never smoking COPD	-0.088 (-0.245 to 0.068)	-0.087 (-0.239 to 0.064)
Former smoking non-COPD	-0.012 (-0.159 to 0.135)	-0.013 (-0.152 to 0.126)
Former smoking COPD	-0.005 (-0.115 to 0.104)	-0.016 (-0.121 to 0.088)
Sustained quitter-non-COPD	0.201 (-0.126 to 0.527)	0.174 (-0.143 to 0.490)
Sustained quitter COPD	0.206 (0.020 to 0.393)	0.211 (0.032 to 0.390)
Intermittent smoker COPD	0.040 (-0.170 to 0.250)	0.044 (-0.160 to 0.248)
Continuous smoker non-COPD	0.124 (-0.128 to 0.375)	0.088 (-0.142 to 0.318)
Continuous smoker COPD	-0.179 (-0.306 to -0.052)	-0.184 (-0.305 to -0.062)

Adjusted for age, sex, Townsend score, and all comorbidities. The table shows the actual slope and intercept of BMI over time for the reference group as well as the differences in slope and intercept between each subgroup and the reference group. Note: Intermittent smoker non-COPD patients were collapsed into continuous smoking non-COPD patients because of too few numbers to properly estimate effect size.

Mortality

631 patients died during follow-up. Former smokers (HR= 1.95, 95% CI: 1.52 to 2.49 and HR= 1.46, 95% CI: 1.09 to 1.97 for those with and without COPD, respectively), continuous smokers (HR= 2.38, 95% CI: 1.78 to 3.19, and 2.67, 95% CI:1.65 to 4.31 for those with and without COPD) and those with COPD who were sustained quitters (HR=2.92, 95% CI: 2.01 to 4.23) had significantly higher risks of mortality compared to non-COPD never smokers after adjustment for potential confounders (which excluded BMI) (Figure 4.2 and Supplementary Table 4.2). Intermittent smoking people without COPD had the largest association with mortality with nearly 5 times the rate of mortality but had a wide confidence interval (95% CI: 1.74 to 13.0). Time-varying BMI showed a marginally significant inverse association with mortality (HR= 0.99; 95% CI: 0.97 to 1.00 for each increase in BMI kg/m^2).

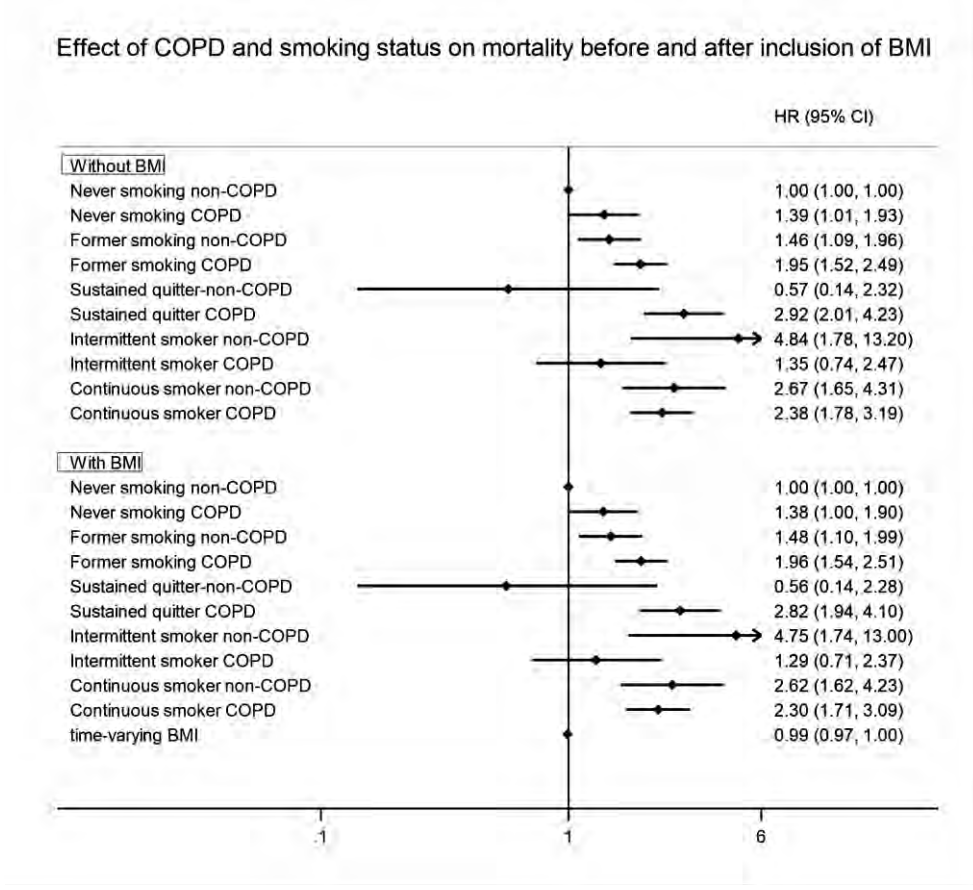


Figure 4.2: Forest plot showing the results of two separate models of the association between Smoking-COPD status groups and mortality. One model before (top) and one after (bottom) the inclusion of time-varying BMI in the model. Other covariates in both models are shown in the table below.

Supplementary Table 4.2: The association between status group and mortality before (left column) and after (right column) adjustment for changes in BMI (kg/m^2) over time in incident and prevalent THIN COPD patients and people without COPD (N=2704) using multivariable Cox survival analysis.

	HR (95% CI)	HR (95% CI)
Never smoking non-COPD	(reference)	(reference)
Never smoking COPD	1.39 (1.01 to 1.93)	1.38 (1.00 to 1.90)
Former smoking non-COPD	1.46 (1.09 to 1.96)	1.48 (1.10 to 1.99)
Former smoking COPD	1.95 (1.52 to 2.49)	1.96 (1.54 to 2.51)
Sustained quitter-non-COPD	0.57 (0.14 to 2.32)	0.56 (0.14 to 2.28)
Sustained quitter COPD	2.92 (2.01 to 4.23)	2.82 (1.94 to 4.10)
Intermittent smoker non-COPD	4.84 (1.78 to 13.2)	4.75 (1.74 to 13.0)
Intermittent smoker COPD	1.35 (0.74 to 2.47)	1.29 (0.71 to 2.37)
Continuous smoker non-COPD	2.67 (1.65 to 4.31)	2.62 (1.62 to 4.23)
Continuous smoker COPD	2.38 (1.78 to 3.19)	2.30 (1.71 to 3.09)
time-varying body mass index - per one kg/m^2 increase	.	0.99 (0.97 to 1.00)
age - per one year increase	1.07 (1.06 to 1.08)	1.07 (1.06 to 1.08)
male	1.37 (1.16 to 1.61)	1.36 (1.15 to 1.60)
Townsend score - per one quintile increase in deprivation	1.13 (1.07 to 1.20)	1.14 (1.08 to 1.20)
heart failure	1.53 (1.19 to 1.96)	1.53 (1.19 to 1.96)
coronary heart disease	1.05 (0.88 to 1.26)	1.06 (0.89 to 1.28)
stroke/TIA	1.05 (0.82 to 1.33)	1.05 (0.82 to 1.34)
liver disease	1.50 (0.80 to 2.81)	1.52 (0.81 to 2.84)
diabetes	1.21 (1.01 to 1.45)	1.26 (1.05 to 1.51)
kidney disease	0.68 (0.52 to 0.88)	0.69 (0.53 to 0.90)

Incident COPD patients tended to have a stronger association between COPD-smoking status and mortality than the main analysis (Supplementary Table 4.3). However, the effect estimates still remained relatively unchanged before and after adjusting for BMI which also showed only a marginal inverse association with mortality (HR =0.99; 95% CI: 0.97 to 1.01).

Supplementary Table 4.3: The association between status group and mortality before and after adjustment for changes in BMI (kg/m^2) over time in incident THIN COPD patients and people without COPD (N=1866) using multivariable Cox survival analysis.

	HR (95% CI)	HR (95% CI)
Never smoking non-COPD	(reference)	(reference)
Never smoking COPD	1.89 (1.17 to 3.07)	1.86 (1.15 to 3.02)
Former smoking non-COPD	1.82 (1.15 to 2.87)	1.85 (1.17 to 2.92)
Former smoking COPD	2.27 (1.56 to 3.31)	2.29 (1.57 to 3.34)
Sustained quitter-non-COPD	0.72 (0.10 to 5.30)	0.70 (0.10 to 5.11)
Sustained quitter COPD	3.17 (1.84 to 5.48)	3.03 (1.75 to 5.25)
Intermittent smoker COPD	0.97 (0.34 to 2.73)	0.92 (0.32 to 2.58)
Continuous smoker non-COPD*	2.93 (1.49 to 5.79)	2.85 (1.44 to 5.63)
Continuous smoker COPD	2.94 (1.93 to 4.49)	2.80 (1.83 to 4.29)
time-varying body mass index - per one kg/m^2 increase	.	0.98 (0.96 to 1.00)
age - per one year increase	1.07 (1.06 to 1.08)	1.07 (1.05 to 1.08)
male	1.27 (1.00 to 1.60)	1.25 (0.99 to 1.58)
Townsend score - per one quintile increase in deprivation	1.10 (1.02 to 1.19)	1.10 (1.02 to 1.19)
heart failure	1.42 (0.98 to 2.07)	1.44 (0.99 to 2.10)
coronary heart disease	1.01 (0.78 to 1.32)	1.03 (0.79 to 1.35)
stroke/TIA	0.89 (0.60 to 1.31)	0.88 (0.60 to 1.30)
liver disease	1.61 (0.75 to 3.43)	1.63 (0.77 to 3.49)
diabetes	1.15 (0.89 to 1.50)	1.21 (0.93 to 1.59)
kidney disease	0.99 (0.73 to 1.33)	1.00 (0.74 to 1.35)

*Intermittent smoker non-COPD patients were collapsed into continuous smoking non-COPD patients because of too few numbers to properly estimate effect size. HR for continuous smoking non-COPD patients before the collapsed group was formed was 3.02

Combined with previous results showing strong positive associations between status groups with both BMI trajectories and mortality, time-varying BMI showed a marginally significant inverse association with mortality after adjustment for other factors. However, adjustment for time-varying BMI had little effect on the

coefficients for the status groups, suggesting little impact in mediating their effects on mortality.

DISCUSSION

We found that people with COPD had a slightly lower baseline BMI than non-COPD controls with the same smoking behaviour. Smoking status was more influential; former smokers from both groups had the highest BMI, followed by never smokers, with the lowest baseline BMI measurements observed among COPD patients who were recently or currently smoking. There were only two groups that demonstrated a significant difference in trajectory compared with the reference group, indicating the importance of both smoking and COPD jointly on BMI. There was a significantly more rapid decline in BMI among COPD patients who continued to smoke. Conversely, sustained quitters with COPD experienced a significant increase in BMI over time. Furthermore, although COPD and smoking independently affected mortality (where smoking seemed to have the strongest effect), BMI did not appear to act as a mediator.

On average, body weight tended to decrease over time in all people regardless of COPD status, which is similar to findings in another study of older (mean age about 73 years) men and women, some with obstructive lung disease (213). This is in contrast to many general population studies which include younger people and have shown that overall, adults gain approximately 0.3 kg to 1.2 kg/year (225–231). Weight gain is more pronounced in healthy young adults whereas with increasing age, the rate of weight gain decreases (232). Age-related decline in body weight in older adults is often due to decreases in skeletal muscle, fat mass, lean mass, and bone mineral content (213). Additionally, general practitioners may be more likely to perform weight measurements if they are worried about a patient losing weight over time in the presence of disease. Overall, the effects of smoking and COPD on BMI trajectories shown in the present study may only be relevant in patients who are older and already experiencing an age-related decline in body weight.

Our results showed that the greater increase in BMI after quitting in COPD seemed to be mirrored by the greater rate of decline in BMI among continuous smokers with COPD. These findings make sense within the context of prior literature. BMI trajectories were altered mainly in those who were current smokers or recent quitters which agrees with evidence that nicotine may have a short-term effect on increasing energy expenditure and a reduction in appetite (105). This effect of

smoking on body weight reduction may be worsened in COPD because there is more work associated with breathing when a patient has impaired lung function and respiratory symptoms (233). In addition, dyspnoea while eating or preparing meals as well as COPD-related depression and anxiety may alter a patient's eating habits and appetite (102,234) and result in weight loss. Also, low-grade systemic inflammation (235,236) and prolonged physical inactivity (237) may result in a loss in skeletal muscle mass and contribute to muscle wasting and reduced body weight (238).

On the other hand, smoking cessation is associated with a short-term increased dietary intake (105) and the effect may even remain past one year of follow-up (239). Weight gain after quitting may be due to an increased energy intake and decreased energy expenditure (105). COPD sustained quitters may have a greater rate of BMI gain than similar people without COPD because many COPD patients may rebound after the combined effect of both smoking and COPD decreasing their weight over time. Smoking cessation may increase BMI in COPD patients more than people without COPD because cessation can more dramatically improve respiratory symptoms, inflammation, physical inactivity, and muscle wasting if these factors are already worse, to begin with. Quitting smoking may not only improve nutritional health in COPD patients but it also alters the natural history of COPD (210) which may further improve nutritional status (and health status) for the reasons mentioned above.

Several studies have investigated the effect of smoking on body composition in COPD (213–217). However, results are mixed as to whether smoking or COPD status plays a primary role in body composition changes over time or if these two factors have a joint effect. A longitudinal analysis of 3,075 Health, Aging and Body Composition (ABC) cohort participants from the US showed that smoking may compromise body composition regardless of COPD status attributing this similarity to a common smoking-related insult earlier in life (213). The trajectories of body weight over time were similar to patients from THIN, however, our conclusion is more consistent with a joint effect of smoking and COPD on BMI over time. This may be due to our ability to distinguish smoking status groups within COPD which was not possible in the ABC cohort due to a smaller sample (n= 260). Also, the Health-ABC study included only participants aged 70-79 years old and COPD was not clinically diagnosed. On the other hand, a study using the ECLIPSE cohort found that the percentage of patients with an increase (>0.5) or a decrease (< 0.5) in fat-free mass index and fat-mass index over three years was similar for COPD patients and smoking and non-smoking controls (214), which suggests that

smoking and COPD may not have a large role in changes in body composition. Also, ECLIPSE participants with a continuous decline in fat-free mass had a slight, non-significantly higher number of pack-years of smoking compared to the remaining patients (45 versus 43, respectively) (240). However, changes in smoking status were not examined in ECLIPSE. In 32 smokers (smoking history >10 pack/years), 32 mild/ moderate COPD (current smokers or former smokers), and 32 never smokers, smoking and early COPD both jointly reduced body composition (fat-free mass) in a Brazilian population (215). Finally, in 64 patients with stable COPD, the decline in fat-free mass was associated with continued smoking (216), although no people without COPD were included. These studies were unable to assess smoking behaviour in COPD and people without COPD due to low sample sizes and often lacked generalisability. Also, some studies were cross-sectional while the others often had shorter follow-up times with relatively few longitudinal body composition measurements.

We showed that COPD and smoking both influence mortality. The associations between certain status groups and mortality were surprising. For instance, patients who were sustained quitters had a higher rate of mortality than continuous smokers among COPD patients. However, COPD patients with more severe disease may have been more likely to quit when compared to those with less severe disease. Unfortunately, we were not able to adjust for the degree of airflow limitation, breathlessness, or other measures of COPD severity due to high levels of missing data. Intermittent smoking people without COPD had a very high rate of mortality but the wide confidence interval was largely due to very few individuals in this particular group. Unsurprising was the finding that incident patients had a worse prognosis given the survival bias found in cohorts containing prevalent cases (224). There does not seem to be an indirect effect of COPD-smoking status on mortality that goes through lowering BMI. This conclusion is evidenced by only slightly altered effect estimates after adjusting for BMI over time, which itself was only marginally significant in the full model. This indicates that while COPD and smoking may both reduce BMI, clinicians need to consider these factors separately and, ideally, in a holistic and personalised manner given that they impact prognosis via distinct pathways. For instance, pharmacotherapy can improve COPD symptoms, nutritional support may be given to patients who are malnourished, and smoking cessation advice can help current smokers to quit. All three of these treatment pathways may help patients with low BMI to increase their weight over time and reduce their risk of mortality.

There are several limitations in this study. The recording of smoking may be less frequent in the non-COPD cohort given that these patients are less likely to suffer from QOF conditions (241) that reward GPs for recording smoking status. People without COPD may quit smoking, and these may not be recorded, biasing BMI trajectories toward a less rapid decline. Next, we are relying on reported weight measures, and know that GPs do not routinely weigh patients and are more likely to weigh in the context of chronic disease or if worried about excess weight gain or loss. The likelihood that GPs weigh patients may also vary by the type of disease individuals are diagnosed with. For instance, we found that people without COPD are more likely to have diabetes than COPD patients. People without COPD may be more likely to be treated with diabetes as their primary condition where weight is a bigger concern for General Practitioners and so these patients would receive more weight measurements. Therefore, these patients would be more likely to be included in our study. Finally, smoking tends to increase abdominal obesity but not overall obesity (242). This indicates that smokers have different fat distributions and/or decreased muscle mass which may be more appropriate measures than BMI when describing adverse health. Secondly, BMI may not be as clinically relevant for COPD patients as muscle mass and skeletal muscle mass (i.e., muscle wasting). Cachexia and muscle wasting is a common and reversible feature in COPD that contributes to decreased exercise capacity and health-related quality of life, and increased mortality (243). However, muscle and fat measurements are not possible in certain healthcare settings. With this in mind, two different definitions of cachexia were established in a recent paper (103): Consensus cachexia ("weight-loss > 5% in 12-months or low BMI in addition to 3/5 of decreased muscle strength, fatigue, anorexia, low FFMI, and inflammation") and weight loss cachexia ("The weight-loss definition incorporated weight-loss > 5% or weight-loss > 2% (if low BMI) in 12-months"). Both had a similarly strong and independent association with mortality.

In conclusion, among never smokers and former smokers, and in people with and without COPD, there is a similar rate of decline in weight over time. However, weight loss due to continuous smoking is accelerated if a person has COPD. Quitting in those with COPD results in an accelerated weight gain compared to those without COPD. Finally, weight loss does not mediate the association between COPD-smoking and mortality.

CHAPTER V: TRENDS IN MODERATE AND SEVERE EXACERBATIONS AMONG COPD PATIENTS IN THE UK FROM 2005 TO 2013

Olorunfemi A. Oshagbemi*[2,3,4,8], Spencer J. Keene*[1,2,4], Johanna. H.M. Driessen[2,3,8], Rachel Jordan[1], Emiel F.M. Wouters[4,6,7], Anthonius de Boer[3], Frank de Vries[2,3,8], Frits M.E. Franssen[4,6,9]

*denotes joint first authorship

Affiliations

[1] Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom.

[2] Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center+, Maastricht, the Netherlands

[3] Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht the Netherlands.

[4] CIRO+, Horn, the Netherlands

[5] NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, UK

[6] Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands

[7] Ludwig Boltzman Institute for Lung Health, Vienna, Austria

[8] Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+, Maastricht, the Netherlands

[9] Department of Respiratory Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre+, Maastricht, the Netherlands.

ABSTRACT

Introduction*:* Exacerbations of chronic obstructive pulmonary disease (COPD) are characterised by increased symptoms such as dyspnoea, cough, and sputum production and/or purulence, leading to a greater risk of hospitalisation and mortality. Very few studies have measured long-term trends in the incidence of exacerbations of chronic obstructive pulmonary disease. We, therefore, investigated the incidence of moderate-to-severe and severe exacerbations in the United Kingdom (UK) general population.

Methods: A population-based study including Clinical Practice Research Datalink (CPRD) patients ≥ 40 years of age with a current diagnosis of COPD within the UK from 2004 to 2013 was conducted. Individuals with a history of asthma were excluded from the main analyses. We calculated the incidence rates for moderate-to-severe and severe exacerbations. Patients contributed time at risk from 1 January up to the date of the first outcome within each year. The incidence rate for moderate-to-severe and severe COPD exacerbations in each calendar year was calculated as follows: the sum of moderate-to-severe or severe COPD exacerbations in that year divided by the total duration of follow-up in the same calendar year from 2005 through to 2013. We then analysed these rates by gender and age categories (40-59 years, 60-79 years, and ≥80 years).

Results: Among 213,561 patients with incident COPD diagnosis, 86,300 patients were included in the study. From 2005 to 2013, the incidence rate of moderate-to-severe exacerbations increased from 89 events to 98 events per 1000 person-years (PYs). Women had higher incidence rates of moderate-to-severe exacerbation for each calendar year when compared to men ($p<0.0001$). The incidence rate of moderate-to-severe exacerbations increased with age from 2005 to 2007. The incidence of severe exacerbations decreased from 2005 to 2007 before increasing from 2008 until the end of follow-up (43 events per 1000 PYs (95% confidence interval, 42-45/1000PYs) in 2013). Incidence rates of severe exacerbations were similar by gender and patients aged 80+ years had a higher incidence rate of severe exacerbation from 2005 to 2008 after which their incidence rates dropped in subsequent years.

Conclusions: To our knowledge, this is the first study that reports the long-term changes in the incidence rates of moderate-to-severe and severe exacerbations within the UK general practice. Women showed a substantially higher incidence rate of moderate-to-severe COPD exacerbations, and their rate increased across calendar years. The incidence rates of exacerbations, especially severe exacerbations, increased during the study period.

The Chapter was published as: Oshagbemi OA*, Keene SJ*, Driessen JHM, Jordan R, Wouters EFM, de Boer A, et al. Trends in moderate and severe

exacerbations among COPD patients in the UK from 2005 to 2013. Respir Med. 2018;144(Nov):1–6.

INTRODUCTION

Exacerbations of chronic obstructive pulmonary disease (COPD) are defined as acute episodes of increased respiratory symptoms necessitating additional therapy (244). The most prevalent and impactful symptoms during exacerbations tend to be increased dyspnoea, cough, sputum production and/or purulence. Exacerbations of COPD negatively impact lung function (245) health status (246) and muscle function (247). They are important drivers of hospitalisations (46) and are associated with high mortality risk (248). There are over a million bed days and 140,000 hospital admissions each year in the United Kingdom (UK) due to COPD (1.7% of all hospital admissions and bed days) (249) where £253 million British Pounds (GBP) is spent yearly on COPD management, with more than 50% of the costs attributed to exacerbations (250). Thus, prevention of exacerbations of COPD is one of the main goals of pharmacologic treatment of the disease (251). Understanding trends in acute exacerbations and related hospitalisations can help redirect healthcare policies and interventions to subgroups most affected by exacerbations of COPD, allow comparison between countries to aid healthcare planning, predict future healthcare challenges, and provide a basis for improving future management, but this has not been adequately described in a UK population. The role of demographic characteristics in shaping the trends in exacerbations and related hospitalisations over time is also poorly understood. Thus, there is a need to understand the constantly changing trends and to subsequently target health planning and policies towards groups who have a higher incidence of exacerbations of COPD (252). Therefore, this study aims to describe the incidence rates of moderate-to-severe and severe COPD exacerbations by age and gender within the UK primary care setting from 2005-2013.

METHODS

Data source

This study was conducted with data from the Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database (GPRD). CPRD contains computerized medical records of 674 primary care practices in the UK. Data collection started in January 1987 and over 11 million persons are currently included, corresponding to 7% of the UK population (253). The introduction of the Quality and Outcomes Framework (QOF) in April 2004 was aimed at facilitating quality reporting of various diseases by General Practitioners (GPs), including COPD and its related outcomes (254). The quality management

system uses indicators recorded by GPs to monitor effectiveness in COPD reporting and to reduce the rate of misdiagnosis. Indeed, a high positive predictive value in identifying patients with COPD based on these Read codes has been reported (253), and the CPRD has been used in various studies on COPD (255–257). The independent scientific advisory committee of the Medicines and Healthcare product Regulatory Agency (MHRA) database research approved this study. (ISAC protocol No: 18_046R).

Study population

We selected all patients aged ≥40 years with a diagnosis of COPD as recorded by Read codes within the CPRD. The study period began on 1 January 2004, corresponding to the period since the introduction of the Quality and Outcomes Framework (QOF), and ended on 31 December 2013. However, we calculated incidence rates starting from 2005 to allow practices at least one year to record demographic characteristics and outcomes under the new scheme. For the main analyses, we excluded all patients with a history of asthma from the study and COPD diagnosis prior to 2004. Follow-up ended at the earliest of the study end date (31 December 2013), the patient's death, or transfer out of the practice. The primary endpoint was moderate-to-severe exacerbation defined as the first acute exacerbation of COPD in a given calendar year (i.e. patients with an outcome only contributed time at risk from 1 January up to the date of the first outcome within each year), identified using validated Read codes for exacerbations of COPD (258) from the referral and/or clinical files. The secondary outcome was the first severe exacerbation in a given calendar year. This was defined using Read codes for COPD-related hospitalisations/accident and emergency (AE) visit from both clinical and/or referral files in addition to validated Read codes for COPD exacerbations from the referral file. Referral files contain referral details recorded by GPs while the clinical files contain all the medical history data entered by the GP (259).

Statistical analysis

The incidence rates for moderate-to-severe and severe COPD exacerbations in each calendar year were calculated as the sum of moderate-to-severe or severe COPD exacerbations in that year divided by the total duration of follow-up in the same calendar year. We only calculated incidence rates from 2005 through 2013. The incidence rates were expressed as the number of exacerbations per 1000 person-years (PY). We then analysed these rates by gender and age categories (40-59 years, 60-79 years, and ≥80 years). The incidence rates are accompanied by 95% confidence intervals (CI). All analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC).

Sensitivity analysis

In the first sensitivity analysis, we no longer counted the first event within a given calendar year, but we added up all exacerbations that occurred in a calendar year. To overcome the problem of potentially counting the same event more than once,

we stipulated a gap of at least 30 days between consecutive events of moderate-to-severe exacerbations of COPD. This sensitivity analysis was carried out to depict the overall trend of moderate-to-severe exacerbations of COPD. In the second sensitivity analysis, we included patients with a history of asthma and estimated the incidence rates considering only the first exacerbation.

RESULTS

We identified 213,561 patients with COPD diagnosis within the CPRD of whom 86,300 met the inclusion criteria. The mean age of patients in our study was 68 years and 45.5% (n=39,241) were women (Table 5.1). Approximately 18% of patients were taking LAMAs and less than 9% were on LABAs.

Table 5.1. Baseline characteristics of COPD patients

	n=86,300	%
Females	39,241	45.5
Mean age (years, SD)	68.1	11.3
Age category (years)		
40-59	19,475	22.6
60-79	51,982	60.2
80+	14,843	17.2
BMI (kg/m^2) in the past 6 months		
Underweight (BMI < 18.5 kg/m^2)	4,784	5.5
Normal weight (BMI 18.5-24.9 kg/ m^2)	29,808	34.5
Overweight (BMI 25.0-29.9kg/ m^2)	26,529	30.7
Obese (BMI ≥ 30,0 kg/ m^2)	20,938	24.4
Missing	4,241	4.9
Smoking status at index date		
Never	9,005	10.4
Current	38,207	44.3
Former	38,662	44.8
Missing	426	0.5
Drug use (in the past 6 months)		
SABAs	48,624	56.3
LABAs	7,542	8.7
SAMAs	7,576	8.8
LAMAs	15,102	17.5
Xanthine derivatives	770	0.3
Antidepressants	17,063	19.8
History of co-morbidities		
Diabetes Mellitus	9,619	11.1
Anxiety	12,267	14.2
Osteoporosis	15,063	5.9
Malignancies excluding non-melanoma skin cancer	12,357	14.3
Chronic liver disease	292	0.3
Ischaemic heart disease	12,493	14.5

Abbreviations: SD, standard deviation; COPD, chronic obstructive pulmonary disease; BMI, body mass index; SABAs, short-acting beta-2 agonists; LABAs, long-acting beta-2

agonists; SAMAs, short-acting muscarinic antagonists; LAMAs, long-acting muscarinic antagonists; ICS, inhaled corticosteroids.

Trends in moderate-to-severe COPD exacerbations

Table 5.2 shows the overall incidence rates of moderate-to-severe COPD exacerbations. We observed 30,996 COPD exacerbations during the study period. From 2005 to 2007, the incidence rate of the exacerbations remained stable at around 88 events per 1000PYs. A rise in the incidence rate of exacerbations was noted from 2008 to 2012 (112 events per 1000PYs (95%CI, 109-114/1000PYs)). However, we observed a decrease in the incidence of exacerbations to 98 events per 1000 PYs in 2013.

Table 5.2. Incidence rates[a] of moderate-to-severe COPD exacerbations from 2005-2013[b]

Year	No. of moderate-to-severe exacerbations n=30,996	PY at risk	IR /1000 PY (95% CI)
2005	1,110	12514.4	89 (84-95)
2006	1,678	18981.8	88 (84-93)
2007	2,194	24905.1	88 (85-92)
2008	2,838	30441.4	93 (90-97)
2009	3,356	35161.5	95 (92-99)
2010	4,315	40319.5	107 (104-110)
2011	4,839	44777.5	108 (105-111)
2012	5,500	49260.1	112 (109-114)
2013	5,166	52893.7	98 (95-100)

[a] Only one event per calendar year was counted.
Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; HR, hazard ratio; AE, accident, and emergency; PY, person-years; CI, confidence interval.
[b]using validated read codes for AECOPD from clinical and/or referral files.

Gender-specific incidence rates are shown in Figure 5.1 (top). In both men and women, incidence rates for moderate-to-severe exacerbations followed a somewhat similar pattern of year-to-year change. Women had greater incidence rates of exacerbations in each calendar year compared to men ($p<0.0001$). The incidence rates for both men and women increased from 84 events to 95 events in 2005 to 90 events and 107 events per 1000 PYs in 2013, respectively.

Figure 5.2 (top) shows the incidence rates of moderate-to-severe exacerbations by age. There was an increasing incidence rate of moderate-to-severe exacerbations with increasing age group from 2005 to 2007 which disappeared from 2009 to 2013. We observed a decrease in year-to-year incidence rates of moderate-to-severe exacerbations for 80+ year-old patients. In contrast, exacerbation rates increased across the study period for patients in the 40-59 and the 60-79 year age groups.

Trends in severe COPD exacerbations

Between 2005 and 2013 we found 8032 severe COPD exacerbations. From 2005 to 2007 there was a decline in the incidence of severe COPD exacerbations from 18 events to 11 events per 1000 PYs (Table 5.3). However, there was a steady increase from 2008 until the end of the study period. In 2013, the incidence rate was 43 events per 1000 PYs.

Table 5.3. Incidence rates of severe COPD exacerbations from 2005-2013[b]

Year	No. of severe exacerbations [a] n=8032	PY at risk	IR /1000 PY (95% CI)
2005	229	12896.0	18 (16-20)
2006	248	19646.9	13 (11-14)
2007	277	25792.1	11 (10-12)
2008	455	31421.6	14 (13-16)
2009	556	36382.1	15 (14-17)
2010	821	41713.3	20 (18-21)
2011	1,224	46192.4	26 (25-28)
2012	1,902	50388.8	38 (36-39)
2013	2,320	53691.0	43 (42-45)

[a]Only one event per calendar year was counted.

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; HR, hazard ratio; AE, accident, and emergency; PY, person-years; CI, confidence interval.

[b]using read codes for hospitalisation/AE visits for COPD from clinical and/or referral files in addition to validated read codes for AECOPD from referral file.

Figure 5.1 (bottom) shows the incidence rates of severe exacerbations by gender. Similar to the overall trend, both men and women showed a flattened ‘U’ shaped decrease in severe exacerbation incidence rates before an increase from 2008 to their peak rates in 2013. Women and men had similar incidence rates in each

calendar year of the study. Figure 5.2 (bottom) shows the incidence rates of severe COPD exacerbations by age. For each age group, the incidence rates for severe exacerbations decreased from 2005 to 2007 before increasing from 2008 to 2013. We noted an increasing incidence rate of severe exacerbations by age from 2005 to 2008. However, in 2012 and 2013 patients aged 60-79 years had a higher incidence rate compared to other age groups. For all age groups, the rates in 2009 were similar.

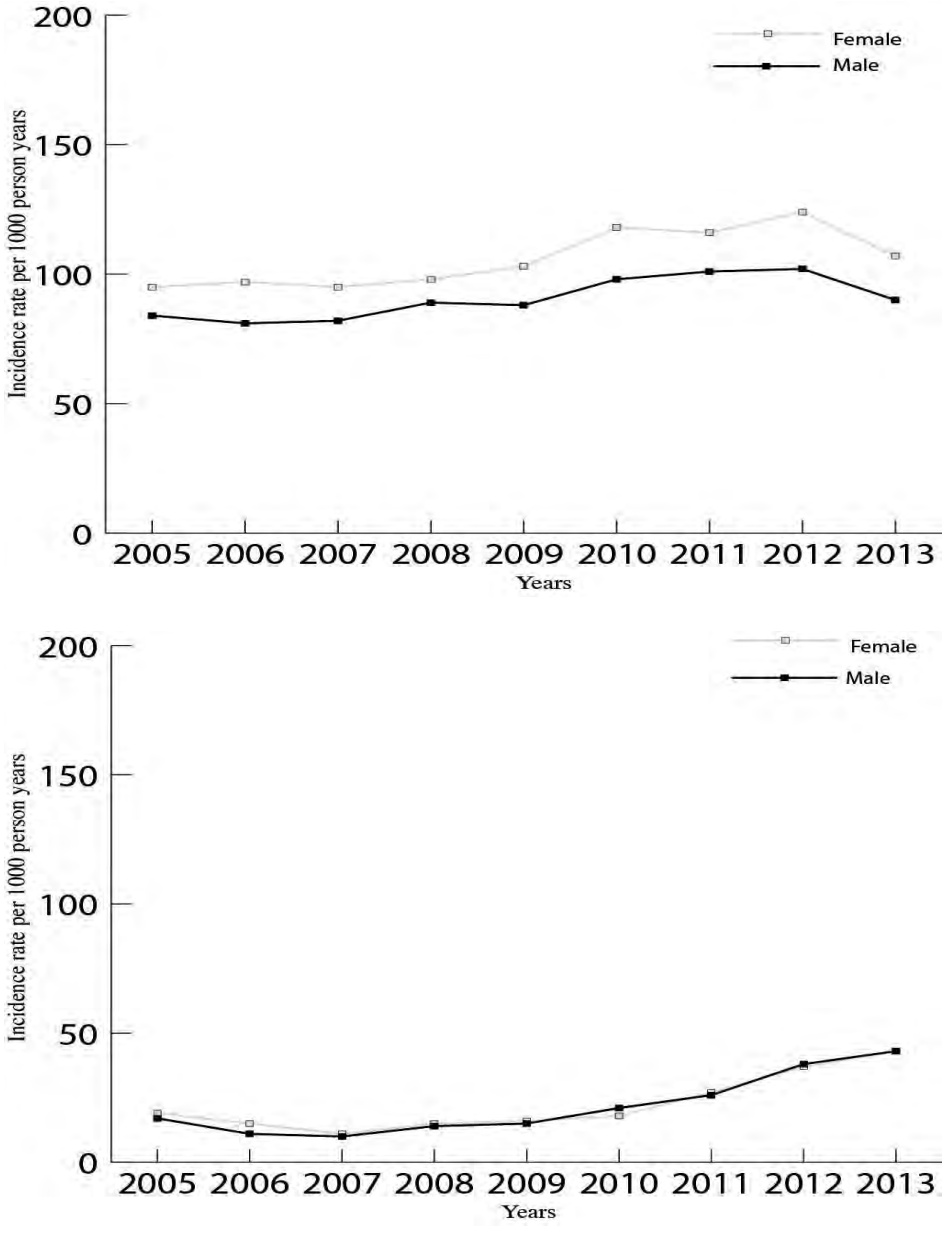


Figure 5.1. Incidence rates of (top) moderate-to-severe[a] exacerbations or (bottom) severe[b] COPD exacerbations by gender.

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; AE, accident, and emergency; PY, person-years.

[a] using validated read codes for AECOPD from clinical and/or referral files.

[b]using read codes for hospitalisation/AE visits for COPD from clinical and/or referral files in addition to validated read codes for AECOPD from referral file.

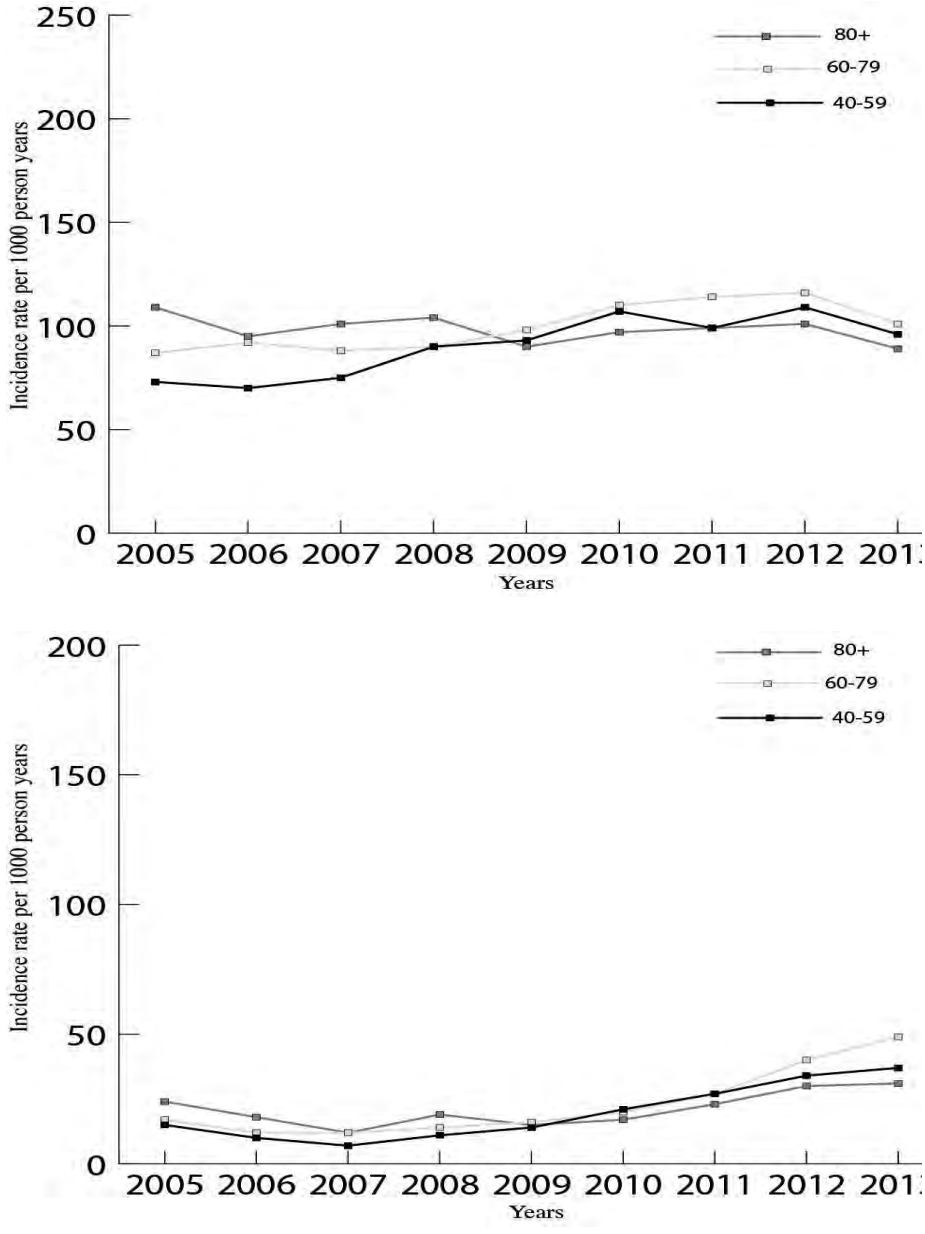


Figure 5.2. Incidence rates of (top) moderate-to-severe[a] exacerbations or (bottom) severe[b] COPD exacerbations by age.

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; AE, accident, and emergency; PY, person-years.

[a] using validated read codes for AECOPD from clinical and/or referral files.

[b]using read codes for hospitalisation/AE visits for COPD from clinical and/or referral files in addition to validated read codes for AECOPD from referral file.

Sensitivity analysis of trends of moderate-to-severe exacerbations of COPD. For the first sensitivity analysis, we considered multiple events in a given calendar year (see Table 5.4). A total of 44,183 exacerbations of COPD were observed during the study period. The trends were similar to when we evaluated only one event in each calendar year. The incidence rates were similar from 2005 to 2009 before increasing to >130 events per 1000 PYs from 2010 before returning to 113 events per 1000 PYs in 2013.

Table 5.4 Incidence rates[a] of moderate-to-severe COPD exacerbations from 2005-2013[b]

Year	No. of moderate-to-severe exacerbations n=44,183	PY at risk	IR /1000 PY (95% CI)
2005	1,471	13350.9	110 (105-116)
2006	2,260	20607.8	109 (105-114)
2007	3,034	27540.5	110 (107-114)
2008	3,934	34209.7	114 (112-118)
2009	4,760	40181.9	118 (115-122)
2010	6,247	46885.5	133 (130-136)
2011	7,137	52995.1	134 (132-138)
2012	8,090	59217.2	137 (134-139)
2013	7,250	64304.4	113 (110-115)

[a]We counted all events occurring 30 days between consecutive events within a calendar year.

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; HR, hazard ratio; AE, accident and emergency; PY, person-years; CI, confidence interval.

[b]using validated read codes for AECOPD from clinical and/or referral files.

In the second sensitivity analysis we included patients with a history of asthma. A total of 53,514 COPD exacerbations were observed during the study period (Table 5.5). The year-on-year incidence rates changed less dramatically over time and were higher when compared to the main analysis but the overall trend was similar (Table 5.2).

Table 5.5 Incidence rates[a] of moderate-to-severe COPD exacerbations from 2005-2013 among COPD patients with history of asthma[b]

Year	No. of moderate-to-severe exacerbations n=53,514	PY at risk	IR /1000 PY (95% CI)
2005	2,098	19984.5	105 (101-109)
2006	3,100	30311.7	102 (99-106)
2007	4,082	39632.7	103 (100-106)
2008	5,106	48203.1	106 (103-109)
2009	5,858	55284.1	106 (103-109)
2010	7,390	63121.3	117 (115-120)
2011	8,273	69617.8	119 (116-121)
2012	9,204	76043.7	121 (119-123)
2013	8,403	81196.9	103 (101-106)

[a]Only one event per calendar year was counted.
Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; IR, incidence rate; HR, hazard ratio; AE, accident, and emergency; PY, person-years; CI, confidence interval.
[b]using validated read codes for AECOPD from clinical and/or referral files.

DISCUSSION

Summary of main findings

Using the world's largest primary care database, this study showed an increase in the incidence rates from 2005 to 2013 for moderate-to-severe exacerbations and, especially, severe exacerbations of COPD. Female patients had higher incidence rates of moderate-to-severe exacerbations compared to male patients throughout the study period, but they had similar incidence rates of severe COPD exacerbations.

Comparison with existing literature and interpretation

To the best of our knowledge there has been no previous large-scale population-based studies on the trends of moderate-to-severe exacerbations of COPD in the UK. Previous studies have focused mainly on the prevalence rates of COPD (260–262). Using the Health Improvement Network database, Snell et al (249), reported a 27% increase in the prevalence of COPD in the UK from 2004 to 2012. The increase in the prevalence of COPD is concurrent with the increase in the incidence of moderate-to-severe and severe exacerbations of COPD in our study. A study conducted among 423 COPD patients within the Dutch general practice from 1980 to 2006 reported a reduction in overall annual exacerbation rates, independent of age and sex (252). A decline in COPD exacerbation rates might be related to changes in treatment guidelines for COPD and increased emphasis on vaccination during the study period (252). In our study, we also found that the incidence rates of acute exacerbations increased with increasing age in certain years. This might be due to disease progression and the severity of the disease state. In other years, the oldest age group did not have the highest rates of exacerbations. However, investigators have previously reported a relationship between age and underreporting of acute exacerbations (263), which means that the incidence rates might be underestimated among older patients and the degree of underreporting may vary by calendar year in our study. Still, we examined that severe exacerbation rates are lowest in the oldest age group and highest in the middle age group and this is more difficult to explain.

Fuhrman et al (264), examined the temporal trends in acute exacerbations related to hospitalisations from 1998 to 2007 in France and found that admission rates increased significantly, especially among females. Although, our study also reported an increase in severe exacerbations there were only slight differences by gender for all years. Another study conducted in Brazil found no changes in hospitalisation rates from 1998 to 2009 (265). The Hospital Episode Statistics published by the UK Department of Health from 1998 to 2003 showed an increase in the number of admissions for COPD of 13%, with most admissions for emergency reasons (266). It has been reported that 30% of patients hospitalised for exacerbations will be seen again and possibly admitted with another exacerbation within 8 weeks (266). Contrary to our findings, a study in Canada investigating the incidence of COPD which defined COPD diagnosis based on AE visit and hospitalisation reported a reduction in the incidence of COPD from 1996 to 2007 (260). Similarly, Kinnula et al,(267) reported a decrease in the rates of hospitalisations associated with COPD in Finland from 1998 to 2007.

The low incidence rates of severe exacerbations in our study might be related to the fact that most COPD patients die from various fatal comorbidities - associated with COPD severity - before hospitalisation for acute COPD exacerbations (268).

Another explanation is that many patients have problems in identifying symptom aggravation and fail to report exacerbations to health experts (269,270), resulting in spontaneous hospitalisations and AE visits. Additionally, GPs often record COPD hospitalisation using less specific Read codes (271).
A dissociation has been reported between adherence to guidelines and actual management of COPD patients (272). A study conducted among 24,957 COPD patients in the UK showed that patients were not managed following GOLD and National Institute for Health and Care Excellence recommendations, with a substantial proportion of patients not receiving appropriate medications (273). Despite current developments with LAMA/LABA and ICS in the treatment of COPD patients, we found no objective reduction in exacerbations in our study. Low adherence to therapy (274), and improper inhaler technique among COPD patients (251) may have contributed to the observed trends. It is also important to note that the use of long-acting agents was low in our study cohort.

Strengths and limitations

A major strength of this study was the inclusion of patients from one of the world's largest primary care databases, thus providing a very large sample size. Using CPRD ensured that our results were generalizable to the UK population, especially since management of patients with COPD in the UK is performed mainly within the primary care setting (147). Second, we were able to assess the incidence rates over a long period. Third, we considered periods since the introduction of the QOF ensuring greater quality of data recording. Fourth, we used validated Read codes for acute exacerbations of COPD. Lastly, a validation study of COPD patients in the CPRD concluded that patients with COPD could be identified easily using specific Read codes (253).
Despite the numerous strengths, this study had some limitations. While the method of diagnosis of COPD has not changed since 2005, GPs ability to identify exacerbations of COPD might have changed over time (275), which may have affected our findings. The use of the Read codes for acute exacerbation may have underestimated the true incidence rates of COPD exacerbations. However, the Read codes used in this study have been reported to have a high positive predictive value (PPV) of 96% in identifying patients with COPD exacerbation in the CPRD (258), and we explored both clinical and referral files to ensure all exacerbations were identified. Nevertheless, we may have missed a considerable number of exacerbations that may have been miscoded (e.g. as respiratory tract infections or pneumonia). Similarly, the incidence rate for severe exacerbations is likely to be an underestimate of the true incidence in the UK. The PPV and

sensitivity for identifying hospitalisations for COPD within the CPRD using only GP-reported Read codes are quite low (50.2% and 5.4%, respectively) (271). Although we excluded asthma patients from the main analyses, it was impossible to rule out the inclusion of patients with reversible airflow limitation in this study (276). Merinopoulou et al (275), reported that the rates of COPD-related hospitalisations from 2011 to 2013 were higher in patients with more severe disease, with the most severe patients (i.e. GOLD D) having 3 times the number of exacerbations compared to the least severe groups (i.e. GOLD A). The lack of information on the disease stage in our study made it impossible to corroborate their finding.

Implication for future research and clinical practice

The higher incidence rates of moderate-to-severe exacerbations among women and the increasing rates of severe exacerbations suggests that efforts should be placed on adherence to treatment guidelines and other interventions. ECLIPSE investigators suggest that patients with two or more exacerbations in a year represent a distinct “frequent exacerbators” phenotype, and have an increased risk of future exacerbations (277). Fundamentally, GPs need to identify these patients by carefully exploring the patients’ history and targeting interventions based on recommendations from clinical guidelines. Also, a greater emphasis should be made on treatment adherence, as “frequent exacerbators” and patients with a history of hospitalisation have been reported to be less likely to adhere to therapy (274). Our results have the potential to help redirect health policies, planning, and interventions to target subgroups more effectively, and may provide a basis for improving overall COPD management in the future. Additional resources may need to be allocated toward better planning and treatment of severe exacerbations in the hospital if the rates of these events are truly increasing but further insight is needed into these findings.

Conclusion

To our knowledge, this is the first study that reports the long-term changes in the incidence rates of exacerbations as recorded by UK general practitioners. The incidence rates of exacerbations increased during the study period. This was especially the case for severe exacerbations. Women showed a substantially higher incidence of moderate-to-severe COPD exacerbations.

CHAPTER VI: EXTERNAL VALIDATION OF TWO PROGNOSTIC MODELS PREDICTING EXACERBATIONS IN ECLIPSE COPD PATIENTS

Spencer J Keene[1,2,4], Rachel E Jordan[1], Frank de Vries[2,3,8], Alice Sitch[1,5], Emiel F.M. Wouters[4,6,7], Peymane Adab[1], Frits M.E. Franssen[4,6,9]

Affiliations

[1] Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom.

[2] Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center+, Maastricht, the Netherlands

[3] Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht the Netherlands.

[4] CIRO+, Horn, the Netherlands

[5] NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, UK

[6] Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands

[7] Ludwig Boltzman Institute for Lung Health, Vienna, Austria

[8] Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+, Maastricht, the Netherlands

[9] NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, the Netherlands.

ABSTRACT

Rationale: The Birmingham Lung Improvement Studies (BLISS) and Bertens' models have sufficient methodological rigour, performance, and practicality to be used in practice for the prediction of exacerbations, but both were only developed (and validated) in primary care.

Objectives: To test and compare the performance of the BLISS and Bertens' scores in patients with more severe COPD.

Methods: 1,817 Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints COPD cohort patients (age= 63 years (SD:7); 65% male; FEV_1%predicted= 49(SD:16)) were used to validate and compare both models for predicting moderate-to-severe and severe exacerbations within 2-years. Secondary endpoints were 1- and 3-year time horizons. Area-under-the-curve (AUC), calibration slope, and calibration-in-the-large (CITL) determined discrimination, whether under- or overprediction was maintained across all patients, and the average under- or overprediction, respectively.

Measurements and Main Results: For predicting severe exacerbations, the BLISS score showed better discrimination than Bertens' at 1- (AUC 0.76 versus 0.70), 2- (0.73 versus 0.68), and 3-years (0.73 versus 0.69), with more accurate calibration slopes and less pronounced over-prediction at 1- and 2-year time horizons. The BLISS score also had better discrimination for predicting moderate-to-severe exacerbations at 1- (AUC 0.72 versus 0.70), 2- (0.73 versus 0.70), and 3-years (0.74 versus 0.71), and better calibration slopes at 1- and 2-years. Both models suffered from under-prediction at 1- and 3-years, however, the BLISS score had greater under-prediction at all time horizons.

Conclusions: The BLISS score more accurately predicted severe exacerbations but neither model should be used to predict moderate-to-severe exacerbations without first updating their intercepts. Future work should test if the BLISS score can effectively guide patient management.

INTRODUCTION

Much of the personal and societal burden caused by chronic obstructive pulmonary disease (COPD) is due to exacerbations (22), defined as an acute worsening of symptoms requiring additional respiratory medication (278). Exacerbations requiring hospitalisation are associated with substantial healthcare costs (46), high readmission rates (279), and mortality risk (280). Thus, the prevention of severe exacerbations is a central goal in the care of COPD patients (278). Before treatment decisions are made, however, potential adverse effects and costs of pharmacotherapy should be weighed against the predicted risk of exacerbations and hospitalisations in individual patients (138).

The Birmingham Lung Improvement Studies (BLISS) model was recently developed to predict respiratory hospitalisations among primary care COPD patients in the United Kingdom (281). Unlike many previously developed models predicting exacerbations, the BLISS score was developed using best practice methodology, is accurate (AUC= 0.75), and contains predictors that are easily accessible across a wide range of settings (148). A recent systematic review (139) showed that the only other prediction model for exacerbations that was developed with a low risk of bias was Bertens' model, which was also developed (and externally validated) in primary care (149). However, neither the BLISS nor Bertens' models have been tested in patients with more severe COPD, where exacerbations and hospitalisations are more likely to occur (26). These models may have a different accuracy in this patient population (138). Accurate models across the COPD population are needed to appropriately guide clinical decision-making.

In this external validation study, we aimed to test and compare the accuracy of the BLISS and Bertens' models in predicting exacerbations in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) COPD population (282).

METHODS

Study design

This external validation study was written following the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement (161).

Patients

The methodology of the ECLIPSE study has been summarized elsewhere (282). Briefly, 2,138 patients aged 40–75 years previously diagnosed with moderate to severe COPD were recruited from December 2005 until February 2010 (283). Patients with a post-bronchodilator forced expiratory volume in the 1st second

(FEV_1) of <80% (GOLD II to IV) of the predicted value, baseline post-bronchodilator FEV_1/forced vital capacity (FVC) of ≤0.7, and smoking history of ≥10 pack-years were recruited from 46 secondary and tertiary care centres in 12 countries in North America and Europe. COPD patients were excluded from this analysis if they were missing one or more predictor variables from either model, exacerbation outcome data were missing, or (in the main analysis) a patient's observation time was shorter than the time horizon (1-, 2-, or 3-years) being evaluated (i.e., lost to follow-up at the selected time horizons).

Predictors

The BLISS score was developed using the Birmingham COPD cohort, which consists of 1,558 prevalent, and 331 case-found COPD patients aged 40 years of age or older from 71 primary care practices in the West Midlands, United Kingdom (162). The following predictors were included after backward selection: age, COPD assessment test (CAT) score (284), one or more respiratory admissions in the previous 12 months, body mass index (BMI), diabetes, and FEV1% predicted (281). Since the CAT score (284) was not collected in ECLIPSE, the Saint George's Respiratory Questionnaire for COPD (SGRQ-C) (285) was converted to CAT using the regression equation developed by Jones and colleagues (286). In addition, respiratory admission in the previous 12 months was replaced with any exacerbation in the previous 12 months. Bertens' model was developed in 240 COPD patients aged 65 years or older and selected from 51 general practices in the Netherlands from 2001 to 2003. It includes the following predictors: one or more previous exacerbations in 12 months, FEV_1% predicted, smoking pack-years, and history of vascular disease (149). Vascular disease was defined as stroke, minor stroke, or peripheral arterial disease (PAD). However, as PAD is not available in the ECLIPSE dataset, we defined vascular disease as a history of any cardiovascular disease (excluding high blood pressure) or stroke.

Outcome

In the ECLIPSE cohort, exacerbation assessments were undertaken at each participant visit using case report forms supplemented by monthly phone calls. Moderate exacerbations were defined as the decision by primary clinicians or study personnel to prescribe antibiotics or systemic corticosteroids (26). Severe exacerbations were defined as exacerbation events that resulted in hospital admission (26). The two main outcomes for this validation study were 1) ≥1 severe exacerbation within 2-years and 2) ≥1 moderate-to-severe exacerbation within 2-years. Secondary endpoints were these outcomes at 1-year and 3-year time horizons.

For the development of Bertens' model, the outcome was consistent with the definition for a moderate-severe exacerbation ("symptomatic deterioration requiring pulsed oral steroid use or hospitalisation") and was assessed within 2-years of baseline (149). The outcome for the BLISS score development study was acute

hospitalisation from all respiratory causes, also within 2 years (281), which is more consistent with the definition of severe exacerbations.

Analysis

Simple descriptive statistics were used to compare the characteristics of COPD patients with and without an exacerbation within two years of observation time. In the main comparative analysis, the regression coefficients of the predictors and intercepts from the formulas published in BLISS and Bertens' model development studies were used to obtain predictions in ECLIPSE patients. To assess discrimination, area-under-the-curve (AUC) was estimated with a 95% confidence interval (95% CI) (168). Calibration was assessed by comparing the predicted probability to the observed probability of an exacerbation. An estimate of the calibration-in-the-large (CITL) indicated whether the predictions were systematically too high or too low while an estimate of the calibration slope measured whether the level of under-or-over prediction was maintained across the range of patients (287).

Sensitivity analyses

In the first sensitivity analysis (SA1), we included patients with less observation time than the specified time horizon (1-, 2-, or 3- years) only if they had an exacerbation event within that particular time horizon. In the second sensitivity analysis (SA2), all patients were included regardless of observation time. A final sensitivity analysis showed the accuracy of Bertens' model among only patients with complete data for both models.

RESULTS

Of 2,138 COPD patients from the ECLIPSE cohort, 321 had less than 2-years of observation time or were missing 2-year exacerbation data for other reasons (Figure 6.1). Six patients had at least one predictor missing from Bertens' model while 68 had at least one predictor missing from the BLISS score. 1,811 and 1,749 patients remained in the main 2-year analysis for the Bertens' and BLISS scores, respectively. For both models, fewer than 5% of patients were excluded due to missing predictors so multiple imputation was not used.

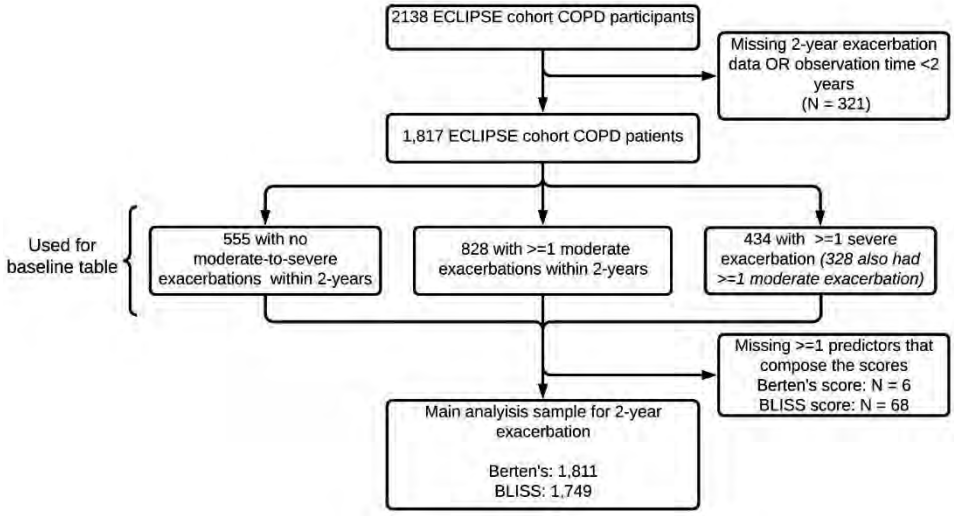


Figure 6.1: Flow of ECLIPSE COPD patients into the study.

Baseline characteristics

Table 6.1 shows the baseline characteristics of patients from the ECLIPSE cohort according to whether a moderate or severe exacerbation had occurred within 2-years of observation time. 434 (24%) had at least one severe exacerbation (some with and some without moderate exacerbations in the same period), and 828 (46%) had at least one moderate exacerbation (excluding those who had severe exacerbations). Participants with severe exacerbations were slightly older than those without. There were more current smokers among patients without exacerbations (39%) than those with exacerbations (34%). Patients with severe or moderate exacerbations were more likely to report depression at baseline (33% and 26%, respectively) than those without an exacerbation (17%). They also had lower FEV_1% predicted (42%, 50%, and 55%, respectively) and were more likely to have at least one exacerbation in the year prior to baseline assessment (66%, 52%, and 23%, respectively). Patients with severe exacerbations had worse mMRC scores and health-related quality of life (CAT score 22 (SD: 6) and SGRQ-C 56 (SD: 17)) than those with only moderate (CAT score 18 (SD: 6) and SGRQ-C 47 (SD: 17)) and no exacerbations (CAT score 16 (SD: 7) and SGRQ-C 41 (SD: 18)). It should be noted that ECLIPSE patients were younger than Bertens development cohort and were more likely to be current smokers, have previous exacerbations, and more severe FEV_1% predicted than patients from both development cohorts (149,281).

Table 6.1: Baseline characteristics of ECLIPSE COPD patients by exacerbation status within 2-years of observation time.

Characteristic		no exacerbations (N = 555)	≥1 moderate exacerbations (N = 828)	≥1 severe exacerbations (N = 434)
Age (y) – mean (SD)		62.9 (7.5)	63.1 (6.9)	64.0 (6.8)
No. males (%)		408 (74)	489 (59)	282 (65)
<High school education, n (%)		202 (37)	266 (33)	185 (44)
Current smoker n (%)		216 (39)	284 (34)	146 (34)
Heart failure n (%)		42 (8)	35 (4)	40 (9)
Diabetes n (%)		67 (12)	73 (9)	34 (8)
Cardiovascular disease n (%)		323 (58)	438 (53)	235 (54)
Depression* n (%)		91 (17)	210 (26)	140 (33)
BMI (kg/m^2) – mean (SD)		27.1 (5.7)	26.6 (5.5)	25.8 (5.5)
>=1 exacerbation in Previous 12 months n (%)		125 (23)	434 (52)	287 (66)
FEV1% predicted – mean (SD)		54.6 (15.3)	49.6 (14.9)	41.5 (14.4)
mMRC score				
	0	105 (20)	101 (13)	28 (7)
	1	228 (42)	308 (38)	91 (22)
	2	139 (26)	258 (32)	164 (39)
	3	57 (11)	113 (14)	83 (20)
	4	10 (2)	27 (3)	52 (12)
SGRQ-C – mean (SD)		40.6 (18.4)	46.6 (17.0)	56.2 (16.6)
CAT* - mean (SD)		16.2 (6.6)	18.3 (6.1)	21.8 (6.0)
BODE score – mean (SD)		2.3 (1.9)	2.9 (1.9)	4.2 (2.1)

Characteristics are expressed as n (%) unless otherwise specified. Patients in the moderate exacerbation group have not had a severe exacerbation but those in the severe exacerbation group may have had at least one moderate exacerbation. * assessed using CES-D (288), a self-administered questionnaire that measures the presence of depression in the previous week. BMI, body mass index; mMRC, modified Medical Research Council;

SGRQ-C, Saint George's Respiratory Questionnaire for COPD; CAT, COPD Assessment Test; FEV, Forced Expiratory Volume in the first second; BODE (BMI, Obstruction, Dyspnoea, and Exercise Capacity).

Predicting severe exacerbations

Table 6.2 shows the accuracy of the BLISS and Bertens models in predicting severe exacerbations. The AUC (discrimination) for the BLISS score performed best in terms of discrimination at 1-year (AUC 0.76) with an AUC of 0.73 at 2- and 3-year time horizons. Calibration slopes were 1.08 at 1-year and 0.92 at 2- and 3-year time horizons. The CITL was most accurate at 2-years (CITL = -0.15). Bertens' model produced AUCs slightly under 0.70 for all time horizons, with poorer calibration slopes than the BLISS score. Overprediction was evident at 1-year (-1.7) but was better at 2- (-1.0) and 3-year (-0.31) time horizons.

Table 6.2: Accuracy of BLISS and Bertens model for predicting severe exacerbations in ECLIPSE cohort COPD patients.

	BLISS score *Main analysis*	Bertens' model *Main analysis*
1-year exacerbation		
N	1894	1959
AUC (95% CI)	0.763 (0.734 to 0.792)	0.698 (0.667 to 0.729)
Calibration slope (95% CI)	1.08 (0.914 to 1.24)	0.779 (0.627 to 0.931)
CITL (95% CI)	(-)0.751 (-0.923 to -0.580)	(-)1.65 (-1.78 to -1.52)
2-year exacerbation		
N	1749	1811
AUC (95% CI)	0.733 (0.706 to 0.760)	0.679 (0.651 to 0.707)
Calibration slope (95% CI)	0.921 (0.788 to 1.05)	0.683 (0.556 to 0.810)
CITL (95% CI)	(-)0.151 (-0.318 to 0.017)	(-)1.00 (-1.12 to -0.892)
3-year exacerbation		
N	547	571
AUC (95% CI)	0.733 (0.691 to 0.776)	0.686 (0.641 to 0.730)
Calibration slope (95% CI)	0.926 (0.714 to 1.14)	0.722 (0.518 to 0.925)

CITL (95% CI)	0.573 (0.276 to 0.869)	(-)0.309 (-0.492 to -0.125)

Abbreviations: AUC, area-under-the-curve (i.e., discrimination); CITL, calibration-in-the-large; CI, confidence interval

The calibration plots for predicting severe exacerbations show over-prediction for the Bertens' score, especially at higher predicted risks, that improves with increasing time horizons (Figure 6.2). On the other hand, the BLISS score shows slight over-prediction at the 1-year time horizon, slight under-prediction at 3-years, and accurate prediction at 2-years.

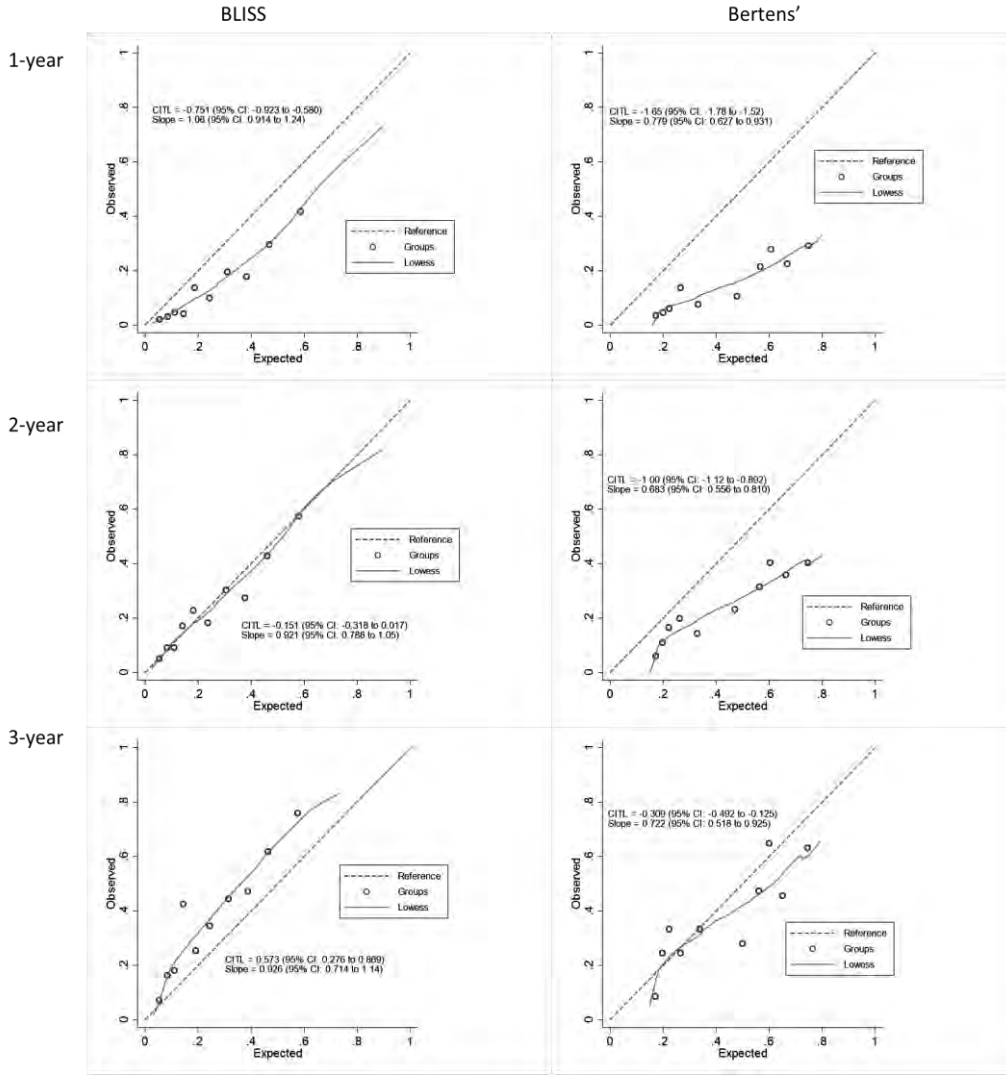


Figure 6.2 Calibration plots for predicting severe exacerbations

Sensitivity results were generally similar to the main analysis (Supplementary Table 6.1), although the BLISS and Bertens' models tended to have better calibration slopes and CITLs at 2-years. Compared to the main analysis, both models had more pronounced underprediction (SA1) and worse calibration slopes (SA2) at 3-years.

Supplementary Table 6.1: Sensitivity analyses showing the accuracy of BLISS and Bertens models for predicting severe exacerbations in ECLIPSE cohort COPD patients.

	BLISS model *SA1*	BLISS model *SA2*	Bertens' model *SA1*	Bertens' model *SA2*
1-year exacerbation				
N	1926	2057	1994	2131
AUC (95% CI)	0.765 (0.738 to 0.793)	0.759 (0.731 to 0.786)	0.705 (0.675 to 0.734)	0.701 (0.672 to 0.730)
Calibration slope (95% CI)	1.09 (0.934 to 1.25)	1.05 (0.897 to 1.20)	0.811 (0.665 to 0.957)	0.797 (0.652 to 0.942)
CITL (95% CI)	(-)0.633 (-0.799 to -0.468)	(-)0.760 (-0.922 to -0.599)	(-)1.54 (-1.67 to -1.42)	(-)1.63 (-1.75 to -1.50)
2-year exacerbation				
N	1831	1920	1898	1988
AUC (95% CI)	0.743 (0.718 to 0.768)	0.738 (0.713 to 0.763)	0.689 (0.664 to 0.715)	0.686 (0.661 to 0.712)
Calibration slope (95% CI)	0.969 (0.843 to 1.10)	0.944 (0.820 to 1.07)	0.726 (0.607 to 0.846)	0.716 (0.597 to 0.834)
CITL (95% CI)	0.061 (-0.098 to 0.220)	(-)0.039 (-0.195 to 0.116)	(-)0.824 (-0.930 to -0.718)	(-)0.892 (-0.997 to -0.788)
3-year exacerbation				
N	989	1815	1027	1882
AUC (95% CI)	0.737 (0.705 to 0.769)	0.728 (0.704 to 0.752)	0.695 (0.661 to 0.728)	0.678 (0.653 to 0.703)
Calibration slope (95% CI)	0.936 (0.779 to 1.09)	0.892 (0.777 to 1.01)	0.734 (0.582 to 0.886)	0.670 (0.559 to 0.780)
CITL (95% CI)	1.73 (1.48 to 1.97)	0.432 (0.273 to 0.591)	0.832 (0.686 to 0.978)	(-)0.422 (-0.522 to -0.321)

SA1 (sensitivity analysis 1): Patients were included with less observation time than a time horizon (1-, 2-, or 3- years) as long as they had an exacerbation event within that particular time horizon. SA2 (sensitivity analysis 2): All patients were included in each analysis regardless of observation time. The median and interquartile range of the observation time was 1083 (1067 to 1095) for all prediction model and outcome combinations. AUC, area-under-the-curve (i.e., discrimination); CITL, calibration-in-the-large; CI, confidence interval

Predicting moderate-to-severe exacerbations

Table 6.3 shows the accuracy of BLISS and Bertens' models in predicting moderate-to-severe exacerbations. For the BLISS score, discrimination at 2-years exacerbation was 0.73 and remained similar at 1- (AUC= 0.72) and 3-year (AUC =

0.74) time horizons. The calibration slope improved but underprediction worsened with increasing time horizons from 1- (slope= 0.87; CITL= 1.4) to 2- (slope= 0.93; CITL= 2.2) to 3-years (slope= 0.97; CITL= 2.9), respectively. For Bertens' model, discrimination at 2-years was lower at 0.70 but remained stable at 1- (AUC= 0.70) and 3-year (AUC= 0.71) time horizons. Calibration slopes were more inaccurate than the BLISS score for 1- (slope= 0.81) and 2-years (slope= 0.84) but had a similar slope at the 3-year time horizon. Underprediction also worsened with increasing time horizons from CITL= 0.54 at 1-year exacerbation to CITL= 2.0 at 3-year exacerbation but was less pronounced than with the BLISS score.

Table 6.3: Accuracy of BLISS and Bertens models for predicting moderate-to-severe exacerbations in ECLIPSE cohort COPD patients.

	BLISS scores *Main analysis*	Bertens' models *Main analysis*
1-year exacerbation		
N	1894	1959
AUC (95% CI)	0.722 (0.699 to 0.745)	0.698 (0.675 to 0.721)
Calibration slope (95% CI)	0.874 (0.765 to 0.983)	0.813 (0.705 to 0.922)
CITL (95% CI)	1.37 (1.19 to 1.55)	0.539 (0.432 to 0.645)
2-year exacerbation		
N	1749	1811
AUC (95% CI)	0.732 (0.706 to 0.757)	0.699 (0.673 to 0.725)
Calibration slope (95% CI)	0.927 (0.801 to 1.05)	0.843 (0.716 to 0.969)
CITL (95% CI)	2.18 (1.95 to 2.42)	1.25 (1.12 to 1.38)
3-year exacerbation		
N	547	571
AUC (95% CI)	0.740 (0.690 to 0.789)	0.711 (0.662 to 0.760)
Calibration slope (95% CI)	0.966 (0.703 to 1.23)	0.965 (0.681 to 1.25)
CITL (95% CI)	2.94 (2.42 to 3.47)	2.02 (1.70 to 2.34)

Abbreviations: AUC, area-under-the-curve (i.e., discrimination); CITL, calibration-in-the-large; CI, confidence interval

The calibration plots for predicting moderate-to-severe exacerbations show substantial under-prediction, especially for the BLISS score (Figure 6.3). At 1- and 2-year time horizons, both the BLISS and Bertens' scores had less pronounced under-prediction at the lowest and highest predicted risks and more inaccurate under-prediction at moderate predicted risks (around 30% to 50%). Predictions more accurately reflected observed exacerbations for the Bertens' score at 1-year time horizon.

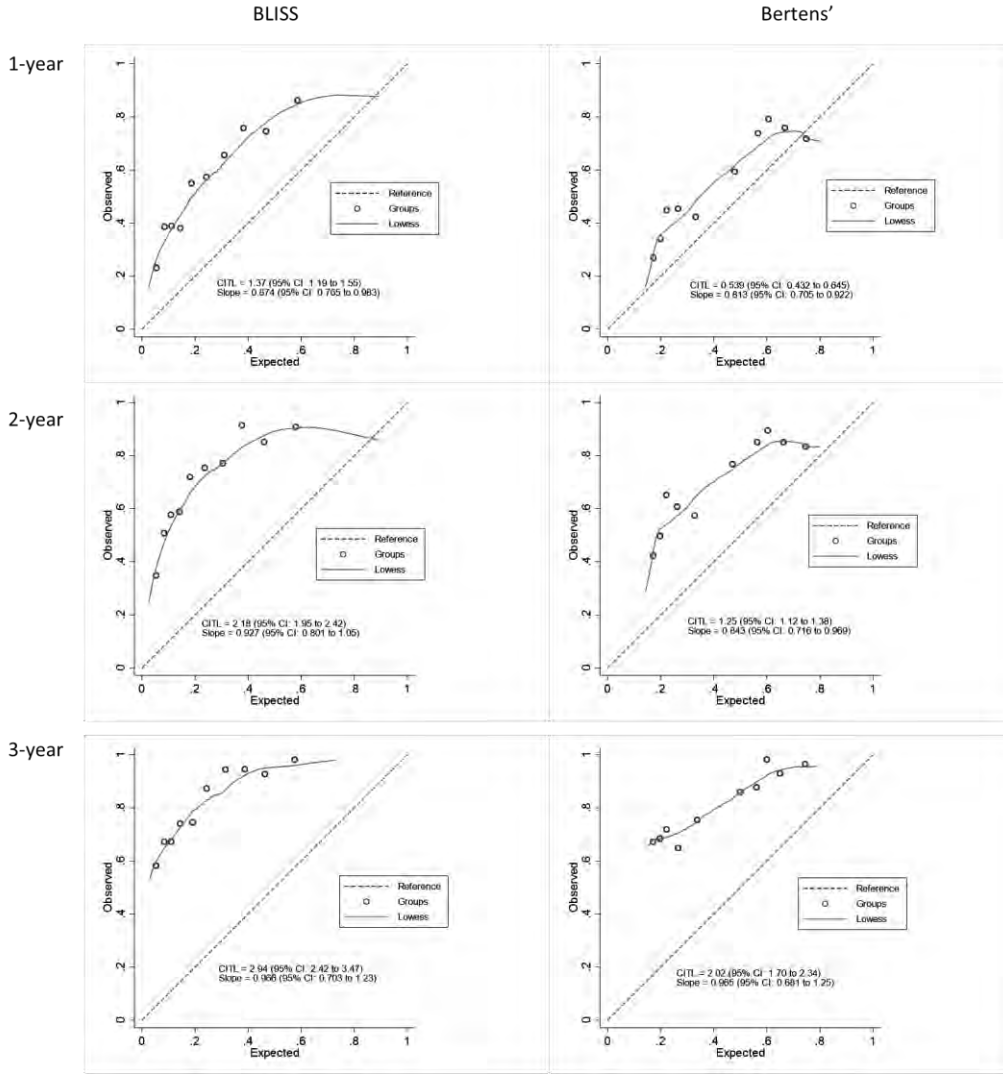


Figure 6.3 Calibration plots for predicting moderate-to-severe exacerbations.

With a few exceptions, the results for the sensitivity analyses were similar (Supplementary Table 6.2). Notably, compared to the main analysis, both models had more pronounced under-prediction at 3-years in SA1. On the other hand, calibration slopes were improved at 2-years for both models compared to the main analysis. In SA2, the calibration slope for the Bertens' model was less accurate at 3-years (slope =0.85 versus 0.97 in the main analysis).

Supplementary Table 6.2: Sensitivity analyses showing the accuracy of BLISS and Bertens' models for predicting moderate-to-severe exacerbations in ECLIPSE cohort COPD patients.

	BLISS model *SA1*	BLISS model *SA2*	Bertens' model *SA1*	Bertens' model *SA2*
1-year exacerbation				
N	1968	2057	2038	2131
AUC (95% CI)	0.728 (0.706 to 0.750)	0.716 (0.693 to 0.738)	0.704 (0.681 to 0.727)	0.697 (0.675 to 0.720)
Calibration slope (95% CI)	0.901 (0.792 to 1.01)	0.839 (0.736 to 0.942)	0.838 (0.731 to 0.946)	0.812 (0.708 to 0.915)
CITL (95% CI)	1.46 (1.29 to 1.64)	1.26 (1.10 to 1.43)	0.610 (0.505 to 0.715)	0.490 (0.389 to 0.590)
2-year exacerbation				
N	1926	1964	1995	2034
AUC (95% CI)	0.743 (0.719 to 0.768)	0.737 (0.713 to 0.761)	0.710 (0.684 to 0.735)	0.706 (0.682 to 0.731)
Calibration slope (95% CI)	0.978 (0.854 to 1.10)	0.948 (0.828 to 1.07)	0.885 (0.760 to 1.01)	0.871 (0.750 to 0.993)
CITL (95% CI)	2.37 (2.14 to 2.60)	2.25 (2.03 to 2.46)	1.39 (0.760 to 1.53)	1.31 (1.19 to 1.44)
3-year exacerbation				
N	1627	1918	1688	1987
AUC (95% CI)	0.753 (0.708 to 0.797)	0.737 (0.710 to 0.764)	0.728 (0.685 to 0.771)	0.701 (0.673 to 0.729)
Calibration slope (95% CI)	1.04 (0.793 to 1.28)	0.942 (0.807 to 1.08)	1.02 (0.748 to 1.29)	0.852 (0.712 to 0.992)
CITL (95% CI)	4.27 (3.76 to 4.77)	2.76 (2.50 to 3.02)	3.26 (2.95 to 3.57)	1.80 (1.65 to 1.95)

SA1 (sensitivity analysis 1): Patients were included with less observation time than a time horizon (1-, 2-, or 3- years) as long as they had an exacerbation event within that particular time horizon. SA2 (sensitivity analysis 2): All patients were included in each analysis regardless of observation time. The median and interquartile range of the observation time was 1083 (1067 to 1095) for all prediction model and outcome combinations. AUC, area-under-the-curve (i.e., discrimination); CITL, calibration-in-the-large; CI, confidence interval

Final remarks and sensitivity analysis

When predicting severe exacerbations, after including patients with complete data on all predictors of both the BLISS and Bertens' models, the results remained the same (Supplementary Table 6.3). Similarly, the main and supplementary results

were nearly identical when predicting moderate-to-severe exacerbations. It should be noted that patients without missing predictors for both the BLISS and Bertens' score matches those patients included in the BLISS score analyses.

Supplementary Table 6.3: Sensitivity analysis showing the accuracy of Bertens' model after using a sample in which patients were excluded if they had at least one missing predictor from both BLISS and Bertens' models*.

	moderate-to-severe exacerbations			severe exacerbations		
	Bertens' model *Main analysis*	Bertens' model *SA1*	Bertens' model *SA2*	Bertens' model *Main analysis*	Bertens' model *SA1*	Bertens' model *SA2*
1-year exacerbation						
N	1,894	1,968	2,057	1,894	1,926	2,057
AUC (95% CI)	0.697 (0.673 to 0.721)	0.704 (0.680 to 0.727)	0.697 (0.674 to 0.720)	0.700 (0.669 to 0.731)	0.707 (0.677 to 0.737)	0.703 (0.673 to 0.733)
Calibration slope (95% CI)	0.807 (0.696 to 0.917)	0.835 (0.725 to 0.944)	0.808 (0.703 to 0.914)	0.787 (0.632 to 0.942)	0.819 (0.669 to 0.968)	0.802 (0.654 to 0.950)
CITL (95% CI)	0.538 (0.430 to 0.646)	0.608 (0.501 to 0.715)	0.489 (0.387 to 0.591)	(-)1.65 (-1.79 to -1.52)	(-)1.55 (-1.68 to -1.42)	(-)1.64 (-1.76 to -1.51)
2-year exacerbation						
N	1,749	1,926	1,964	1,749	1,831	1,920
AUC (95% CI)	0.699 (0.672 to 0.726)	0.710 (0.684 to 0.736)	0.707 (0.681 to 0.732)	0.680 (0.652 to 0.708)	0.690 (0.663 to 0.716)	0.687 (0.660 to 0.713)
Calibration slope (95% CI)	0.841 (0.711 to 0.970)	0.885 (0.757 to 1.01)	0.870 (0.747 to 0.994)	0.687 (0.558 to 0.816)	0.726 (0.604 to 0.848)	0.714 (0.594 to 0.835)
CITL (95% CI)	1.25 (1.11 to 1.38)	1.39 (1.26 to 1.53)	1.31 (1.18 to 1.44)	(-)0.997 (-1.11 to -0.883)	(-)0.821 (-0.929 to -0.713)	(-)0.891 (-0.998 to -0.785)
3-year exacerbation						
N	547	1,627	1,918	547	989	1,815
AUC (95% CI)	0.703 (.652 to 0.753)	0.724 (0.679 to 0.768)	0.700 (0.671 to 0.728)	0.685 (0.639 to 0.730)	0.696 (0.662 to 0.731)	0.679 (0.654 to 0.704)
Calibration slope (95% CI)	0.928 (0.641 to 1.21)	0.993 (0.720 to 1.27)	0.841 (0.700 to 0.983)	0.719 (0.511 to 0.927)	0.739 (0.584 to 0.895)	0.673 (0.560 to 0.785)
CITL (95% CI)	1.99 (1.67 to 2.31)	3.25 (2.93 to 3.56)	1.79 (1.64 to 1.94)	(-)0.301 (- 0.490 to - 0.114)	0.847 (0.697 to 0.996)	(-)0.414 (-0.517 to -0.312)

*The set of patients without missingness for any predictors found in both the BLISS and Bertens' score matches those patients included in the BLISS score analyses. AUC, area-under-the-curve (i.e., discrimination); CITL, calibration-in-the-large; CI, confidence interval

DISCUSSION

The BLISS score accurately predicted the occurrence of severe exacerbations requiring hospitalisation within 2 years (the purpose for which it was developed) in the ECLIPSE cohort of COPD patients and performed slightly better than the Bertens' model. Neither model was sufficiently valid in predicting moderate-to-severe exacerbations.

Both models were developed using best practice methodology with a low risk of bias (139,289). Neither contains biomarkers or other tests/measurements that require advanced equipment or space. A systematic review of COPD prediction models for exacerbations found that most other models were not developed using the recommended statistical techniques, did not present both discrimination and calibration statistics, or were not comprised of predictors that are easily obtained or measured (148). These deficiencies indicate that the BLISS and Bertens' models are likely to be the most useful prognostic models predicting exacerbations (139). Therefore, it was important to validate these models among populations outside of those they were developed in (138). Proper validation is essential before impact studies can be performed to measure the effect of using models to guide clinical decisions (290).

The Bertens' model saw a drop in discriminative power from 0.75 to 0.66 from development to their external validation (149). We found a less pronounced drop in discrimination (AUC= 0.70 for moderate/severe and 0.68 for severe exacerbations at the 2-year time horizon). The original authors found agreement between the observed and expected risk of exacerbation and—unlike our study—no systematic under- (or over-) prediction of risk in their external validation cohort. However, this agreement is in line with what was anticipated since their model was developed and externally validated in general practice populations. Internal validation of the BLISS score using bootstrap techniques had only marginally reduced the discriminative performance from AUC= 0.76 to 0.75 in the BLISS development study (281). We showed that external validation reduced the discriminative power for predicting both severe and moderate-to-severe exacerbation to 0.73 at 2 years.

We are aware of only a few prediction models originally developed to predict COPD exacerbations and created using statistical selection criteria (26,291–299). Validation of these models in a separate cohort has been very uncommon. The discriminative power of the short-term risk of COPD exacerbations (SCOPEX) score to predict an exacerbation within 6-months in moderate-to-severe COPD patients from randomised controlled trials was adequate (AUC= 0.67) (294) but improved when predicting 1-month exacerbation (AUC = 0.74) in an external cohort of pulmonary rehabilitation COPD patients (300). In our study, the BLISS score also showed improved accuracy (although slight) when predicting severe exacerbations at a shorter time horizon than the model was developed for. Recently, an exacerbation prediction tool was developed in randomised trial participants and showed accuracy in ECLIPSE patients for predicting at least two exacerbations (AUC= 0.81) and at least one severe exacerbation (AUC= 0.77)

within one year (301). The model was slightly less discriminative in those with a history of exacerbations (AUC= 0.73 and 0.74, respectively) but showed accurate calibration throughout. This model and other exacerbation prediction models cited above could not be tested in the present validation study because either the predictors were not available in the ECLIPSE dataset, the model was already validated in ECLIPSE, the outcome definition was different, the development cohort was not from primary care, the development paper did not contain a published formula, or the development of the score did not have a low risk of bias (139,148).

Calibration statistics are important for testing the validity of prognostic models because predicted and observed risks must be similar for the risk of an exacerbation to be properly weighed against the costs and adverse effects of treatment (158). When predicting moderate-to-severe exacerbations, we found systematic under-prediction of risk in both models. This was likely because both the BLISS and Bertens' models were developed in patients with less severe COPD than patients participating in ECLIPSE. Additionally, the BLISS score likely had a more pronounced under-prediction of risk when compared to Bertens' model because it was only developed to predict severe exacerbations and other respiratory hospitalization events. Updating the intercept terms of these models using cohorts from multiple healthcare settings may increase their validity in predicting moderate-to-severe exacerbation in patients with more advanced COPD. However, for the time being, these models are not valid for predicting moderate-to-severe exacerbations, and their use could lead to under-treatment in patients who have the potential to benefit from therapy.

The present study has several strengths and limitations. First, we predicted the CAT score using SGRQ-C since the CAT score was not collected in the ECLIPSE cohort. This may not accurately represent the real CAT scores that ECLIPSE patients would have obtained if they completed this questionnaire. However, both SGRQ-C and CAT measure the impact COPD has on a patient's quality of life and the conversion equation we used was from a previously published paper authored by one of the original developers of both the CAT and SGRQ-C questionnaires (286). Second, the outcome of severe exacerbations in the present validation study is more specific to COPD-related causes of hospitalisation than the BLISS development study, which used all-cause respiratory hospitalisation as its outcome. Although using hospitalised exacerbations may be important for determining etiology, predicting all-cause respiratory admission is likely a more practical and patient-centered outcome since respiratory treatments may reduce the risk of hospitalised exacerbations but increase the risk of respiratory hospitalisation due to pneumonia (302). There is some authorship overlap between the BLISS development study (281) and the present study. However, since the BLISS score's authors had no involvement in the ECLIPSE cohort, techniques and specific idiosyncrasies that often creep into recruitment, data collection, and recording practices would not have carried over across cohorts and studies. This may have otherwise resulted in slightly better BLISS validation performance. Next, the 1- and 3-year endpoints are secondary to 2-year exacerbations since both the BLISS and Bertens' models were only developed for predicting events at 2 years. However, it

is important to note that this is one of several types of transportability tested in this study (303). Follow-up period transportability was examined by determining whether the accuracy of the models was maintained across longer and shorter time horizons. Secondly, we tested spectrum transportability by including ECLIPSE patients who, on average, suffer from more severe disease than the development cohorts for both models. ECLIPSE patients were also younger than the patients included in Bertens' development cohort (149) (mean age: 63 versus 73 years old, respectively). As mentioned above, methodologic transportability tested the models after using slightly different outcome and predictor definitions. Fourth, while the ECLIPSE cohort participants came from 12 countries, patients from the BLISS and the Bertens' model development studies only came from a single country (UK and Netherlands, respectively) which indicates that some degree of geographic transportability was also tested (303).

Prognostic models have hitherto not been used successfully in practice to predict COPD exacerbations because they have been lacking in methodological rigour, performance, and practicality. Guidelines overtly call for useful and practical prognostic models to guide clinical decision-making (304). We have demonstrated in our validation study that there are two good prognostics models for predicting COPD hospitalisations, particularly of use in primary care. The BLISS score accurately predicted severe exacerbations requiring hospital admission in ECLIPSE COPD patients and performed better than the Bertens' model. However, due to systematic under-prediction of risk, neither the BLISS nor Bertens' model should be used to predict less severe exacerbations without first updating their intercepts. There is no need to develop any further models. Future work should test if the BLISS score can guide patient management and successfully reduce expensive and harmful hospital admissions.

CHAPTER VII: PERSISTENT RESPIRATORY SYMPTOMS IN INDIVIDUALS WITH AND WITHOUT NORMAL LUNG FUNCTION − A BIRMINGHAM COPD COHORT STUDY.

Spencer J Keene[1,2,4], Rachel E Jordan[1], Andrew P. Dickens[1], Johanna H.M. Driessen[2,3,7,] Alice Sitch[1,5], Peymane Adab[1], Frits M.E. Franssen[4,6*]

Affiliations

[1] Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom.

[2] Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center+, Maastricht, the Netherlands

[3] Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht the Netherlands.

[4] CIRO+, Horn, the Netherlands

[5] NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, UK

[6] Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands

[7] Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+, Maastricht, the Netherlands

ABSTRACT

Rationale: Some people with persistent respiratory symptoms will not progress to spirometrically defined COPD. Still, further clinical investigation of airway disease may be needed in those with normal spirometry, especially if persistent symptoms show prognostic relevance and if the features of symptom persistence are similar in those with and without airflow limitation.

Objectives: Determine factors associated with persistence of moderate-to-severe symptoms, and whether both the pattern and stability of symptom burden and the prognosis of individuals with persistent moderate-to-severe symptoms vary by whether or not patients have airflow limitation.

Methods: 1528 participants were recruited between 2012 and 2014 from 71 United Kingdom general practices as part of the Birmingham COPD Cohort study and followed up for a median of 2.86 years (interquartile range= 2.38 to 3.20). They consisted of prevalent diagnosed COPD patients, newly identified (i.e., incident) COPD patients found through screening, and pre-COPD individuals screened with respiratory symptoms and normal lung function. Persistence of moderate-to-severe symptoms was defined as ≥8 points on cough, breathlessness, and sputum COPD Assessment Test (CAT) questions for at least all but one of the assessments completed every 6-months during the study. We described the patterns of symptom scores by patient group using repeated measures mixed-effect models. We then evaluated factors associated with moderate-to-severe symptom persistence using multivariable logistic regression and determined the association between moderate-to-severe persistent symptoms and the occurrence of frequent exacerbations or respiratory hospitalisation (defined as at least one year in which ≥2 moderate exacerbations or ≥1 respiratory hospitalisation during follow-up) in each group.

Results: Prevalent patients were over twice as likely to have moderate-to-severe symptom burden (>50% of prevalent patients had a total symptom score of ≥8 at most time points) compared to the other groups. Cough, phlegm, and breathlessness scores improved by 0.3 to 0.5 points in all groups during follow-up, but prevalent patients had higher average scores for individual components than the other groups, especially for breathlessness (3.2; 95% CI: 3.0 to 3.3). 517 (33%) prevalent patients had a score of <8 throughout follow-up whereas the proportion was higher in the incident (N= 184, 56%) and pre-COPD patients (N= 241, 58%). The proportion of patients with a score of ≥8 throughout follow-up was higher in the prevalent group (N= 667, 43%) than incident (N= 67, 20%) and pre-COPD (N= 78, 19%). Younger age, worse FEV_1 at baseline, current smoking, greater deprivation, stomach condition, worse exercise capacity, and history of exacerbations increased the risk of persistent moderate-to-severe symptoms. Persistent moderate-to-severe symptoms similarly increased the odds of frequent exacerbations or respiratory hospitalisation across all groups by around 2.5-fold (interaction by patient group P = 0.813).

Conclusion: Normal spirometry may not rule out the need for further clinical investigation of airway disease and people with pre-COPD may have unmet needs consistent with people with newly identified COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most common long-term conditions and it is now the third leading cause of death worldwide (305). International guidelines recommend that COPD is diagnosed by demonstrating airflow obstruction in people with relevant risk factors and chronic respiratory symptoms such as chronic cough, sputum, or breathlessness (1). However, a considerable number of patients suffer from chronic respiratory symptoms but have normal spirometry. It was once thought that these patients have an 'early phase' of COPD since changes to the alveoli and peripheral and large airways produce symptoms well before airway obstruction can be identified using spirometry (306). However, the Global initiative for chronic Obstructive Lung Disease (GOLD) committee removed diagnosis and treatment guidelines for these GOLD stage 0 patients because there was insufficient evidence that individuals with symptoms and normal spirometry necessarily progressed to COPD (21,307).

Persistent respiratory symptoms with normal lung function are associated with significant morbidity. Depending on the definitions used, 2 to 32% of the general population fall into this category (17,20,308,309). It has been shown that among people with normal lung function, those with chronic respiratory symptoms have an increased risk of respiratory hospitalisation and death when compared to individuals without respiratory symptoms (20). Also, those with chronic respiratory symptoms have a more rapid decline in forced expiratory volume in 1 second (FEV_1) (310). However, it is still unclear if symptoms are more likely to remain stable in those with airflow limitation when compared to those without. Similarly, studies have yet to show the importance of persistent symptom burden on prognosis and whether the prognostic impact is similar in those with and without airflow limitation. Even though some patients with persistent respiratory symptoms will not progress to spirometrically defined COPD, normal spirometry may not rule out the need for further clinical investigation of airway disease (e.g., CT scans and further pulmonary tests).

In this study, we used data from the Birmingham COPD Cohort study to 1) describe the stability/variability of respiratory symptoms over time in people with and without normal lung function, 2) determine which factors are associated with persistent moderate-to-severe symptoms, and 3) examine whether the association between persistent moderate-to-severe symptoms and the occurrence of frequent exacerbation/respiratory hospitalisation or mortality varied by whether individuals had normal or abnormal spirometry.

METHODS

Study Design

A prospective observational cohort study.

Study population

Birmingham COPD cohort (BLISS) patients were recruited from 71 UK general practices across the West Midlands, United Kingdom (162). The BLISS cohort consists of three groups: 1) 1,565 patients with known COPD (aged 40 years and over) on practice Quality and Outcomes Framework COPD registers (prevalent COPD patients), 2) 413 pre-COPD individuals identified as having respiratory symptoms and normal lung function and 3) 331 symptomatic patients with newly detected COPD (incident COPD patients) confirmed by spirometry (post-bronchodilator forced expiratory volume in the first second (FEV_1)/ forced vital capacity (FVC)<0.7). Groups 2) and 3) were identified through a linked case-finding trial (163,311). Patients were considered symptomatic if they had any of a) cough or phlegm on most days for three or more consecutive months during the year and two or more consecutive years, b) wheeze in the chest in the last twelve months, or c) breathlessness defined as grade ≥2 on the (modified Medical Research Council) mMRC scale (164). Baseline assessments took place at cohort entry from 31 May 2012 to 25 June 2014 then participants received postal questionnaires every six months (at 6, 12, 18, 24, and 30 months). A follow-up study assessment visit and routine data abstraction were conducted between 2015 and 2016 for patients that were remaining in the study approximately two to three years after baseline. For this paper, we first described the pattern and stability of symptoms for all participants, but the remaining analyses included only participants with at least three completed component CAT scores (284,312) for cough, phlegm, and breathlessness (described below).

Assessment of persistent moderate-to-severe symptoms

We used responses to the three respiratory symptom items (chronic cough, phlegm (sputum), and breathlessness) from the COPD Assessment Test (CAT) to define symptom severity (284,312). A total CAT respiratory symptom score was calculated by summing the cough score (question number 1), the phlegm/sputum score (question number 2), and the breathlessness score (question number 4) together. A score of ≥8 out of a maximum of 15 was defined as ‘moderate-to-severe symptom’ burden for this analysis. Individuals were defined as having persistence of moderate-to-severe symptoms if they maintained a score of ≥8 for at least all but one of the completed assessments. For instance, if a patient had four complete CAT measurements, they would need a score of ≥8 on at least three occasions. Eight was chosen as the threshold because at baseline assessment this was the median of the summed score for the CAT respiratory symptom items for all participants.

Assessment of covariates

Demographic factors included age (years from the patient-reported date of birth), sex, and Index of Multiple Deprivation (IMD) score (using Index of Multiple Deprivation derived from home postal code) (313). Physiologic covariates included sit-to-stand test (standardised protocol counting the number of repetitions within one minute) and handgrip strength (in kg) (314). Comorbidities comprised cardiovascular disease history (coronary heart disease, heart failure, other heart conditions, or stroke), stomach condition (gastroesophageal reflux disease, GERD) defined as heartburn, nausea, regurgitation more than once a month, or self-reported dyspepsia or stomach ulcer), and diabetes, and were obtained by patient self-report through standardised questionnaires. COPD disease characteristics included baseline values of the total CAT score, FEV_1% of predicted, FEV_1 in litres, FVC in litres. A trained researcher administered the nddEasy One Spirometer (ndd, Switzerland) in a standardised way before (max eight blows) and after (max six blows) 400µg salbutamol. FEV_1 and FVC recordings were considered useable if they met ATS acceptability criteria and were within 200 mL and the highest recording was taken. FEV1% predicted was estimated using the Global Lung Function Initiative equations (165). Additionally, breathlessness was measured using the mMRC (modified Medical Research Council breathlessness) score (315). History of exacerbations was defined as ≥1 moderate-to-severe exacerbation in the year before baseline. Finally, body mass index (BMI; weight (standardised measurements of weight in kilograms (kg)) and height (m)) and self-reported smoking status (current, former, never) were recorded.

Outcomes

The following two outcomes were examined: 1) All-cause mortality was obtained for all cohort participants from the Office of National Statistics through NHS Digital for the period of recruitment until 31 March 2016; 2) the occurrence of frequent exacerbation or respiratory hospitalisation (as represented by GOLD groups C/D (1)) was defined as two or more moderate exacerbations (i.e., symptom worsening after asking the question: “have you had a period when your cough, volume of phlegm, colour of phlegm (becoming yellow or greener than usual), or breathlessness have been worse than usual for more than a few days and you had to change or increase your treatment?”) or self-reported use of antibiotics or corticosteroids) or at least one self-reported respiratory hospitalisation or accident and emergency admission for lung problems within a single year.

Analysis

Stability of symptoms

We described symptom persistence and the baseline characteristics of the prevalent patients, incident patients, and pre-COPD individuals in the BLISS cohort. For the main analyses, using repeated measures mixed effect models we described the pattern of cough, phlegm, and breathlessness (repeated measurements used as separate dependent variables) over time by patient group and by whether or not patients were available and completed the CAT score at the follow-up assessment. An incomplete CAT score at follow-up assessment was

used as an indicator for individuals who may have been lost-to-follow-up. We performed the analysis before and after adjustment for age, sex, FEV1% of predicted, smoking status, diabetes, cardiovascular disease (CVD), stomach condition, and IMD score. We also presented the stability of the total symptom score by patient group using Sankeymatic (316) graphics using a total CAT respiratory symptom items score of eight as the threshold.

Prognostic significance, and factors associated with persistence of moderate-to-severe symptoms

We determined which covariates were independently associated with symptom persistence using backward selection logistic regression with a p-value threshold of 0.05. The association between the persistence of moderate-to-severe symptoms and the occurrence of frequent exacerbation/respiratory hospitalisation was assessed using logistic regression models to derive odds ratios and 95% confidence intervals (CI). We examined whether the association between moderate-to-severe symptom persistence and the occurrence of frequent exacerbation or respiratory hospitalisation varied by patient group by including an interaction term (between persistent moderate-to-severe symptoms and patient group) in the model. A sensitivity analysis examined the same effect after restricting pre-COPD patients to those who did not develop airflow limitation at the follow-up assessment. Finally, we examined the association between persistence of moderate-to-severe symptoms and mortality using Cox proportional hazards regression models to derive hazard ratios and 95% CIs for patients regardless of their group. Individuals contributed person-time from the date of baseline assessment until the earliest of the date of death, withdrawal, or loss of follow-up. For each outcome, the base model was adjusted for age and sex, with a second model that was further adjusted for FEV_1% of predicted, smoking status, diabetes, CVD, stomach condition, and IMD score. Stata 16 was used for all analyses.

RESULTS

Sample and baseline characteristics

2,309 BLISS participants (1,565 prevalent cases, 331 incident cases, and 413 pre-COPD individuals) were eligible for inclusion in the analyses. Out of 331 pre-COPD individuals, 53 (17.5%) had developed COPD (based on airflow obstruction on spirometry) at the follow-up assessment. Symptom persistence could be calculated in 285 pre-COPD individuals, 227 incident cases, and 1,016 prevalent cases (total N= 1,528). The median follow-up was 2.86 years (interquartile range= 2.38 to 3.20).

Table 7.1 shows the baseline characteristics of BLISS cohort participants. Pre-COPD individuals were on average, three years younger than incident patients who were themselves three years younger than prevalent patients. 53% of pre-COPD individuals were male but the incident and prevalent COPD cases had 8% and 11% more males, respectively. There were also fewer current smokers (18% versus

31% and 27% respectively) and more never smokers (21%, 16%, 11%, respectively). Breathlessness tended to be worse in prevalent patients (mMRC ≥2: 59%) than incident and pre-COPD groups (mMRC ≥2: 32%). Similarly, prevalent patients tested five points higher on the CAT score and had approximately four fewer sit-to-stand repetitions than the other groups. 44% of prevalent patients had persistence of symptoms whereas a much lower proportion was found in the incident (16%) and pre-COPD (14%) patients.

Table 7.1: Baseline characteristics of BLISS cohort participants by patient group.

Characteristics	Pre-COPD (N = 285)	Incident patients (N = 227)	Prevalent patients (N= 1,016)	Totals (N = 1,528)
age (in years) - mean (SD)	62.5 (9.3)	66.2 (8.2)	69.2 (8.8)	67.5 (9.3)
Male sex	151 (53.0)	138 (60.8)	645 (63.5)	934 (61.1)
IMD deprivation score - mean (SD)	23.7 (15.4)	27.3 (15.6)	27.7 (16.7)	26.9 (16.4)
BMI - mean (SD)	30.2 (5.9)	28.8 (5.1)	28.4 (5.6)	1,438 (28.8)
sit-to-stand test (repetitions)	22.5 (7.9)	21.8 (6.9)	18.4 (6.1)	19.7 (6.8)
handgrip strength (kgs)	32.5 (11.9)	32.3 (11.9)	30.1 (11.0)	30.8 (11.3)
smoking status				
never	59 (20.9)	34 (15.6)	105 (10.6)	198 (13.3)
former	172 (61.0)	117 (53.7)	616 (62.3)	905 (60.8)
current	51 (18.1)	67 (30.7)	268 (27.1)	386 (25.9)
diabetes	43 (15.3)	28 (12.4)	143 (14.2)	214 (14.1)
CVD	73 (26.0)	62 (27.4)	292 (29.0)	427 (28.2)
stomach condition	111 (39.0)	79 (34.8)	386 (38.0)	576 (37.7)
FEV_1 % of predicted - mean (SD)	97.1 (16.5)	82.7 (17.2)	64.0 (20.1)	73.1 (23.2)
persistence of moderate-to-severe symptoms	41 (14.4)	36 (15.9)	445 (43.8)	522 (34.2)
mMRC breathlessness score				
0	118 (42.9)	80 (35.9)	163 (16.7)	361 (24.4)
1	71 (25.8)	73 (32.7)	240 (24.5)	384 (26.0)
2	40 (14.6)	43 (19.3)	215 (22.0)	298 (20.2)
3	31 (11.3)	17 (7.6)	164 (16.8)	212 (14.4)
4	15 (5.5)	10 (4.5)	197 (20.1)	222 (15.0)
CAT score - mean (SD)	13.5 (7.56)	14.1 (7.6)	19.4 (8.7)	17.5 (8.7)

Presented as number of patients (%) unless otherwise specified. abbreviations: IMD = index of multiple deprivation; CAT = COPD Assessment Test for health-related quality of life; mMRC = modified Medical Research Council; FEV = forced expiratory volume; BMI= body mass index; CVD= cardiovascular disease.

Pattern and stability of symptom burden over time

Figure 7.1 shows the change in the level of cough, phlegm, and breathlessness symptoms (from the relevant questions in the CAT score) over time and by patient group. All three patient groups had higher breathlessness scores compared to their cough and phlegm component scores. In the adjusted model (Figure 6.1, right side) prevalent patients had a much higher baseline breathlessness score of 3.2 points (95% CI: 3.0 to 3.3) compared to cough (2.5; 95% CI: 2.4 to 2.6) and phlegm (2.3; 95% CI: 2.2 to 2.4). Across all three components, prevalent patients had higher baseline scores than the other two groups, especially for breathlessness (incident patients: 2.6; 95% CI: 2.4 to 2.8 and pre-COPD patients: 2.8; 95% CI: 2.6 to 2.9) and phlegm (prevalent: 2.3; 95% CI: 2.2 to 2.4 versus incident patients: 1.8; 95% CI: 1.7 to 2.0, and pre-COPD patients: 1.7; 95% CI: 1.6 to 1.9). Across all groups and component scores, the score tended to decrease by 0.3 to 0.5 points from baseline to follow-up assessment, but both incident and pre-COPD patients showed similar symptom severity and trajectories of symptoms over time, especially for phlegm and cough and after adjustment for confounders. Patients who were missing the total CAT score questionnaire at follow-up assessment and were considered lost-to-follow-up tended to have higher scores (indicating worse symptoms) within each group.

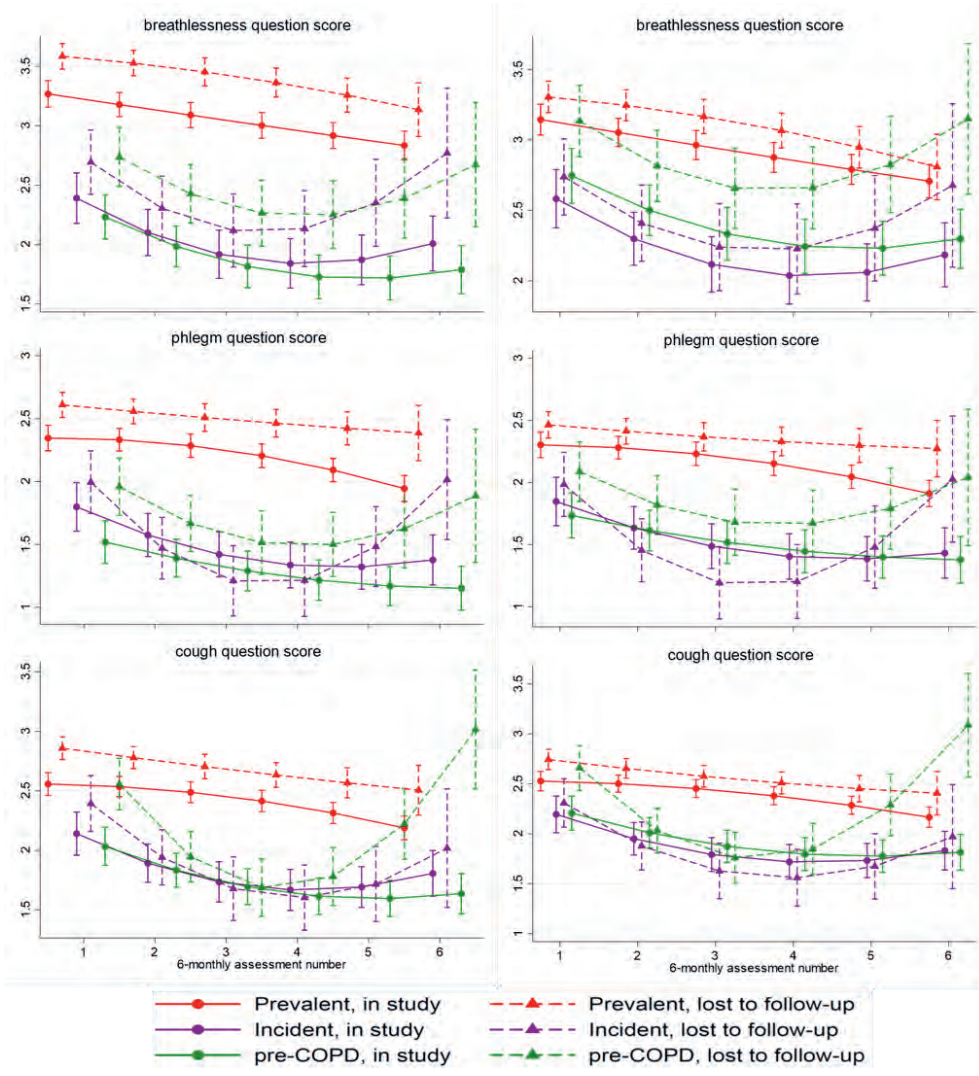


Figure 7.1: Pattern of individual components of symptom severity over time in prevalent, incident, and pre-COPD patients and by whether patients were available for follow-up assessment at the end of BLISS cohort. Left: crude mixed effect models. Right: adjusted for age, sex, FEV1% of predicted, smoking status, diabetes, cardiovascular disease, stomach condition, and IMD score. 6 monthly assessment number 1= baseline assessment and 6= follow-up assessment (the final assessment).

Most (63%) prevalent patients had a total CAT respiratory symptom (i.e., breathlessness, cough, and phlegm items) score of 8 or more at baseline assessment (Figure 7.2). On the other hand, <40% of the incident and pre-COPD individuals had a score of ≥8. After the baseline assessment, average symptom severity dropped in all patient groups and then remained relatively stable throughout the remaining follow-up assessments. It was much less common for pre-COPD and incident patients to have a score of ≥8 (all ≤25%) than prevalent patients after baseline. ≥50% of prevalent patients had a high score, except at the final assessment (41%). 517 (33%) of prevalent patients had a score of <8 throughout follow-up whereas the proportion was higher in the incident (N= 184, 56%) and pre-COPD patients (N= 241, 58%). The proportion of patients with a score of ≥8 throughout follow-up was higher in the prevalent group (N= 667, 43%) than incident (N= 67, 20%) and pre-COPD (N= 78, 19%).

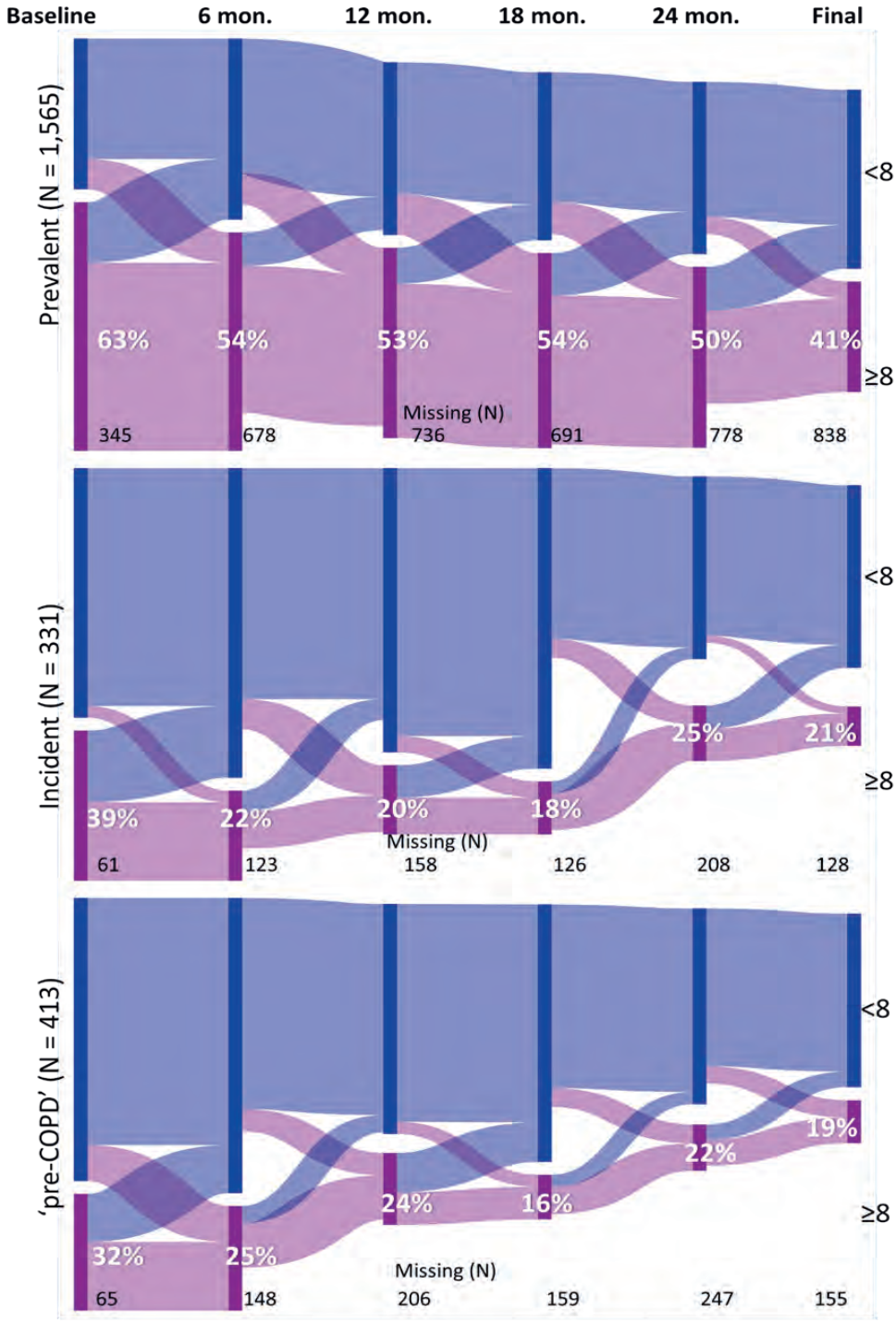

Baseline
6 mon.
12 mon.
18 mon.
24 mon.
Final
Prevalent (N = 1,565)
63%
54%
53%
54%
50%
41%
<8
≥8
Missing (N)
345
678
736
691
778
838
Incident (N = 331)
39%
22%
20%
18%
25%
21%
<8
≥8
Missing (N)
61
123
158
126
208
128
'pre-COPD' (N = 413)
32%
25%
24%
16%
22%
19%
<8
≥8
Missing (N)
65
148
206
159
247
155

Figure 7.2: Stability of symptoms within each patient group. <8 points (blue nodes) and ≥8 points (purple nodes) for CAT score questions 1, 2, and 4 are shown with the percentage of patients with ≥8 at each time point.

Factors associated with persistence of moderate-to-severe symptoms

Table 7.2 shows factors significantly associated with symptom persistence after statistical selection. Current smokers (OR = 2.15; 95% CI: 1.34 to 3.44), those with a prior history of exacerbations (OR = 1.73; 95% CI: 1.03 to 1.82) and those living in more deprived areas (2% for every one-point increase in IMD score; 95% CI: 1% to 2%) were more likely to have persistent moderate-to-severe symptoms while patients with increased age (OR = 0.98 per additional year of age; 95% CI: 0.96 to 0.99), higher baseline FEV_1 (OR = 0.50 per litre; 95% CI 0.41 to 0.62) and higher sit-to-stand test repetitions (OR = 0.93 per repetition; 95% CI: 0.91 to 0.95) were less likely to have persistent moderate-to-severe symptoms. Finally, there was a 64% increase in the odds of persistence of moderate-to-severe symptoms (95% CI: 24% to 116%) among those with a stomach condition.

Table 7.2: Factors associated with persistent moderate-to-severe symptoms (N = 1,234).

		Odds ratio (95 % CI)	p-value
age (years)		0.98 (0.95 to 0.99)	0.003
male sex		1.37 (1.03 to 1.82)	0.031
≥1 moderate-to-severe exacerbation in the year before baseline		1.73 (1.31 to 2.29)	<0.001
FEV_1 (litres)		0.50 (0.41 to 0.62)	<0.001
smoking status (ref: never)			
	Former	1.20 (0.778 to 1.84)	0.412
	Current	2.15 (1.34 to 3.44)	0.001
IMD score		1.02 (1.01 to 1.02)	<0.001
stomach condition		1.64 (1.24 to 2.16)	0.001
sit-to-stand test (no. of repetitions)		0.93 (0.91 to 0.95)	<0.001

Factors presented are only those with statistically significant associations remaining after backward elimination using a P-value threshold of 0.05. Eliminated factors: CVD, diabetes, BMI, handgrip strength, and FVC.

Prognosis of persistence of moderate-to-severe symptoms

Table 7.3 shows effect size (ES) for the association between persistence of moderate-to-severe symptoms and the occurrence of frequent exacerbation or respiratory hospitalisation as well as mortality. Persistent moderate-to-severe symptoms were associated with a significantly higher risk of frequent exacerbation or respiratory hospitalisation for all patient groups. After multivariable logistic regression analysis, the effect size was largest in pre-COPD patients (OR= 2.79; 95% CI: 1.24 to 6.25) and smallest in incident patients (2.36; 95% CI:1.07 to 5.26) but there was no evidence of effect modification by the patient group (P = 0.813). After restricting the included pre-COPD patients to those who did not develop airflow limitation at the follow-up assessment (N= 240/285 (84%)), the effect size was of similar magnitude to that of incident patients but was no longer statistically significant (P = 0.064). After performing a Cox regression analysis on all patients (all groups together), moderate-to-severe symptom persistence was associated with an 85% (95% CI: 15% to 196%) increased risk of death. The effect size was attenuated in the further adjusted model (HR= 1.21; 95% CI: 0.73 to 2.01) and was no longer statistically significant.

Table 7.3: The effect of the persistent moderate-to-severe symptoms on prognosis according to patient group.

Outcome	Patient group	Number of events (%)	Minimal adjustment ES (95% CI)	Further adjustment ES (95% CI)
frequent exacerbation/respiratory hospitalisation	All	728 (47.6)	OR = 3.11 (2.43 to 3.97)	OR = 2.61 (1.99 to 3.42)
	Prevalent	633 (62.3)	OR = 3.02 (2.29 to 3.97)	OR = 2.62 (1.94 to 3.54)
	Incident	52 (22.9)	OR = 3.20 (1.51 to 6.81)	OR = 2.36 (1.07 to 5.26)
	pre-COPD	43 (15.1)	OR = 3.82 (1.79 to 8.12)	OR = 2.79 (1.24 to 6.25)
	pre-COPD^	36 (17.6)	OR = 3.26 (1.42 to 7.48)	OR = 2.32 (0.95 to 5.69)
Mortality	All*	70 (4.6)	HR= 1.85 (1.15 to 2.96)	HR= 1.21 (0.73 to 2.01)

^ restricted to pre-COPD individuals who maintained an $FEV_1/FVC \geq 0.70$ at follow-up assessment
*Groups were combined to give a more stable estimate due to only 14 events in pre-COPD and incident patients.
Minimal adjustment = age and sex.
Further adjustment = age, sex, FEV % of predicted, smoking status, diabetes, CVD, stomach condition, IMD score

DISCUSSION

In a sample from the BLISS cohort, which included prevalent COPD patients, case-found patients with abnormal spirometry, and symptomatic individuals with normal spirometry, we found that the occurrence of frequent exacerbations or respiratory hospitalisations was common in all groups but was more likely in prevalent cases. Overall, 34% of participants reported persistent moderate-severe symptoms, which was highest in the prevalent group but lower and comparable in the incident and pre-COPD individuals. Breathlessness, cough, and phlegm scores were highest among prevalent patients, similar between the incident and pre-COPD patients, and tended to decrease over time in all groups. Breathlessness was the most severe symptom in all groups although the severity of cough was most similar between groups. Next, we found that several factors were associated with persistent moderate-to-severe symptoms and the strongest effect was shown among current smokers and those with fewer sit-to-stand test repetitions at baseline. Finally, in all groups, symptom persistence at the level described resulted in similarly increased risks of the occurrence of frequent exacerbations or respiratory hospitalisations (2-3-fold) compared with those where symptoms did not persist.

Along with evidence of symptoms, GOLD recommends diagnosis of COPD if patients have an FEV_1 /FVC ratio below 0.70 (317). However, treatment guidelines only consider the severity of COPD using a combination of symptoms and exacerbation history. Thus, many patients suffering from persistent respiratory symptoms may not receive the care that they need due to having normal spirometry. Indeed, an overreliance on spirometry, rather than disease burden and the rate of progression, may not identify many patients who could benefit from earlier treatment intervention (318). Patients with and without normal spirometry still suffer a substantial disease burden, including debilitating persistent symptoms, exacerbations, reduced exercise tolerance, and physical inactivity, and excess lung function decline (318). Respiratory symptoms such as cough, phlegm, and breathlessness are non-specific and clinicians are left without guidance on how to treat patients who do not have abnormal spirometry consistent with COPD (319). The term “pre-COPD” implies that not everyone will develop abnormal spirometry (similar to how people with “prehypertension” do not necessarily develop hypertension) (307). The term is useful to identify people who currently have normal spirometry but also have a higher risk of developing COPD than the general population (307). Without further investigation of respiratory symptoms, airflow limitation may become much more apparent and problematic in some of these individuals.

Prior literature has shown that patients with chronic respiratory symptoms have a worse prognosis when compared to those without symptoms. Chronic bronchitis significantly increased the risk of both incident airflow limitation and all-cause mortality by over two-fold among Tucson Epidemiological Study of Airway Obstructive Disease participants (1972–1973) who were <50 years old but showed no association among those ≥50 years old (320). The presence of respiratory

symptoms (cough, phlegm, wheezing, or dyspnea) in those with normal spirometry was associated with lung function decline and two or more exacerbations (OR = 2.6; 95% CI 1.2 to 6.5) (321). Chronic mucus hypersecretion was associated with both excess FEV1 decline and an increased risk of hospitalisation in 5,354 women and 4,081 men participating in the Copenhagen City Heart Study (310). Among 97,955 individuals from the Copenhagen General Population Study, when compared to participants with normal spirometry and without chronic respiratory symptoms, the addition of chronic respiratory symptoms to those with and without obstruction increased the risk of hospitalised exacerbations, but less so with mortality (20). Given this evidence, it remains unclear if the effect of persistent severe symptoms on prognosis varies by whether patients have airflow limitation. In addition, it is important to show whether the stability of symptom severity is different between patients with and without airflow limitation to show whether treatment is likely to have some effect.

We found that persistent moderate-to-severe symptoms increased the risk of the occurrence of frequent exacerbations or respiratory hospitalisations, and the effect was similar across patients with and without obstruction. Some pre-COPD patients had spirometrically defined COPD at the follow-up assessment, however, the number was small, and the association was only slightly weaker after restricting to pre-COPD individuals who maintained an $FEV_1/FVC \geq 0.70$ at the follow-up assessment. Thus, exacerbation risk may be increased in pre-COPD patients who eventually develop airflow limitation in the future. This is supported by prior evidence that shows that there may be an interplay between level of obstruction and symptom burden, with respiratory symptoms increasing the rate of FEV_1 decline (320,322) and decline being more rapid in those who suffer from respiratory symptoms for a longer time (17,323). We found that prevalent patients were more likely to have a high symptom burden and were more likely to go from low to high symptom burden during follow-up than the other groups. However, the proportion of patients with high symptoms within each group tended to be stable over time and pre-COPD patients and incident COPD patients had similar levels of symptom severity over time. Given the similarities in both the prognosis and the stability of symptom persistence that pre-COPD patients experience when compared to patients with airflow limitation, it seems that normal spirometry may not rule out the need for further clinical investigation of underlying airway disease using, for instance, using CT scans and diffusion capacity testing. This and other techniques may help inform a diagnosis that is differential to COPD (319).

Several previous studies have examined which factors are consistently associated with symptom persistence. In an analysis of 1,061 COPDGene participants, those with chronic bronchitis symptoms tended to be younger, smoked more, suffered from wheeze, cough, and dyspnoea, were more likely to have troubled sleep due to these respiratory symptoms, had worse health status, and have an increased history of severe exacerbations than those without chronic respiratory symptoms (309,324). Our definition of symptom persistence is broader than previous literature as it includes cough and sputum as well as breathlessness. Also, previous studies have not used individual CAT item scores to define chronic symptoms. There may

be variation in the individual causes of moderate-to-severe symptoms between patients (e.g., some patients may suffer from cough more than breathlessness) and the contribution of these components may themselves vary over time within patients. We wanted to capture the overall symptom burden. Despite these differences in definition, the factors that we found were associated with symptom persistence in our study agrees with prior evidence. We found strong evidence that younger age, lower FEV_1, current smoking status, higher deprivation, and exacerbation history all increased risk of persistent moderate-to-severe symptoms. It should be noted that younger age seems to be associated with chronic bronchitis (309,324) and also with a worse prognosis in those with chronic bronchitis (320). Current smoking behavior showed the strongest association with persistent moderate-to-severe symptoms. People may reduce the severity of symptoms if they have improved exercise capacity (I.e., sit-to-stand test in our study) and this is the basis for recommending COPD patients with complex disease for pulmonary rehabilitation treatment (1). This intervention has also been shown to improve non-respiratory symptoms such as fatigue (325). Stomach condition is not directly related to COPD but pulmonary manifestations such as COPD and chronic persistent cough have been recognised as a consequence of GERD (326). Altogether, this indicates that smoking cessation, especially in younger adults, may have a large clinical impact by not only altering the natural history of COPD (210) but also reducing the persistence of symptoms and, subsequently, improving prognosis.

Our study had several strengths and limitations. The main strength of our study is that very few studies have examined the stability of symptom severity and whether the effect of persistent moderate-to-severe symptoms on the occurrence of frequent exacerbations or respiratory hospitalisation differs in patients with and without airflow limitation. One limitation includes the fact that our definition of persistent moderate-to-severe symptoms has not been validated and is not an accepted standard in guidelines. We show that the proportion with high symptoms decreases slightly over time in all three groups, especially at 6 months assessment. This may be due to patients with a high symptom burden being more likely to drop out or die. Still, the association between persistent moderate-to-severe symptoms and the occurrence of frequent exacerbations or respiratory hospitalisations showed similar strength across groups and minimally adjusted estimates showed significant association with mortality for all groups combined. Next, the number of mortality events was low in pre-COPD and incident patients and so we could not determine whether the effect of persistent moderate-to-severe symptoms on mortality varied by the patient groups. However, the low number of deaths was predictable given that these patients either do not have COPD or were only recently diagnosed.

GOLD stage I patients and smokers with normal spirometry suffer a similar burden of respiratory symptoms and poor exercise capacity (7). However, there is still insufficient evidence that GOLD stage 0 patients necessarily progress to COPD (5). Given our results, normal spirometry may not rule out the need for further clinical investigation of airway disease and people with pre-COPD may have unmet

needs consistent with people with newly identified COPD. Further research may be needed to determine if monitoring and treating patients with persistent moderate-to-severe respiratory symptoms may be beneficial (318), even if they do not have nor will ever develop airflow limitation.

CHAPTER VIII: SUMMARY AND DISCUSSION

Aims

Chronic obstructive pulmonary disease (COPD) is an umbrella term for patients with chronic airflow limitation resulting from chronic airway inflammation and loss of alveolar tissue due to environmental exposures and endogenous predisposing factors (9). Airflow obstruction, often expressed as the forced expiratory volume in the first second of expiration (FEV_1), has been the hallmark measurement to describe the severity of COPD. Serial measurements of FEV_1 are used to determine the rate of COPD progression (93,327). However, it is acknowledged that FEV_1 alone is a poor predictor of patient-related outcomes and prognosis (145). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has recommended additionally considering symptoms and exacerbation history and for the latter two to guide treatment decisions (1). Thus, there has been a shift toward recognising COPD as a heterogeneous and multidimensional disease both in research and in care (60).

This thesis aimed to highlight how components beyond FEV_1 affect prognosis in people with COPD, as well as to validate and expand the role of new and existing multicomponent COPD prognostic scores that include these components. To accomplish these objectives, we first validated the ADO score which was developed to predict mortality. Then we described how it could be used to monitor disease worsening. Next, we determined how the relationship between smoking and body mass index (BMI) in COPD patients compared to that of individuals without COPD. After showing that the rate of exacerbations had increased from 2008 to 2013, we then validated the BLISS and Bertens' scores for predicting exacerbations, an outcome that is often the cause of respiratory mortality in COPD. Finally, we determined whether moderate-to-severe symptom burden showed similar stability over time and whether persistence of these symptoms showed similar prognostic relevance in those with and without airflow limitation.

Gaps in knowledge and summary of the main findings

This thesis can be broken up into three parts that accomplish the aims that we set out to achieve. In the one part, we highlight the components that do not include FEV_1 that affect outcomes of COPD patients. In the next, we validate prognostic scores that include some of these components. Lastly, we expand the role of a

prognostic score to determine whether it can potentially be used to monitor disease worsening.

Important components beyond FEV_1

Smoking and BMI

Cigarette smoking is the most common risk factor in COPD (177) and many COPD patients do not quit smoking post-diagnosis (210). Continuous smoking behaviour is associated with an increased rate of disease progression (90,328) and a worse prognosis (210,328). Additionally, weight loss and low BMI are considered to be important extra-pulmonary manifestations of the disease (217), and they are associated with mortality (102,212). However, in the general population, cigarette smoking also leads to loss of weight (105,209) and so it was unclear whether loss of weight over time was due to the effects of the disease itself or continuous smoking. But there was limited evidence of a relationship between smoking and BMI in COPD patients before our study in Chapter 4, as many studies did not use longitudinal BMI measurements and/or were not adequately powered to place COPD patients into smoking subgroups. Therefore, in Chapter 4 we set out to determine whether smoking or COPD primarily influences BMI trajectories and if longitudinal changes in BMI mediate the association between COPD, smoking, and mortality.

We found that former and never smokers had a similar rate of decline in BMI, but former smokers had a higher baseline BMI than never smokers. COPD patients only had a marginally lower baseline BMI within these smoking groups. Recent and continuous smokers had the lowest BMI at baseline. Moreover, a more rapid decline in BMI was found among COPD patients who continue to smoke compared to non-COPD continuous smokers who had a reduced rate of decline. Sustained quitters with COPD experienced increasing BMI trajectories and the rate of increase was greater than in sustained quitters without COPD. However, we did not find that BMI mediated the association between COPD status and smoking behavior and mortality. Thus, although low BMI is prognostically independent and COPD and smoking influence BMI trajectories, COPD and smoking impact mortality independently of these trajectories. Interpretation of the hazard ratios for mortality for each of the COPD/smoking subgroups is difficult since some groups had very few patients (e.g., intermittent smoking non-COPD patients) but the size of these groups also reflects the prevalence of smoking behaviors within COPD and non-COPD patients captured from real-world data. In summary, these results indicate that, while not a prognostic mediator, BMI loss may not just be a general feature of COPD but of smoking as well.

Respiratory symptoms and their persistence over time

Many patients have respiratory symptoms but normal spirometry and the relevance of these symptoms is still debated (21). Some patients with symptoms and normal spirometry progress to spirometrically defined COPD while others do not (17). But, in those with normal spirometry (i.e., pre-COPD), respiratory symptoms may still need to be monitored and treated especially if these symptoms are stable and impact prognosis similarly to those with abnormal spirometry. In Chapter 7 we found that the association between persistent moderate-to-severe symptoms and the risk of frequent exacerbations/respiratory hospitalisation was similar in symptomatic patients with normal spirometry and patients with newly identified and long-standing COPD. Moreover, the association was maintained even among pre-COPD individuals who did not develop spirometrically defined COPD during follow-up. While symptoms were stable in all three patient groups, prevalent patients tended to suffer from worse symptoms for longer and, overall, symptom severity over time was more similar between incident cases and pre-COPD individuals, especially after adjustment for confounders. Finally, we found that younger age, worse airway obstruction, stomach condition, current smoking status, worse deprivation, lower sit-to-stand test results, and exacerbation history were all associated with the risk of persistent symptoms. Our analysis shows that normal spirometry may not rule out the need for further clinical investigation of airway disease.

Exacerbations of COPD

In Chapter 5 we showed that the incidence rate of exacerbations, especially severe ones, are increasing year-to-year in the UK. The increase in severe exacerbations indicates that more resources may need to be placed in caring for patients in hospital and in preventing these events. Exacerbations lead to an increased rate of COPD progression (23), reduced health status, and increased risk of respiratory failure, hospital admission, and mortality (24). FEV_1 is commonly used as an outcome in randomised controlled trials of COPD patients (329) but exacerbations might be a more patient-focussed and patient-reported outcome as the unpredictablility and severity of exacerbations increases fear, stress, and the overall burden of COPD among patients. As stated above, exacerbations may even be occurring in those without spirometrically-defined COPD, however, incidence rates of exacerbations in these individuals were not evaluated here. Excluding patients from trials based on their FEV_1/FVC decreases the generalisability of results to making conclusions on the potential of reducing exacerbations in those without airflow obstruction with various treatments.

Validation of prognostic scores

Several multi-component prediction models were externally validated in this thesis. COPD prediction models for mortality often include FEV_1 *a priori* but also include one or more additional predictors that make individual risk estimates more accurate

when compared to using obstruction alone (139). Prognostic scores predicting COPD exacerbations often include a history of exacerbations *a priori* but, again, these scores also include additional predictors such as symptoms, smoking, BMI, age, etc. This is the premise of all prognostic model research, to only retain predictors that significantly impact prognostic accuracy. The accuracy of these models can vary when used to make predictions in populations that are different than the one they were developed in. This is often due to variation in the distribution of these risk factor components from one population/healthcare setting, location, or moment in time to the next (303). The ADO (age, dyspnoea, obstruction) score (144) for predicting overall mortality within 3-years had not been adequately tested in patients with less severe disease, while the BLISS and Bertens' scores (330) for predicting exacerbations had not been tested in patients with more severe disease. We decided to externally validate these scores in different severity groups as well as test if these scores maintained accuracy at different time horizons, geographic settings, and, in some cases, using slightly different methods (303).

The ADO score

In Chapter 2 we showed the results of the validation of the ADO score in Birmingham Lung Improvement Studies (BLISS) cohort primary care COPD patients. We found that the ADO score showed accurate discrimination in predicting 3-year mortality, but it tended to over-predict risk in patients with higher predicted risks of mortality at 1 and 2-year mortality. Thus, we recommended that the ADO score be recalibrated if it is to be used to provide risk predictions for 1- or 2-year mortality.

BLISS and Bertens' score

In Chapter 6 we found that the BLISS score more accurately predicted severe exacerbations when compared to Bertens' score in Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) COPD participants. Both scores showed stable discriminative accuracy across different time horizons. However, neither model showed accurate calibration statistics when predicting moderate-to-severe exacerbations as both scores showed substantial under-prediction, especially the BLISS score. Thus, we stated that both scores may require updating (specifically to the intercept term) before it can be determined which is better for predicting moderate-to-severe exacerbations. However, the BLISS score is more accurate when predicting severe exacerbations and may require further external validation and impact assessment (290) for this outcome.

Expand the use of prognostic scores

Finally, we attempted to expand the function of multicomponent prognostic scores using the ADO score as an example. By combining multiple components measured at a single time point (e.g. first clinical visit), prognostic scores take account of the heterogeneity found in COPD patients to make predictions of adverse outcomes within a period of time (60). But the progression of COPD is also heterogeneous (95). Traditionally, serial measurement FEV_1 alone has been used to track progression (177) but "in patients with FEV_1 lower than 50% predicted, the 6-minute-walk distance changes more over time than lung function...." (95). Progression of COPD can be more adequately described using prognostic scores; however, it was unclear if it is even beneficial to measure prognostic scores serially in COPD patients. In Chapter 3 we found that both changes in the ADO score and subsequent ADO score measurements significantly impacted prognosis above and beyond the baseline ADO score measurements and that the ADO score can identify patients with worsening disease and update their prognosis. Patients who were smokers, depressed, or had lower BMI had an increased rate of worsening ADO scores over time and, therefore, serial assessment may be even more beneficial in these patients. Former smokers had worse ADO score trajectories when compared to never smokers but still had an improved trajectory when compared to patients who continue to smoke. Thus, we found that serial assessment of the ADO score may be advantageous in order to track disease worsening and update a patient's prognosis.

Interpretation and future work

Challenging well-established concepts and theories

COPD is a complex disease, and our understanding of the heterogeneity, aetiology, diagnosis, prognostic factors, and management is still evolving. Lack of clear evidence and differences in interpretation of the evidence has led to ongoing debates about all of these aspects of the condition. Sometimes "old "concepts can resurface later on. For instance, in the Introduction chapter, we discussed whether it was best to define airflow obstruction using the lower-limit-of-normal or the fixed ratio (FEV1/FVC<0.7) method. This is an ongoing source of conflict and debate among scientists and clinicians (14). Secondly, 55 years after the term's introduction 'nonobstructive chronic bronchitis' has resurfaced to describe people

with chronic cough and phlegm and normal spirometry and to differentiate these people from those with chronic bronchitis and abnormal spirometry (307). The goal is to highlight individuals with symptoms that are associated with morbidity and increased risk of progression to spirometrically-defined COPD. This thesis highlights several additional examples of concepts and theories that need to be re-thought.

Establishing pre-COPD so that people with symptoms can be treated

Since there was insufficient evidence that individuals with respiratory symptoms and normal spirometry necessarily progress to COPD, GOLD removed stage 0 from their diagnosis and treatment guidance (21). Only some patients with persistent symptoms develop spirometrically defined COPD and it is unclear why only some individuals seem to have early COPD (17). However, it is known that the destruction of the alveoli and restructuring of the peripheral and large airways can produce symptoms before abnormal spirometry is found (306). It has also been shown that respiratory symptoms (323) and exacerbations (23) increase the rate of lung function decline. Establishing a definition for people with increased risk of spirometrically-defined COPD due to their respiratory symptoms is important because its natural history may be more easily modified at this stage.

The debate continues as to whether symptomatic patients with normal spirometry have 'early disease' or if these patients suffer from a different disease entity altogether (7,17). Chapter 7 shows that it may not matter. Like precancer or preeclampsia, pre-COPD was introduced as a group that, as a whole, has an increased risk of COPD (307). This does not mean that all people with pre-COPD will eventually develop COPD. However, more individuals in this group may develop overt COPD if clinicians do not intervene (307). Clinical investigation of some form of airway disease may benefit patients, regardless of if they currently have or will develop airflow obstruction. This may be especially true for people with chronic cough and phlegm as people with these symptoms are more likely to progress, have excess mucin production which mediates disease severity, and radiographic abnormalities (307). The main exposure variable in our analysis of pre-COPD patients (Chapter 7) was the persistence of moderate-to-severe symptoms such as cough, phlegm, and breathlessness. The latter component is especially non-specific to COPD but is an important factor for the prognosis of COPD patients (144). Additionally, assessing a broader range of symptoms – not just respiratory symptoms but fatigue and other components as well - may also be useful in identifying undiagnosed COPD and account for more of the systemic effects of smoking (17) in those with pre-COPD. For many patients, symptom burden remains high and this may be related to an excess decline in lung function (17). So, monitoring the stability of symptoms may be an early marker of excess of FEV_1 decline toward spirometrically defined COPD.

Ironically, some patients with persistent symptoms and normal lung function may find that spirometry is a barrier to treatment of their respiratory illness (17), a situation that is not improved after the elimination of GOLD stage 0 from treatment and diagnosis guidance. If pre-COPD patients have similar stability of symptom burden and prognostic outlook of this burden to those with newly identified,

spirometrically-defined COPD then trials of treatments (inhalers or pulmonary rehabilitation) used in COPD may need to include pre-COPD patients to see if they can modify prognosis and/or change the natural history of this population. In individuals with pre-COPD, if forced vital capacity (FVC) decreases at a similar or faster rate than FEV_1 (331) then airflow limitation will not be diagnosed using the FEV_1/FVC ratio or LLN methods, even though decreasing FVC over time may itself be an independent prognostic factor (332).

We may need to move away from using spirometry to screen for COPD but instead, use a symptom burden assessment tool. Choosing the right symptoms to be assessed using this tool is important. As mentioned above, evidence suggests that cough and phlegm are the most important symptoms (307) but a broader set of symptoms may more accurately identify at-risk groups (17). Combined with symptoms other signs may indicate the presence of pre-COPD such as early signs of abnormal structure of the airways and physiology (307). The addition of these early markers of airway damage may enable clinicians to capture more individuals who ultimately progress to COPD (307), and prioritise care and resources if individuals are grouped into 'possible', 'probable', and 'definite COPD' groups (307). The question then becomes 'what we should do with these people?' and whether or not the actions that are taken help them. More research is needed to determine if monitoring and treating people with persistent respiratory symptoms and other abnormalities is beneficial (318) and cost-effective, even if some of these individuals do not develop airflow limitation in the future.

New uses for well-validated prognostic scores

Measuring a prognostic score once may inadequately account for changes in risk over time, which may occur from treatment or worsening disease. The ADO score has received some criticism for including only three components, one of which is age, which is not modifiable and not specific to COPD (333). However, it can also be said that a prognostic score that predicts overall mortality and does not include age is incomplete. The purpose of a prognostic score is not to monitor response to treatment (where you would need to include components that can be modified in response to interventions), but rather to inform conversations with patients, make management plans, and plan services. In this context, whether the components are modifiable is not relevant. Trajectories in the ADO score over time will not be influenced by age since aging cannot progress at faster rates for some patients versus others. However, the age component provides a good anchor from which the dyspnoea and obstruction components could drive variation in trajectories in the overall ADO score.

Previous studies have not adequately shown how serial assessment of a prognostic score might be beneficial. In contrast to our results with the ADO score, it was concluded that a single, rather than serial, BODE measurement was sufficient (189). The baseline BODE score (137) predicted both survival and readmission for COPD patients hospitalized for acute exacerbations of COPD whereas serial BODE indices were not predictive of survival at 3 years. However,

the BODE score may be useful as a surrogate outcome to show whether pulmonary rehabilitation (190), lung volume reduction, and other treatments (197) can benefit a patient's disease, with average decreases in the BODE score after treatment summarising the impact of treatment and significant decreases in individual patients representing responders to treatment. Thus, the BODE may be more appropriate as a surrogate marker of treatment efficacy and response while the ADO score is not only more accurate than the BODE score (145) but, given our results, may be better suited to reflect changes in prognosis.

Since prognostic scores are underutilised in COPD research, these results have limited clinical utility. Still, Chapter 3 puts forth the notion that patients and their healthcare workers may benefit from prognostic scores if they are measured more than once. Future research may be needed to determine if other COPD prognostic scores are more sensitive to the effect of COPD activity on patients, with priority given to scores that are also the most accurate.

Smoking's effect on BMI loss and the potential connection to COPD phenotypes

Continuous smoking decreases BMI and quitting results in gains in BMI, especially in COPD patients. This challenges the "chronic bronchitis versus emphysema" paradigm which often manifests itself as "blue bloaters" and "pink puffers", respectively (243). Patients with chronic bronchitis tend to have inflammation of the lining of the bronchial tubes and have symptoms such as cough with sputum, intermittent dyspnea, pulmonary infections, and, eventually, weight gain (4). Emphysema, on the other hand, is characterised by the destruction of the alveoli in the lungs and is exhibited by worsening dyspnoea, wheezing, and, finally, loss of weight.

Cigarette smoking behaviour – being an earlier insult than COPD itself – may produce specific COPD phenotypes that are dissimilar to phenotypes produced by other risk factors. In a cross-sectional analysis, female COPD never-smokers with prior biomass exposure (n=21) had significantly less emphysema than former smokers with COPD and without prior biomass exposure (n=22) (334). This supports the notion that rather than originating from COPD, smoking may itself primarily influence the pathogenesis of emphysema-related COPD which in turn produces the "pink puffer" characteristics and loss of weight over time. In other words, rather than originating from COPD, loss of weight may derive from smoking behavior prior to diagnosis. More studies may be needed to determine whether former and current smokers with COPD are more likely to lose weight over time than never smokers with COPD and a history of biomass exposure. This may help elucidate the root cause and mechanisms of weight loss in COPD. If the duration of weight loss after cigarette smoking exposure is extended by the maintenance of emphysema-related COPD, even after quitting, then this may help determine if some patients are better responders to pulmonary rehabilitation, nutritional support, and other interventions when compared to other COPD patients. In addition, while the efficacy of smoking cessation for increasing weight may be reduced in patients with emphysema-related COPD, it may still improve symptoms.

It is still unclear if COPD patients who continue to smoke lose weight due to the maintenance of an emphysematous phenotype and how this relates to loss of BMI in individuals from the general population who also smoke. COPD patients with primary emphysema may also have poorer nutritional intake (203), increased work of breathing (204), increased resting energy expenditure (205,206), and mechanical inefficiency (207) than other COPD patients. Also, it may be of interest to determine how people with COPD lose weight when compared to those without COPD and the general population. Similar to loss of BMI, loss of muscle mass is prevalent in people with COPD and is a significant prognostic indicator (335) but interventions for optimally treating loss of muscle mass (i.e., pulmonary rehabilitation) versus a loss of fat (i.e., nutritional support) should not completely overlap (102). In conclusion, our study is an early example of how smoking, rather than COPD, may influence BMI which may have clinical implications since smoking behavior is, indeed, more reversible than COPD.

Unmet need for care of women suffering COPD exacerbations.

We found that the rate of any exacerbations was higher among women and so healthcare providers may need to be more aware of the need to recognise and reduce the frequency of exacerbations in these individuals, potentially using risk prediction tools to guide treatment decisions. If the higher rate of exacerbations among women is due to gender phenotypes of disease then stratifying the development of COPD prognostic scores that predict exacerbations by gender may improve the calibration of prognostic scores. However, there are few examples of COPD prognostic scores that have been developed (and used) in this way. COPD is probably not fundamentally different in men and women but may instead be linked to additional traits that tend to affect one gender more than the other. An example may be breathelessness. Women have been shown to have more exacerbations despite smoking less than men among 470 patients with stable COPD with a history of smoking (336). Although women had a higher FEV_1% predicted they had the same level of breathlessness compared to men. These results and the results from chapter 5 indicate that targeted assessment and management of COPD in women and men may be needed.

COPD prognostic scores are accurate… until they aren't

Minor differences in the development of various scores seem to have implications for calibration accuracy, and not discriminative accuracy, during external validation. While discriminative power was relatively stable in the ADO validation study (Chapter 2) and BLISS/Bertens' score validation (Chapter 6) studies, calibration statistics were more sensitive to different time horizons, healthcare settings, and outcome definitions. In all these instances, the results are fairly predictable. If the

outcome definition is broadened or becomes more specific, the allotted time horizon in which outcome events are counted is increased or decreased, or if the patient population that is used for validation is more or less severe then, in all of these cases, the number of outcome events increases or decreases and the prognostic model runs the risk of under or over-prediction, respectively. Calibration statistics are important because predicted and observed risks must be similar for the risk of an adverse outcome to be properly weighed against the costs and adverse effects of treatment. Only calibration statistics can test (and show) the degree of similarity between observed and predicted risk (158). However, any calibration measures, let alone calibration-in-the-large and the calibration slope, are often not reported (148).

There seems to be a lack of understanding that prognostic scores are validated to predict certain outcomes over a particular time horizon. A score developed to predict mortality is not necessarily going to be a good predictor for hospitalisation and vice versa. A score validated to look at a short time horizon (e.g., 12 months), to consider 'end of life' care pathways, will not necessarily be a good long-term (over 5 years) predictor. Sometimes validation studies do not specify what the time-horizon is and often use the total follow-up time as the time horizon for testing scores (337) which decreases the reproducibility of findings. It may be the case that certain time horizons may not be clinically relevant. Additionally, validation studies that support the use of scores in different outcomes and time-horizons may not report calibration slope statistics to allow the readers to decide for themselves (148). But in practice, clinicians need to be careful and not use prognostic scores interchangeably without considering the purpose and context in which the score was originally developed.

A 'one score fits all' approach may not be entirely possible. It is probably better that clinicians can choose the score that most accurately predicts outcomes in the type of patient and setting that they are experienced in treating. On the other hand, testing the accuracy of existing COPD prognostic scores in other populations should be considered before developing new prognostic scores that are not needed (139). Developing new models, instead of validation or updating existing models can lead to confusion among clinicians when too many models are available for the same outcome, time-horizon, and setting (140). If too many prognostic scores are available to clinicians, then this may result in none of them being used in clinical practice.

There is a lot of room to externally validate and/or update existing COPD prognostic scores. However, it is rarely done. In a 2019 study, 408 COPD prognostic models have been developed but only 38 (9%) were externally validated

(139). This is in comparison to 25% of new development studies being externally validated across all disease fields (338). There was a 0.05 median drop in discriminative performance from development to external validation, which shows why testing transportability is so important. There is added complexity with COPD prognostic scores which further highlights the importance of testing them in various settings. Existing COPD scores have been primarily tested in North American and European populations and could not be easily generalised to other settings such as low and middle-income countries where risk factors such as tuberculosis and indoor air pollution are more common (139). There are several reasons why external validation studies are so rarely performed:

- the development methodology has pitfalls;
- the prognostic model formula was not published;
- the outcome definition was different from the one that was collected (e.g., developed prognostic score predicts hospitalisation but hospital episodes were not ascertained);
- patients in the validation sample are too similar to that of the development sample;
- and predictors included in the score may not have been measured in cohorts available to researchers.

Of these reasons, it seems that the only plausible explanation for why COPD prognostic models are less likely to be validated than prognostic models in other disease fields is that COPD models use predictors that have not been collected in cohort studies and routine data, and are, therefore, probably not accessible across clinical settings either. The wide range of predictors associated with adverse outcomes in COPD patients may be due to the complex and diverse nature of COPD and the large number of tests needed to fully describe COPD patients. Developing models that use easily measured predictors is not only better for clinical practice but external validation as well. After external validation, the next best option for testing the generalizability of a prognostic score is internal validation, however, only 25% of COPD models have been tested in this way (139).

However, a validated prediction model alone is unlikely to modify treatment decisions in daily clinical practice. The second stage is to test whether a well-validated model has clinical utility and impacts patient and healthcare providers' decisions (139). Impact studies are defined as studies that quantify the impact of using a prognostic score on patient and healthcare providers' behaviors and decisions and, subsequently, patients' health outcomes and the cost-effectiveness of care (140). It is important to note, however, that "prediction models are not

developed to replace doctors but to provide objective estimates of health outcome risks for both individuals (including patients) and healthcare providers, to assist their subjective interpretations, intuitions, and guidelines" (140). Guidelines on optimal treatments matched to thresholds of predicted risk estimates of adverse outcomes may also be needed, similar to the cardiovascular disease field (339) where treatment is advocated in the top groups (>20% for AHA/ACC 2019 guidelines and >10% for ESC 2016 guidelines) and a discussion of adding or removing treatment is recommended for the next highest group (≥7.5 to <20% and ≥5 to <10%, respectively) (340,341). To establish predicted risk thresholds for COPD, decision analysis and cost-benefit modelling approaches can be used (342) but GOLD would have to shift away from its A/B/C/D treatment classification system (278) to avoid confusing healthcare workers.

To our knowledge, only one impact study has been published (151). It tested the impact of the DECAF score, originally developed to predict mortality in patients admitted to hospital with an exacerbation (150), and found that hospital-at-home for patients admitted to hospital with a low DECAF score (0 or 1) was safe, clinically effective, saved an average of £1016, and was preferred by 90% of patients after 90-days compared to patients with a low DECAF score randomised to "usual-care" in a non-inferiority design (151). Although the study randomised patients instead of clusters there was little chance of contamination since the individuals from each arm were separated. However, using this design did not allow the researchers to test how the use of risk estimates derived from a prognostic score may alter clinical or patient decision-making and subsequent patient outcomes. This more 'human element' was removed because the use of the DECAF score itself was not randomised to clusters of patients treated at separate care centres.

The overabundance of COPD prognostic scores makes it difficult for clinicians to decide which one is best to use. Often, the best score is the one that has the most accessible predictors, which is going to be dependent on the healthcare setting. It is important that scores have predictors that are easily measured not only so that they can be used across multiple healthcare settings but also so that these scores can be externally validated. Future research needs to test existing models with accessible predictors in new populations so that they can be tested for impact and, if effective, used in clinical practice. The ADO score for predicting mortality and the BLISS score for predicting exacerbations may be the best candidates.

Smoking cessation is vital

While recent studies have shown that COPD can be attributed to many risk factors other than smoking (343,344), we found in Chapter 4 that COPD patients are still much more likely to smoke than non-COPD patients and this has been observed in other studies (210). It has been shown that in mild to moderate COPD, smoking cessation also reduces the risk of disease progression (193) while mortality was reduced in more severe cases (210). It should be noted that many COPD patients have delays in their diagnosis (345). An important factor seems to be the lack of awareness and knowledge about COPD among healthcare providers (345) but many patients may also ignore their symptoms until they become persistent, attributing unstable symptom burden to more transient respiratory health issues. If symptoms can be recognised before they become chronic then the downward trends that lead toward abnormal spirometry (17) may be altered via smoking cessation advice (210).

Despite the substantial improvement in the natural history and prognosis of COPD patients who decide to quit smoking, over 40% of people continue to smoke after a diagnosis of COPD (346). Among smokers with moderate-to-severe COPD participating in RCTs, 12-month continuous abstinence rates were estimated to be 1.4% for usual care, 2.6% for minimal counselling, 6.0% for intensive counselling, and 12.3% for pharmacotherapy (347). The effect of pharmacotherapy and intensive counseling on abstinence rates is large but the absolute abstinence rates are still low and are lower when compared to the rates observed in the general population (10% and 17%, respectively). This may be due to the finding that smokers with COPD have low self-efficacy and have less motivation to quit than other smokers (346). The most optimal approach for smoking cessation was found to include a nicotine replacement agent for 3 months and individual or group support, with retreatment available if the patient begins smoking again (348). But this may only work in highly motivated individuals who may or may not have poor self-efficacy. If self-efficacy is high but motivation is low, then it may be more useful to start with health education and motivational interviewing. If both self-efficacy and motivation are low then the intensity of support needs to increase (346). Still, three out of every four individuals with a COPD diagnosis intend to quit smoking but fewer than 5% follow through (210). More research is needed for ways to help COPD patients to quit smoking, especially those who have more severe disease, lifelong smokers, and those with strong nicotine dependence. Public health interventions such as restricting smoking to fewer areas in a community may help

in general population settings but it is unclear if these interventions impact smoking cessation among individuals with certain diseases, like COPD.

A seminal review has summarised that, among the general population, body weight is lowered by smoking on a short-term basis but that gains in body weight may be achieved even years after quitting (105). Our results reflect these observations since former smokers had the highest BMI among all other smoking groups. The rate of gain in BMI over time may be substantial in COPD patients who quit smoking which may have implications for increasing the intensity of smoking cessation guidance and support for COPD patients who are underweight. Detailing this reasoning to the patient may help them to quit, even though the mechanisms behind weight loss and gain due to changes in smoking behaviour are unclear (105). However, COPD patients have comorbidities to contend with (52) and a gain in weight after quitting may be met with an increased incidence of other diseases on top of COPD, such as cardiovascular disease. Among 16,663 Australian adults aged 18 or over (mean age was 44), participants who quit smoking tended to have a gain in BMI compared to continuous smokers, the rate of death was reduced by 74% (95% CI: 55% to 84%) among quitters who gained more than 2 kg/m^2, and there was no association with an increased risk of chronic diseases in quitters (349). This needs further study among COPD patients, but it is likely that gains in weight while someone with COPD is already overweight (potentially a “blue bloater”) is harmful whereas gains in weight while underweight (potentially a “pink puffer”) is beneficial.

Methodological considerations

Secondary data analysis

In this thesis, we used data from large cohort studies of people with COPD and routine health data from general practice to answer research questions related to prognosis. No data collection was undertaken and secondary analysis of existing data was used throughout. But there are benefits and drawbacks to secondary data analysis that are directly counter to that of primary data analysis. Primary data analysis is defined as the “analysis of data by members of the research team that collected the data, which are conducted to answer the original hypotheses proposed in the study” (350). For primary analyses, the research question is conceived before data collection so relevant covariates would have been collected by the research team. Secondary analyses of existing data comprise all other analyses of data that can either originally be collected for specific research studies

or collected for other purposes. Routine primary care data is an example of data collected for purposes other than for research. Our secondary analysis studies suffered from residual confounding due to many potential confounders not being measured/collected by General Practitioners or the original research team of the cohort that we analysed. One example was our inability to adjust for alcohol use, exercise, and eating/nutrition in the association between smoking and body mass index trajectories (Chapter 4). We may have overestimated our effect estimates since adjustment often results in effect sizes approaching the null. One way to minimise unmeasured confounding is using longitudinal data and repeated measures of both the exposure and the outcome in fixed-effect models (68). This allows only within-person changes to be analysed and any heterogeneity between individuals, which produces confounding, is reduced. Instead, we opted to only use longitudinal measurements of the outcome in our mixed effect models because this was simpler to interpret and allowed comparisons to be made between groups of individuals defined by our exposures/covariates. However, it is unclear if, even when using mixed effect models in this way, effect estimates are less likely to be affected by confounding when compared to cross-sectional analyses because covariates must be associated with not just the dependent variable measured at a single time point, but over multiple time points to bias results.

One strength of our studies is the generalizability of our findings. The THIN database is a longitudinal, clinical primary care database that covers ~6% of the UK population and the population of patients captured in THIN is generalisable to the whole of the UK for demographics, disease prevalence, and mortality rates (351). Although studies using THIN may provide a large sample size, patients from urban areas may be over-represented because the use of software used by General Practitioners to capture data on patients is clustered in large urban areas (200). Therefore, THIN patients may be more likely to live in urban areas than the people in the whole of the UK and this may be related to increased smoking behaviour and a higher prevalence of COPD as a result (352). THIN was used for Chapters 3 and 4 and these studies had extended follow-up. This is an important strength because in these chapters we examined the trajectories in both BMI and the ADO scores over time and fewer longitudinal data points may result in altered estimated patterns of change. There was some evidence of this in Chapter 4 when we compared the results for a set of patients with 2 or more BMI measurements to those with 3 or more measurements. However, the conclusions remained the same.

The Birmingham Lung Improvement Studies (BLISS) cohort is comprised of primary care patients from the West Midlands, UK with previously diagnosed COPD (162). The BLISS cohort also included two more groups of patients identified through a case-finding trial: previously undiagnosed patients with respiratory symptoms and spirometrically-confirmed airflow obstruction and symptomatic patients with normal lung function. Thus, while not geographically and ethnically (mostly white) diverse, the BLISS cohort includes participants in various stages of COPD. It also includes patients with a range of COPD severities, especially with mild-to-moderate disease.

Although the potential for extended follow-up is a feature of routine primary care databases, there is a possibility that Read codes for clinical manifestations and measurements change over time. Read codes can be added (or taken away) and healthcare professionals may change their use of these codes, especially with additional knowledge of the coded condition. While our THIN projects had relatively long follow-up periods, the repeated measurements that were being modeled were simple (body mass index, obstruction, and dyspnoea) and their relevant codes - and usage of these codes - are not likely to change over time. However, the codes used to capture a case of COPD are often more complex and COPD patients captured at baseline in 2005 may be very different from those patients captured in 2020. COPD is increasingly being recognized as a more complex and heterogeneous disease (60) and it may now require a broader code list to fully capture the diversity of patients suffering from different aspects of the same illness. Still, a balance has to be struck between having a precise code list with high specificity and low sensitivity or an imprecise list with low specificity and high sensitivity. Even excluding patients who were diagnosed with COPD before they were 40 years of age to reduce the chance of including those with alpha-1 antitrypsin deficiency-related COPD may need to be reconsidered since many patients may have attained a low-maximal attained lung function earlier in life and have a predisposition to COPD (85) regardless of their genetic risk. Still, our results should apply to the vast majority of patients considered to have signs and symptoms consistent with COPD today. Since the 2004 introduction of the Quality and outcomes framework, a performance management and payment system of General Practitioners which rewards “good practice” (241), reporting of diagnoses and measurements made by General Practitioners has improved in THIN. Still missing data is an issue in routine data. However, the use of mixed-effect models in the studies in Chapters 3 and 4 not only accommodated missing repeated measurements without giving biased estimates but also accounted for correlation structures between measurements within patients as well as unbalanced measurements (i.e., repeated measurements at different times) between patients (222).

Outcomes and survivor bias

In all the chapters in this thesis, prevalent patients were included (sometimes along with incident patients). Prevalent cohorts are prone to survivor bias because patients who die soon after diagnosis are more likely to be excluded from these cohorts (224). An analysis of prevalent patients will consist of individuals who have lower risk and better prognosis. However, in several of these chapters, we examine a prognostic score. It has been shown previously that the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk score (353), originally developed to predict risk in prevalent patients, was also valid in predicting risk in newly diagnosed patients (224). The process of explicitly assessing the risk of outcomes in newly diagnosed patients means that survivor bias may be accounted for since the score will give risk estimates that place more of these individuals into the higher risk strata than the lower risk strata (224). In our studies,

more individuals were likely estimated to have lower risk so that any survivor bias inherent in using prevalent patients would be mitigated through risk assessment calculation in individual patients. However, this may only be true if the risk score includes components that explain the increased risk among newly diagnosed individuals and why prevalent patients have a reduced risk. Smoking might be one component that differentiates incident and prevalent COPD patients as prevalent patients are more likely to be older and have quit smoking before the risk assessment measurement. Although it is rare for prognostic scores to be validated it is rarer for validation to be performed because the score requires testing in prevalent or newly identified patients. We wanted to include prevalent and incident patients in our analyses because COPD prognostic scores can be easily used regardless of if the patient was recently diagnosed, and it was of interest to determine if these scores are valid in both populations.

Mortality ascertainment was not complete for the studies using THIN (Chapters 3 and 4) because Office of National Statistics (ONS) data was not linked to patient records. Therefore, death data relied upon General Practitioners coding that their patients had died after hearing about it from various sources. In a study conducted in 1991, 224 self-completed questionnaires (74% response rate) returned to study authors by General practitioners practicing in the Newcastle upon Tyne and Sunderland Family Health Services Authority areas showed that they mainly learn of their patients' deaths from hospital discharge summaries (54%) and patients' relatives (46%) but other sources included newspaper obituary columns (20%) and hospital telephone calls (9%) (187). With the growth and expansion of technology and social media in the intervening years, there may be additional sources where General Practitioners can now become aware of the status of their patients. The study concluded that “General practitioners need and would welcome prompt, accurate and comprehensive information about all their deceased patients.” ONS was formed 2 years after this study was published. Still, it is not expected that the ascertainment of death in our included samples varied by levels of our exposure and covariate groups in Chapters 3 and 4. However, this may be the case if General Practitioners research the status of patients that are performing risky behaviours. We wouldn’t expect substantial underreporting of overall death since we only included THIN practices after they had acceptable mortality reporting (AMR). AMR distinguishes practices for reporting the expected number of deaths compared to national death data after adjusting for the age and sex distribution of the patients attending the practice (354).

A detailed analysis of symptom stability in BLISS participants was performed in Chapter 7. Unfortunately, patients were lost-to-follow-up for various reasons which made longitudinal tracking of symptom changes in BLISS patients less statistically powerful. Since frequent exacerbations/respiratory hospitalisation (our dependent variable) was collected using questionnaires, outcome ascertainment may have been incomplete if some patients dropped out just prior to having a sudden worsening of symptoms leading to an exacerbation. If these individuals were more likely to have persistence of moderate-to-severe symptoms, then we may have underestimated the true effect of this exposure variable. Indeed, those who dropped out had worse symptoms than those that did not, and this was shown by

splitting each patient group under investigation into subgroups defined by whether the patients attended the follow-up assessment (for whatever reason). Multiple imputation to replace missing repeated symptom measurements with substituted values would have been inappropriate since incomplete measurements would have been missing-not-at-random (355).

Prognostic model research

Prognostic model research is plagued with a lack of adequate reporting and methodological pitfalls (356). The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement was designed to help authors report key study items in the domains of patient population, outcome definition and ascertainment, risk model components, results, and other aspects so that researchers and the scientific community can accurately weigh the pros and cons of developed/validated prediction models (161). In Chapters 2 and 6 of this thesis, we followed the TRIPOD statement. However, many other published prognostic model research studies do not report critical information and COPD prognostic model research is no exception. A systematic review stated that only one out of 27 development studies for COPD prognostic scores predicting exacerbations provided information on how to calculate individual probabilities of risk from the predictors included in the regression equation (148). However, we validated the Bertens' score which also reported this information (two out of 27) (330). Without this information external validation by authors who did not develop the prognostic model becomes difficult. External validation can be performed by using the scoring system, but cutoff points (and the number of cutoff points) used for scoring during development are sometimes arbitrary and this may also affect the perceived accuracy of the prognostic model in a new population.

Out of 400 COPD prognostic model development studies, only seven were assessed as having a low risk of bias using the PROBAST tool (289) while only five out of 116 external validation studies of COPD prognostic scores had a low risk of bias (139). Bertens' score had a low risk of bias for both development and external validation which is one reason why we compared the BLISS score to it in Chapter 6. By far the main reason so many models were assessed as having a high risk of bias was due to a lack of proper analytic techniques being undertaken (139). Some examples of analytic guidance notes from PROBAST are 1) calibration and discrimination are evaluated appropriately, 2) model overfitting and optimism in model performance accounted for, 3) participants with missing data are not excluded, and 4) many other items that are not necessarily specific to prediction model studies (e.g. number of events is adequate, selection bias), etc. (289). A systematic appraisal of the methodological conduct and reporting found in multivariable prediction model studies found that complete-case analyses were often used in the presence of missing values for predictors included in models and that calibration was often not conducted and/or not reported (356).

Calibration is used to determine how close the prediction for an individual is to their observed risk (158). Observed and predicted risk is compared and calculated

within subgroups (usually deciles or clinically useful risk thresholds). While discrimination is concerned with the rank order of risk estimates for cases and non-cases in the sample, calibration uses the actual risk estimates themselves, which is more clinically applicable for prognostic models since risk estimates are used for treatment decisions (158). For example, assume two individuals have low risks of mortality that are similar (e.g., individual A: 1.0% versus individual B: 2.0%). If in two years the prognostic score is used to measure their risks again and it is found that both have shown an increase in risk (e.g. individual A: 2.0% versus individual B: 40.0%) due to worsening of disease, the c-statistic would be the same even though the clinical decisions are likely to be different in the latter scenario (especially for individual B) (357). However, if the score is known to overestimate risk in those with high predicted risks of the outcome, then there will be uncertainty about how to treat individual B.

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) was a 3-year longitudinal study of COPD patients with FEV_1 of <80% of the predicted value, baseline post-bronchodilator FEV_1/ FVC of <0.70, and a smoking history of ≥10 pack-years (282). These patients represent the more severe COPD patient population in this thesis. It should be noted that ECLIPSE patients are geographically diverse as they were enrolled at 46 centres in 12 countries. Differences in the spectrum (severity of disease), geography, and methodology between the BLISS and ECLIPSE cohort allowed for a rigorous test of the BLISS score's transportability (303). ECLIPSE authors decided to exclude patients with diseases characterised by significant systemic inflammation (282) because if significant inflammation is shown in a patient it can no longer be primarily attributed to COPD. While this exclusion reduces the generalizability of ECLIPSE, it is difficult to determine the effect of this exclusion on the BLISS score and Bertens' score validation study. On the one hand, testing prognostic models in more particular populations, different from the one they were developed in, provides a more rigorous test of accuracy when compared to testing models in similar populations. However, once these scores are validated it still remains unclear whether they are generalizable to patients with comorbidities such as rheumatoid arthritis and inflammatory bowel disease. The impact on our results is likely to be small.

Conclusions

The identification of early pathological changes in the lungs has been ignored until recently because COPD was viewed as a disease of smoking, primarily in elderly men (7,344). But a fuller understanding of the heterogeneity of burden experienced in COPD should result in further research into the early origins of the disease. Different environmental insults – such as smoking and biomass exposure – early in life may give rise to different COPD phenotypes (334). Smoking-related

phenotypes may result in underweight COPD patients who are more likely to have worsening disease over time. Quitting smoking improves patients' low body weight, even after their diagnosis, and more dramatically than in non-COPD patients. Thus, phenotypes may be dynamic and change as exposures and treatments change.

A decline in FEV_1 that is only slightly more rapid than normal in susceptible smokers may result in a COPD diagnosis if the patient had a lower-than-average FEV_1 in early adulthood (Figure 7.1) due to, for instance, passive smoke exposure *in utero* (7,93). However, some unsusceptible smoking individuals with lower-than-average FEV_1 in early adulthood may remain well due to age-related decline in FEV_1. This level of heterogeneity makes diagnosis more difficult and often delays it (345). At the same time, since persistent respiratory symptoms often lead to exacerbations, it should not matter if only some of these patients will develop COPD later on since individual patients should be treated and not the disease. If some patients suffer primarily from symptoms or systemic manifestations rather than poor lung function, then well-validated prognostic scores for exacerbations and mortality can still accurately account for their overall risk. There may be a need for clinicians to recognise dyspnoea and exacerbations in women so that prognostic scores predicting exacerbations can be used to guide treatment in these patients. Serial measurement of some prognostic scores, such as the ADO score, can better account for any changes in their risk. Although the accuracy of COPD prognostic scores may depend on the context and impact studies are still needed before they can be used in practice.

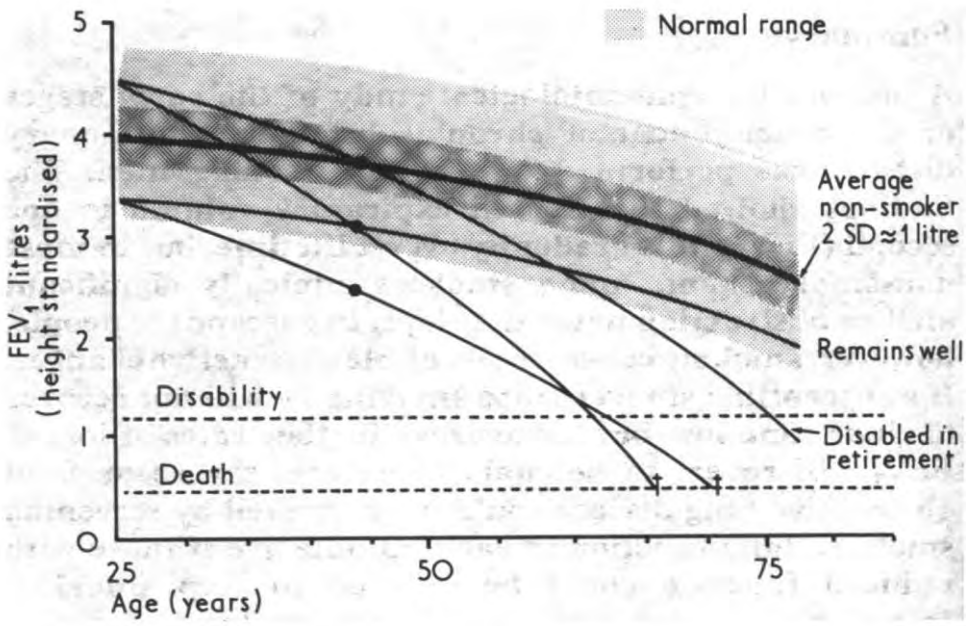


Figure 7.1: The often-overlooked second figure of the seminal paper entitled "The natural history of chronic airflow obstruction." It shows that susceptible smokers may have higher or lower than average FEV_1 in early adulthood, but it is impossible to distinguish between these individuals with just one measurement of obstruction at the age of 40. Smoking individuals with above-average FEV_1 at the age of 25 can have an increased rate of decline when compared to those with below-average FEV_1 at the same age. Reproduced with permission from Fletcher and Peto 1977 (93)*, British Medical Association.*

Impact and personalised care of COPD patients

This thesis aimed to highlight components beyond FEV_1 and explore how they affect COPD patients as well as validate and expand the role of new and existing multicomponent COPD prognostic scores that include these same components. The results of this thesis clearly show that lung function measurements are insufficient in assessing the severity, progression, and prognosis of COPD patients. Regardless of whether clinicians are determining a patient's risk of mortality, exacerbations, or worsening progression, it is important to account for multiple components beyond FEV_1 to account for heterogeneity found in COPD patients

before making treatment decisions. In addition, there is complexity with COPD, shown by how the proportion of clinical characteristics (i.e., treatable factors) can vary from patient to patient, which is one reason why prognostic scores may not remain accurate across different populations. While COPD phenotypes attempted to order heterogeneous patients into clinically similar groups (Figure 7.2B), there has been some criticism that they cannot deal with the disease's complexity (Figure 7.2C) (70). While each of the main COPD phenotypes that have associations with poor prognosis (e.g. frequent exacerbator, mixed COPD-asthma, and emphysema-hyperinflation) is comprised of multiple treatable risk factors (e.g. reflux disease, bacterial load, and low arterial partial pressure of oxygen (PaO_2), psychiatric disorder, etc. for frequent exacerbator phenotype) (69) it may be argued that the contribution of individual treatable factors within COPD phenotypes can still vary from one individual to the next and vary over time within individuals (60). For instance, as just one example, a person suffering from the frequent exacerbator phenotype does not necessarily suffer from reflux disease, but this may change over time. With this variation in mind, it is up to the clinician to decide if, on the whole, a patient has a certain phenotype. It may help to use a "label-free" approach to COPD care since placing COPD patients into groups assumes that their diagnosis and characteristics of their disease are clear and established and ignores the clinical and biological complexity of airway disease (67). Accounting for multiple factors and how they vary in each patient is in line with a personalised medicine approach to COPD care. It looks at alternative pathways for risk assessment and implementation of preventive strategies (70) and, overall, taking a "holistic approach … considering illness as the consequence of dynamic interactions within and between multiple interacting and self-adjusting systems" (358).

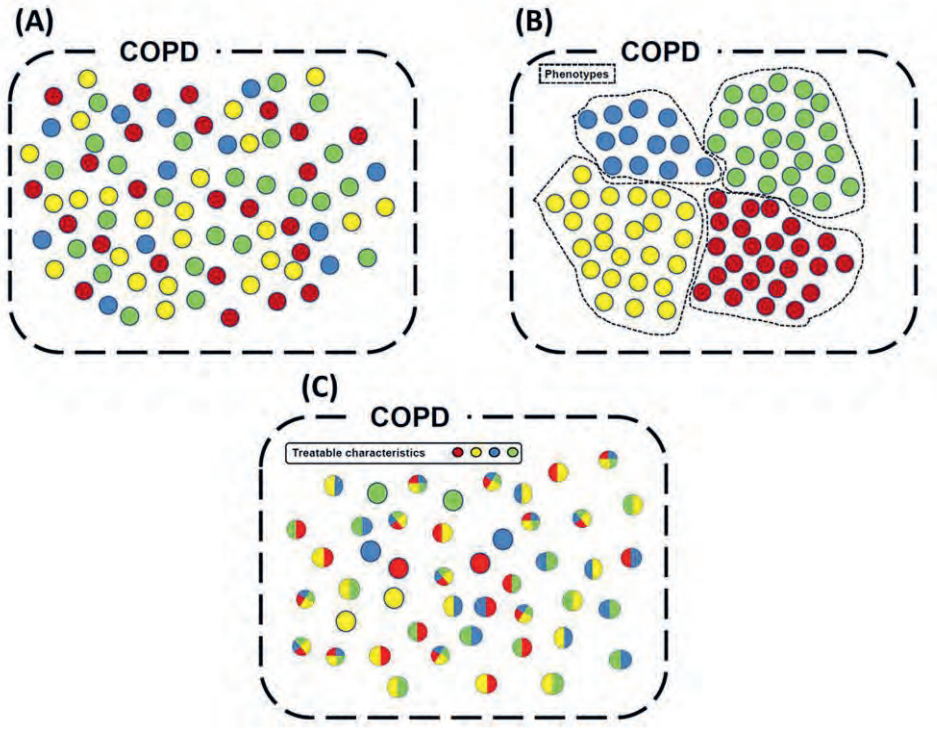


Figure 7.2: Each colour represents one clinical characteristic within each patient (circles). Reproduced with permission from Agusti (70)*, British Medical Association.*

We promote the measurement of symptoms, important risk factors, and systemic manifestations of COPD in individual patients; the aggregate scoring of these factors into an overall prognostic score for the prediction of both mortality and exacerbation; the validation of these scores to test if the score can be reliably applied to particular patients, and the serial measurement of these scores to update prognosis and track disease activity. Altogether, this process can highlight the differences between individual patients that may manifest in changes in clinical management.

REFERENCES

1. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease - 2020 report. GOLD 2020.

2. Wedzicha JA. The heterogeneity of chronic obstructive pulmonary disease. Thorax. 2000;55:631–2.

3. Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med. 2017;5(9):691–706.

4. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet [Internet]. 2012;379(9823):1341–51. Available from: http://dx.doi.org/10.1016/S0140-6736(11)60968-9

5. Li X, Cao X, Guo M, Xie M, Liu X. Trends and risk factors of mortality and disability adjusted life years for chronic respiratory diseases from 1990 to 2017: systematic analysis for the Global Burden of Disease Study 2017. BMJ. 2020;368(m237).

6. Liu Y, Lee K, Perez-Padilla R, Hudson NL, Mannino DM. Outdoor and indoor air pollution and COPD-related diseases in high- and low-income countries. Int J Tuberc Lung Dis. 2008;12(2):115–27.

7. Soriano JB, Polverino F, Cosio BG. What is early COPD and why is it important? Eur Respir J. 2018;52(1801448).

8. Svanes C, Sunyer J, Plana E, Dharmage S, Heinrich J, Jarvis D, et al. Early life origins of chronic obstructive pulmonary disease. Thorax. 2010;65(1):14–20.

9. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med [Internet]. 2017;195(5):557–82. Available from: http://www.atsjournals.org/doi/10.1164/rccm.201701-0218PP

10. Hwang Y Il, Kim CH, Kang HR, Shin T, Park SM, Jang SH, et al. Comparison of the prevalence of chronic obstructive pulmonary disease diagnosed by lower limit of normal and fixed ratio criteria. J Korean Med Sci. 2009;24(4):621–6.

11. Mannino DM, Buist AS, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function? Thorax. 2007 Mar;62(3):237–41.

12. Bhatt SP, Balte PP, Schwartz JE, Cassano PA, Couper D, Jacobs DR, et al. Discriminative Accuracy of FEV_1:FVC Thresholds for COPD-Related Hospitalization and Mortality. Jama [Internet]. 2019;321(24):2438. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2019.7233

13. Çolak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Young and middle-aged adults with airflow limitation according to lower limit of normal but not fixed ratio have high morbidity and poor survival: A population-based prospective cohort study. Eur Respir J [Internet]. 2018;51(3). Available from: http://dx.doi.org/10.1183/13993003.02681-2017

14. Güder G, Brenner S, Angermann CE, Ertl G, Held M, Sachs AP, et al. “GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study.” Respir Res [Internet]. 2012;13(1):13. Available from: http://respiratory-research.com/content/13/1/13

15. Vestbo J, Rodriguez-Roisin R. GOLD and the fixed ratio. Eur Respir J. 2011;38:481–2.

16. Llordés M, Jaen A, Zurdo E, Roca M, Vazquez I, Almagro P. Fixed ratio versus lower limit of normality for diagnosing copd in primary care: Long-term follow-up of EGARPOC study. Int J COPD. 2020;15:1403–13.

17. Rodriguez-Roisin R, Han MK, Vestbo J, Wedzicha JA, Woodruff PG, Martinez FJ. Chronic respiratory symptoms with normal spirometry a reliable clinical entity? Am J Respir Crit Care Med. 2017;(1):17–22.

18. Quanjer PH. Correctly Defining Criteria for Diagnosing Chronic Obstructive Pulmonary Disease Matters. Am J Respir Crit Care Med. 2014;189(2):230.

19. Price DB, Yawn BP, Jones RCM. Improving the differential diagnosis of chronic obstructive pulmonary disease in primary care. Mayo Clin Proc. 2010;85(12):1122–9.

20. Çolak Y, Nordestgaard BG, Vestbo J, Lange P, Afzal S. Prognostic significance of chronic respiratory symptoms in individuals with normal spirometry. Eur Respir J. 2019;54(3).

21. Rodriguez-Roisin R, Rabe KF, Vestbo J, Vogelmeier C, Agustí A. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 20th Anniversary: A brief history of time. Eur Respir J [Internet]. 2017;50(1). Available from: http://dx.doi.org/10.1183/13993003.00671-2017

22. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. Eur Respir J. 2003 Jun;21(41):46S-53S.

23. Cote CG, Dordelly LJ, Celli BR. Impact of COPD exacerbation on patient-centered outcomes. Chest. 2007;131(3):696–704.

24. Anzueto A. Impact of exacerbations on COPD. Eur Respir Rev. 2010 Jun;19(116):113–8.

25. Pavord ID, Jones PW, Burgel PR, Rabe KF. Exacerbations of COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:21–30.

26. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. N Engl J Med [Internet]. 2010;363(12):1128–38. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa0909883

27. Mackay AJ, Donaldson GC, Patel ARC, Singh R, Kowlessar B, Wedzicha JA. Detection and severity grading of COPD exacerbations using the exacerbations of chronic pulmonary disease tool (EXACT). Eur Respir J. 2014 Mar;43(3):735–44.

28. Jones PW, Lamarca R, Chuecos F, Singh D, Agustí A, Bateman ED, et al. Characterisation and impact of reported and unreported exacerbations: Results from

ATTAIN. Eur Respir J. 2014;44(5):1156–65.

29. Xu W, Collet J-P, Shapiro S, Lin Y, Yang T, Wang C, et al. Negative impacts of unreported COPD exacerbations on health-related quality of life at 1 year. Eur Respir J. 2010 May;35(5):1022–30.

30. Quaderi SA, Hurst JR. The unmet global burden of COPD. Glob Heal Epidemiol Genomics. 2018;3:9–11.

31. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, et al. Global and regional estimates of COPD prevalence: Systematic review and meta–analysis. J Glob Health [Internet]. 2015;5(2). Available from: http://www.jogh.org/documents/issue201502/jogh-05-020415.pdf

32. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. Lancet [Internet]. 2007;370(9589):741–50. Available from: http://dx.doi.org/10.1016/S0140-6736(07)61377-4

33. Barnes PJ. Sex Differences in Chronic Obstructive Pulmonary Disease Mechanisms. Am J Respir Crit Care Med. 2016;193(8):813–24.

34. Hitchman SC, Fong GT. Gender empowerment and female-to-male smoking prevalence ratios. Bull World Health Organ. 2011;89:195–202.

35. Shahab L, Jarvis MJ, Britton J, West R. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. Thorax. 2006;61(12):1043–7.

36. Jordan RE, Lam KH, Cheng KK, Miller MR, Marsh JL, Ayres JG, et al. Case finding for chronic obstructive pulmonary disease: a model for optimising a targeted approach. Thorax. 2010 Jun;65(6):492–8.

37. Vanfleteren LEGW, Franssen FME, Wesseling G, Wouters EFM. The prevalence of chronic obstructive pulmonary disease in Maastricht, the Netherlands. Respir Med. 2012;106(6):871–4.

38. Atsou K, Chouaid C, Hejblum G. Variability of the chronic obstructive pulmonary disease key epidemiological data in Europe: Systematic review. BMC Med [Internet]. 2011;9(1):7. Available from: http://www.biomedcentral.com/1741-7015/9/7

39. Jones R. The scale of the problem of obstructive lung disease in Africa becomes clearer, but where are the solutions? Eur Respir J [Internet]. 2018;51(2):1702562. Available from: http://dx.doi.org/10.1183/13993003.02562-2017

40. Lamprecht B, Soriano JB, Studnicka M, Kaiser B, Vanfleteren LE, Gnatiuc L, et al. Determinants of underdiagnosis of COPD in national and international surveys. Chest. 2015;148(4):971–85.

41. Siddharthan T, Pollard SL, Quaderi SA, Mirelman AJ, Cárdenas MK, Kirenga B, et al. Effectiveness-implementation of COPD case finding and self-management action plans in low- and middle-income countries: Global excellence in COPD outcomes (GECo) study protocol. Trials. 2018;19(1):1–15.

42. Vandevoorde J, Verbanck S, Gijssels L, Schuermans D, Devroey D, De Backer J, et al. Early detection of COPD: A case finding study in general practice. Respir Med.

2007;101(3):525–30.

43. Sandelowsky H, Stallberg B, Nager A, Hasselstrom J. The prevalence of undiagnosed chronic obstructive pulmonary disease in a primary care population with respiratory tract infections - a case finding study. BMC Fam Pract. 2011 Nov;12.

44. Gaffney AW, Hawks L, White AC, Woolhandler, Steffie Himmelstein, David Christiani, David C. McCormick D. Health Care Disparities Across the Urban-Rural Divide: A National Study of Individuals with COPD. J Rural Heal. 2020;https://doi.org/10.1111/jrh.12525.

45. Han MK, Steenrod AW, Bacci ED, Leidy NK, Mannino DM, Thomashow BM, et al. Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation Identifying Patients with Undiagnosed COPD in Primary Care Settings: Insight from Screening Tools and Epidemiologic Studies Original Research. Identifying Undiagnosed COPD Prim Care journal.copdfoundation.org JCOPDF ©. 2015;2(2):103–21.

46. Foo J, Landis SH, Maskell J, Oh YM, Van Der Molen T, Han MLK, et al. Continuing to confront COPD international patient survey: Economic impact of COPD in 12 countries. PLoS One. 2016;11(4).

47. Kirsch F, Schramm A, Schwarzkopf L, Lutter JI, Szentes B, Huber M, et al. Direct and indirect costs of COPD progression and its comorbidities in a structured disease management program: Results from the LQ-DMP study. Respir Res. 2019;20(1):1–15.

48. University of Washington. GBD Compare. Institute for Health Metrics and Evaluation (IHME). 2015. p. Available from http://vizhub.healthdata.org/gbd-co.

49. Miniati M, Monti S, Pavlickova I, Bottai M. Survival in COPD: Impact of lung dysfunction and comorbidities. Med (United States). 2014;93(12):1–9.

50. Mannino DM, Brown C, Giovino GA. Obstructive lung disease deaths in the united states from 1979 through 1993: An analysis using multiple-cause mortality data. Am J Respir Crit Care Med. 1997;156(3).

51. Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. Eur Respir J. 2003;22(5):809–14.

52. Divo M, Cote C, De Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186(2):155–61.

53. Zvezdin B, Milutinov S, Kojicic M, Hadnadjev M, Hromis S, Markovic M, et al. A postmortem analysis of major causes of early death in patients hospitalized with COPD exacerbation. Chest. 2009 Aug;136(2):376–80.

54. Burney PGJ, Patel J, Newson R, Minelli C, Naghavi M. Global and regional trends in COPD mortality, 1990-2010. Eur Respir J [Internet]. 2015;45(5):1239–47. Available from: http://dx.doi.org/10.1183/09031936.00142414

55. Ford ES. Trends in mortality from chronic obstructive pulmonary disease among

adults in the United States. Chest [Internet]. 2015;148(4):962–70. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4587987/

56. Conklin JE, Lieberman J V., Barnes CA, Louis DZ. Disease staging: Implications for hospital reimbursement and management. Health Care Financ Rev. 1984;13–22.

57. Romain A, Buist A, Calverley P, Jenkins C, Hurd S. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001;163(5):1256–76.

58. Barrecheguren M, Miravitlles M. COPD heterogeneity: Implications for management. Multidiscip Respir Med [Internet]. 2016;11(1):10–1. Available from: http://dx.doi.org/10.1186/s40248-016-0053-4

59. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009;33(5):1165–85.

60. Houben-Wilke S, Augustin IM, Vercoulen JH, van Ranst D, de Vaate EB, Wempe JB, et al. COPD stands for complex obstructive pulmonary disease. Eur Respir Rev [Internet]. 2018;27(148). Available from: http://dx.doi.org/10.1183/16000617.0027-2018

61. Antonelli-Incalzi R, Imperiale C, Bellia V, Catalano F, Scichilone N, Pistelli R, et al. Do GOLD stages of COPD severity really correspond to differences in health status? Eur Respir J. 2003;22(3):444–9.

62. Sarkar M, Srinivasa, Madabhavi I, Kumar K. Tuberculosis associated chronic obstructive pulmonary disease. Clin Respir J. 2017;11(3):285–95.

63. Zhao J, Li M, Wang Z, Chen J, Zhao J, Xu Y, et al. Role of PM2.5 in the development and progression of COPD and its mechanisms. Respir Res. 2019;20(1):1–13.

64. He F, Liao B, Pu J, Li C, Zheng M, Huang L, et al. Exposure to Ambient Particulate Matter Induced COPD in a Rat Model and a Description of the Underlying Mechanism. Sci Rep. 2017;7(November 2016):1–15.

65. Han M, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, et al. Chronic Obstructive Pulmonary Disease Phenotypes The Future of COPD. Am J Respir Crit Care Med. 2009;182:598–604.

66. Olloquequi J, Jaime S, Parra V, Cornejo-Córdova E, Valdivia G, Agustí À, et al. Comparative analysis of COPD associated with tobacco smoking, biomass smoke exposure or both. Respir Res. 2018;19(1):1–8.

67. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, et al. Treatable traits: Toward precision medicine of chronic airway diseases. Eur Respir J [Internet]. 2016;47(2):410–9. Available from: http://dx.doi.org/10.1183/13993003.01359-2015

68. Castaldi PJ, Benet M, Petersen H, Rafaels N, Finigan J, Paoletti M, et al. Do COPD subtypes really exist? COPD heterogeneity and clustering in 10 independent cohorts. Thorax. 2017;72(11):998–1006.

69. Miravitlles M, Calle M, Soler-Cataluña JJ. Clinical Phenotypes of COPD: Identification, Definition and Implications for Guidelines. Arch Bronconeumol.

2012;48(3):86–98.

70. Agusti A. The path to personalised medicine in COPD. Thorax. 2014;69(9):857–64.

71. Van Den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity: What's in a name? A review of literature. Eur J Gen Pract. 1996;2:65–70.

72. van Manen J, Bindels P, IJzermans C, van der Zee J, Bottema B, Schade E. Prevalence of comorbidity in patients with a chronic airway obstruction and controls over the age of 40. J Clin Epidemiol. 2001;54(3):287–93.

73. Miller J, Edwards L, Agusti A, Bakke P, Calverley P, Celli B. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. Respir Med. 2013;107(9):1376–84.

74. Islam MM, Valderas JM, Yen L, Dawda P, Jowsey T, McRae IS. Multimorbidity and comorbidity of chronic diseases among the senior australians: Prevalence and patterns. PLoS One. 2014;9(1):1–11.

75. Raviv S, Hawkins KA, DeCamp MM, Kalhan R. Lung cancer in chronic obstructive pulmonary disease: Enhancing surgical options and outcomes. Am J Respir Crit Care Med. 2011;183(9):1138–46.

76. Sarkar M, Bhardwaj R, Madabhavi I, Khatana J. Osteoporosis in chronic obstructive pulmonary disease. Clin Med Insights Circ Respir Pulm Med. 2015;9:5–21.

77. Eisner MD, Blanc PD, Yelin EH, Katz PP, Sanchez G, Iribarren C, et al. Influence of anxiety on health outcomes in COPD. Thorax. 2010 Mar;65(3):229–34.

78. Johnson JL, Campbell AC, Bowers M, Nichol AM. Understanding the social consequences of chronic obstructive pulmonary disease: The effects of stigma and gender. Proc Am Thorac Soc. 2007;4(8):680–2.

79. Franssen FME, Smid DE, Deeg DJH, Huisman M, Poppelaars J, Wouters EFM, et al. The physical, mental, and social impact of COPD in a population-based sample: results from the Longitudinal Aging Study Amsterdam. npj Prim Care Respir Med [Internet]. 2018;28(1). Available from: http://dx.doi.org/10.1038/s41533-018-0097-3

80. Lee AL, Goldstein RS. Gastroesophageal reflux disease in COPD: Links and risks. Int J COPD. 2015;10(1):1935–49.

81. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ V. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. Eur J Heart Fail. 2009 Feb;11(2):130–9.

82. Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice? Ther Adv Respir Dis. 2018;12(6):1–16.

83. Chaouat A, Weitzenblum E, Krieger J, Ifoundza T, Oswald M, Kessler R. Association of Chronic Obstructive Pulmonary Disease and Sleep Apnea Syndrome. Am J Respir Crit Care Med. 1995;151:82–6.

84. Kunisaki KM, Dransfield MT, Anderson JA, Brook RD, Calverley PMA, Celli BR, et al. Exacerbations of chronic obstructive pulmonary disease and cardiac events a post hoc cohort analysis from the SUMMIT randomized clinical trial. Am J Respir

Crit Care Med. 2018;198(1):51–7.

85. Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. N Engl J Med [Internet]. 2015;373(2):111–22. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1411532

86. Marott J, Ingebrigtsen T, Çolak Y, Vestbo J, Lange P. Lung Function Trajectories Leading to Chronic Obstructive Pulmonary Disease as Predictors of Exacerbations and Mortality. Am J Respir Crit Care Med. 2020;Epub ahead.

87. Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, et al. Changes in Forced Expiratory Volume in 1 Second over Time in COPD. N Engl J Med [Internet]. 2011;365(13):1184–92. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1105482

88. Shaw JG, Vaughan A, Dent AG, O'Hare PE, Goh F, Bowman R V., et al. Biomarkers of progression of chronic obstructive pulmonary disease (COPD). J Thorac Dis. 2014;6(11):1532–47.

89. Chen S, Wang C, Li B, Shi G, Li H, Zhang J, et al. Risk factors for FEV1 decline in mild COPD and high-risk populations. Int J Chron Obstruct Pulmon Dis. 2017;12:435–50.

90. Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: Results from the TORCH study. Am J Respir Crit Care Med. 2008;178(4):332–8.

91. Donaldson G, Seemungal T, Bhowmilk A, Wedzicha J. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax. 2002;57:847–52.

92. Vestbo J, Lange P. Natural history of COPD: Focusing on change in FEV1. Respirology. 2016;21(1):34–43.

93. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J [Internet]. 1977;1(6077):1645–8. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1607732&tool=pmcentrez&rendertype=abstract

94. Kim J, Yoon H Il, Oh YM, Lim SY, Lee JH, Kim TH, et al. Lung function decline rates according to gold group in patients with chronic obstructive pulmonary disease. Int J COPD. 2015;10(1):1819–27.

95. Casanova C, De Torres JP, Aguirre-Jaíme A, Pinto-Plata V, Marin JM, Cordoba E, et al. The progression of chronic obstructive pulmonary disease is heterogeneous: The experience of the BODE cohort. Am J Respir Crit Care Med. 2011;184(9):1015–21.

96. Meena M, Dixit R, Singh M, Samaria JK, Kumar S. Surgical and bronchoscopic lung volume reduction in chronic obstructive pulmonary disease. Pulm Med. 2014;1–12.

97. Ries AL, Carlin BW, Carrieri-Kohlman V, Casaburi R, Celli BR, Emery CF, et al. Pulmonary rehabilitation: Joint ACCP/AACVPR evidence-based guidelines. Chest

[Internet]. 2007;131:4S-42S. Available from: http://dx.doi.org/10.1378/chest.06-2418

98. Bolton CE, Bevan-Smith EF, Blakey JD, Crowe P, Elkin SL, Garrod R, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults: accredited by NICE. Thorax [Internet]. 2013;68(Suppl 2):ii1–30. Available from: http://thorax.bmj.com/lookup/doi/10.1136/thoraxjnl-2013-203808

99. Moore E, Palmer T, Newson R, Majeed A, Quint JK, Soljak M. Pulmonary Rehabilitation as a Mechanism to Reduce Hospitalizations for Acute Exacerbations of COPD: A Systematic Review and Meta-Analysis. Chest [Internet]. 2016;150(4):837–59. Available from: http://www.chestjournal.org/

100. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. Eur Respir J. 2009;33(2):262–72.

101. Blackstock FC, Lareau SC, Nici L, ZuWallack R, Bourbeau J, Buckley M, et al. Chronic obstructive pulmonary disease education in pulmonary rehabilitation: An official American thoracic society/thoracic society of Australia and New Zealand/Canadian thoracic society/British thoracic society workshop report. Ann Am Thorac Soc. 2018;15(7):769–84.

102. Schols AM, Ferreira IM, Franssen FM, Gosker HR, Janssens W, Muscaritoli M, et al. Nutritional assessment and therapy in COPD: A European respiratory society statement. Eur Respir J. 2014;44(6):1504–20.

103. McDonald MLN, Wouters EFM, Rutten E, Casaburi R, Rennard SI, Lomas DA, et al. It's more than low BMI: Prevalence of cachexia and associated mortality in COPD. Respir Res. 2019;20(1):1–9.

104. Yamauchi Y, Hasegawa W, Yasunaga H, Sunohara M, Jo T, Takami K, et al. Paradoxical association between body mass index and in-hospital mortality in elderly patients with chronic obstructive pulmonary disease in Japan. Int J Chron Obstruct Pulmon Dis. 2014;9:1337–46.

105. Chiolero A, Faeh D, Paccaud F, Cornuz J. Consequences of smoking for body weight , body fat distribution , and insulin resistance. Am J Clin Nutr. 2008;87:801–9.

106. Audrain-McGover J, Benowitz N. Cigarette Smoking, Nicotine, and Body Weight. Clin Pharmacol Ther. 2011;90(1):164–8.

107. Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritrutai W, Charoenratanakul S. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: A randomized controlled study. Chest. 2004;125(6):2011–20.

108. Kopsaftis Z, Wood-Baker R, Poole P. Influenza vaccine for chronic obstructive pulmonary disease (COPD). Cochrane Database of Systematic Reviews. 2018.

109. Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T. Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine Among Adults Aged ≥65 Years: Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2014;63(37):822–5.

110. Hardinge M, Annandale J, Bourne S, Cooper B, Evans A, Freeman D, et al. British

Thoracic Society guidelines for home oxygen use in adults. Thorax. 2015 Jun;70 Suppl 1:i1-43.

111. Dahl R, Chung KF, Buhl R, Magnussen H, Nonikov V, Jack D, et al. Efficacy of a new once-daily long-acting inhaled β2-agonist indacaterol versus twice-daily formoterol in COPD. Thorax. 2010;65(6):473–9.

112. Donohue JF, Fogarty C, Lötvall J, Mahler DA, Worth H, Yorgancioğlu A, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: Indacaterol versus tiotropium. Am J Respir Crit Care Med. 2010;182(2):155–62.

113. Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. Lancet [Internet]. 2009;374(9696):1171–8. Available from: http://dx.doi.org/10.1016/S0140-6736(09)61298-8

114. Kerwin E, Hebert J, Gallagher N, Martin C, Overend T, Alagappan VKT, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: The GLOW2 study. Eur Respir J. 2012;40(5):1106–14.

115. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Molken MPMH, Beeh KM, et al. Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD. N Engl J Med. 2011 Mar;364(12):1093–103.

116. Tashkin DP, Celli BR, Senn S, Burkhart D, Kesten S, Menjoge SM, et al. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. N Engl J Med [Internet]. 2008;359(15):1543–54. Available from: http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:New+engla+nd+journal#0

117. Calzetta L, Rogliani P, Ora J, Puxeddu E, Cazzola M, Matera MG. LABA/LAMA combination in copd: A meta-analysis on the duration of treatment. Eur Respir Rev [Internet]. 2017;26(143):1–11. Available from: http://dx.doi.org/10.1183/16000617.0043-2016

118. Rodrigo GJ, Neffen H. A systematic review of the efficacy and safety of a fixed-dose combination of umeclidinium and vilanterol for the treatment of COPD. Chest [Internet]. 2015;148(2):397–407. Available from: http://dx.doi.org/10.1378/chest.15-0084

119. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al. Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD. N Engl J Med [Internet]. 2016;374(23):2222–34. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1516385

120. Singh D, Maleki-Yazdi MR, Tombs L, Iqbal A, Fahy WA, Naya I. Prevention of clinically important deteriorations in COPD with umeclidinium/vilanterol. Int J Chron Obstruct Pulmon Dis. 2016;11:1413–24.

121. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2007;356(8):775–89.

122. Jenkins CR, Jones PW, Calverley PMA, Celli B, Anderson JA, Ferguson GT, et al.

Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: Analysis from the randomised, placebo-controlled TORCH study. Respir Res. 2009;10:1–9.

123. Calverley PMAM, Magnussen H, Miravitlles M, Wedzicha JA. Triple Therapy in COPD: What We Know and What We Don't. COPD J Chronic Obstr Pulm Dis. 2017;14(6):648–62.

124. Oba Y, Keeney E, Ghatehorde N, Dias S. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): A systematic review and network meta-analysis. Cochrane Database Syst Rev [Internet]. 2018;(12). Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L625335976%0Ahttp://dx.doi.org/10.1002/14651858.CD012620.pub2

125. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper, J. Allen D. J, Criner GJ, et al. Azithromycin for Prevention of Exacerbations of COPD. N Engl J Med. 2011;365(8):689–98.

126. Martinez FJ, Calverley PMA, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): A multicentre randomised controlled trial. Lancet [Internet]. 2015;385(9971):857–66. Available from: http://dx.doi.org/10.1016/S0140-6736(14)62410-7

127. Calverley PM, Rabe KF, Goehring U-M, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet [Internet]. 2009;374(9691):685–94. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0140673609612551

128. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet [Internet]. 2009;374(9691):695–703. Available from: http://dx.doi.org/10.1016/S0140-6736(09)61252-6

129. Brode SK, Campitelli MA, Kwong JC, Lu H, Marchand-Austin A, Gershon AS, et al. The risk of mycobacterial infections associated with inhaled corticosteroid use. Eur Respir J. 2017;50(1700037):1–10.

130. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: Systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax. 2011;66(8):699–708.

131. Ernst P. Blood eosinophils in COPD and the future risk of pneumonia. Eur Respir J. 2018;52(1800981).

132. Vedel-Krogh S, Nordestgaard BG, Lange P, Vestbo J, Nielsen SF. Blood eosinophil count and risk of pneumonia hospitalisations in individuals with COPD. Eur Respir J [Internet]. 2018;51(5):1–10. Available from: http://dx.doi.org/10.1183/13993003.00120-2018

133. Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: just another biomarker? Lancet Respir Med. 2017;5(9):747–59.

134. Pavord ID, Lettis S, Anzueto A, Barnes N. Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis. LANCET Respir Med. 2016 Sep;4(9):731–41.

135. Hemingway H, Croft P, Perel P, Hayden JA, Abrams K, Timmis A, et al. Prognosis research strategy (PROGRESS) 1: A framework for researching clinical outcomes. BMJ. 2013;346(February):1–11.

136. Riley RD, Hayden JA, Steyerberg EW, Moons KGM, Abrams K, Kyzas P, et al. Prognosis research strategy (PROGRESS) 2: A framework for researching clinical outcomes. BMJ. 2013;10(2):1–9.

137. Celli B, Cote C, Marin JM, Casanova C, Montes De Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med [Internet]. 2004;350(10):1005–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14999112

138. Steyerberg EW, Moons KGM, van der Windt DA, Hayden JA, Perel P, Schroter S, et al. Prognosis Research Strategy (PROGRESS) 3: Prognostic Model Research. PLoS Med [Internet]. 2013;10(2):1–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18035647

139. Bellou V, Belbasis L, Konstantinidis AK, Tzoulaki I, Evangelou E. Prognostic models for outcome prediction in patients with chronic obstructive pulmonary disease : systematic review and critical appraisal. BMJ. 2019;367(15358).

140. Moons KGM, Kengne AP, Grobbee DE, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: II. External validation, model updating, and impact assessment. Heart. 2012;98(9):691–8.

141. Moons KGM, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ [Internet]. 2009;338(7709):1487–90. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.b606

142. van Dijk WD, van den Bemt L, van den Haak-Rongen S, Bischoff E, van Weel C, in ’t Veen JC, et al. Multidimensional prognostic indices for use in COPD patient care. A systematic review. Respir Res [Internet]. 2011;12(151). Available from: http://respiratory-research.biomedcentral.com/articles/10.1186/1465-9921-12-151

143. Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, et al. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: The DOSE index. Am J Respir Crit Care Med. 2009;180(12):1189–95.

144. Puhan MA, Hansel NN, Sobradillo P, Enright P, Lange P, Hickson D, et al. Large-scale international validation of the ADO index in subjects with COPD : an individual subject data analysis of 10 cohorts. BMJ Open. 2012;2:1–10.

145. Guerra B, Haile SR, Lamprecht B, Ramírez AS, Martinez-Camblor P, Kaiser B, et al. Large-scale external validation and comparison of prognostic models: An application to chronic obstructive pulmonary disease. BMC Med. 2018;16(1):1–13.

146. Haile SR, Guerra B, Soriano JB, Puhan MA. Multiple Score Comparison: A network meta-analysis approach to comparison and external validation of prognostic scores.

Stat Methods Med Res. 2017;1–12.

147. James GD, Donaldson GC, Wedzicha JA, Nazareth I. Trends in management and outcomes of COPD patients in primary care , 2000 – 2009: a retrospective cohort study. NPJ Prim care Respir Med. 2014;24(14015).

148. Guerra B, Gaveikaite V, Bianchi C, Puhan MA. Prediction models for exacerbations in patients with COPD. Eur Respir Rev. 2017;26:1–13.

149. Bertens LCM, Reitsma JB, Moons KGM, van Mourik Y, Lammers JWJ, Broekhuizen BDL, et al. Development and validation of a model to predict the risk of exacerbations in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis [Internet]. 2013;8:493–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3797610&tool=pmcentrez&rendertype=abstract

150. Steer J, Gibson J, Bourke SC. The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. Thorax. 2012 Nov;67(11):970–6.

151. Echevarria C, Gray J, Hartley T, Steer J, Miller J, Simpson AJ, et al. Home treatment of COPD exacerbation selected by DECAF score: a non-inferiority, randomised controlled trial and economic evaluation. Thorax. 2018;73(8):713–22.

152. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.

153. Moons KGM, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: What, why, and how? Vol. 338, BMJ (Online). 2009. p. 1317–20.

154. Agusti A, Sobradillo P, Celli BR. Addressing the complexity of chronic obstructive pulmonary disease: From phenotypes and biomarkers to scale-free networks, systems biology, and P4 medicine. Am J Respir Crit Care Med. 2011;183(9):1129–37.

155. Agusti A, Calverley PMA, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res. 2010;11(122):1–14.

156. Azarisman MS, Fauzi MA, Faizal MPA, Azami Z, Roslina AM, Roslan H. The SAFE (SGRQ score, air-flow limitation and exercise tolerance) Index: a new composite score for the stratification of severity in chronic obstructive pulmonary disease. Postgrad Med J. 2007;83(981):492–7.

157. Puhan MA, Garcia-Aymerich J, Frey M, ter Riet G, Antó JM, Agustí AG, et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. Lancet [Internet]. 2009;374(9691):704–11. Available from: http://dx.doi.org/10.1016/S0140-6736(09)61301-5

158. Cook NR. Statistical evaluation of prognostic versus diagnostic models: Beyond the ROC curve. Clin Chem. 2008;54(1):17–23.

159. Morales DR, Flynn R, Zhang J, Trucco E, Quint JK, Zutis K. External validation of ADO, DOSE, COTE and CODEX at predicting death in primary care patients with COPD using standard and machine learning approaches. Respir Med [Internet]. 2018;138(January):150–5. Available from: http://www.sciencedirect.com/science/article/pii/S0954611118301112

160. Abu Hussein N, Ter Riet G, Schoenenberger L, Bridevaux PO, Chhajed PN, Fitting JW, et al. The ADO index as a predictor of two-year mortality in general practice-based chronic obstructive pulmonary disease cohorts. Respiration. 2014;88(3):208–14.

161. Moons KGM, Altman DG, Reitsma JB, Ioannidis JPA, Macaskill P, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): Explanation and elaboration. Ann Intern Med. 2015;162:W1–73.

162. Adab P, Fitzmaurice DA, Dickens AP, Ayres JG, Buni H, Cooper BG, et al. Cohort Profile: The Birmingham Chronic Obstructive Pulmonary Disease (COPD) Cohort Study. Int J Epidemiol [Internet]. 2016;46(1):dyv350. Available from: https://academic.oup.com/ije/article-lookup/doi/10.1093/ije/dyv350

163. Jordan RE, Adab P, Sitch A, Enocson A, Blissett D, Jowett S, et al. Targeted case finding for chronic obstructive pulmonary disease versus routine practice in primary care (TargetCOPD): a cluster-randomised controlled trial. Lancet Respir Med [Internet]. 2017;4(9):720–30. Available from: http://dx.doi.org/10.1016/S2213-2600(16)30149-7

164. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581–6.

165. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. Eur Respir J. 2012;40(6):1324–43.

166. NHS. NHS Digital- Quality and Outcomes Framework. 2017. p. https://digital.nhs.uk/Quality-and-Outcomes-Framew.

167. White IR, Royston P, Wood AM. Multiple imputation using chained equations : Issues and guidance for practice. Stat Med. 2011;30:377–99.

168. Altman DG, Bland JM. Statistics Notes: Diagnostic tests 3: Receiver operating characteristic plots. BMJ. 1994;309(188).

169. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Obuchowski N, Pencina MJ, et al. Assessing the performance of prediction models : A framework for some traditional and novel measures. Epidemiology. 2010;

170. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: Current practice and guidelines. BMC Med Res Methodol. 2009;

171. Smith LJE, Moore E, Ali I, Smeeth L, Stone P, Quint JK. Prognostic variables and scores identifying the end of life in COPD: A systematic review. Int J COPD. 2017;12:2239–56.

172. Copas JB. Regression, Prediction and Shrinkage. J R Stat Soc Ser B. 1983;

173. Haroon S, Adab P, Riley RD, Fitzmaurice D, Jordan RE. Predicting risk of undiagnosed COPD: development and validation of the TargetCOPD score. Eur Respir J [Internet]. 2017;49(6):1602191. Available from: http://erj.ersjournals.com/lookup/doi/10.1183/13993003.02191-2016

174. Office for National Statistics. Impact of registration delays on mortality statistics, 2011. Natl Arch. 2011;94–5.

175. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet [Internet]. 2007;370(9589):765–73. Available from: http://dx.doi.org/10.1016/S0140-6736(07)61380-4

176. De Torres JP, Marín JM, Pinto-Plata V, Divo M, Sanchez-Salcedo P, Zagaceta J, et al. Is COPD a progressive disease? A long term BODE cohort observation. PLoS One. 2016;

177. Miller A, Raskin JM. The natural history of COPD: Confirming and going beyond Fletcher and Peto. Eur Respir J. 2014;44(2):280–3.

178. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: Definition, assessment, and prevention. Lancet. 2015;

179. Rennard SI, Vestbo J. Natural Histories of Chronic Obstructive Pulmonary Disease. Proc Am Thorac Soc [Internet]. 2008;5(9):878–83. Available from: http://pats.atsjournals.org/cgi/doi/10.1513/pats.200804-035QC

180. Miravitlles M, Vogelmeier C, Roche N, Halpin D, Cardoso J, Chuchalin AG, et al. A review of national guidelines for management of COPD in Europe. Eur Respir J. 2016;47(2):625–37.

181. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. 2015;1–22.

182. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of the Health Improvement Network (THIN) database: Demographics, chronic disease prevalence and mortality rates. Inform Prim Care. 2011;19(4):251–5.

183. Smith CJP, Gribbin J, Challen KB, Hubbard RB. The impact of the 2004 NICE guideline and 2003 General Medical Services contract on COPD in primary care in the UK. Qjm. 2008;101(2):145–53.

184. World Health Organization. BMI classification. Pharmacotherapy. 2006;(Table 1):4–9.

185. Battaglia S, Benfante A, Spatafora M, Scichilone N. Asthma in the elderly: A different disease? Breathe. 2016.

186. Haroon S, Adab P, Riley RD, Marshall T, Lancashire R, Jordan RE. Predicting risk of COPD in primary care: development and validation of a clinical risk score. BMJ open Respir Res [Internet]. 2015;2(1):e000060. Available from: http://bmjopenrespres.bmj.com/content/2/1/e000060.full

187. Wagstaff R, Berlin A, Stacy R, Spencer J, Bhopal R. Information about patients'

deaths: General practitioners' current practice and views on receiving a death register. Br J Gen Pract. 1994;44(384):315–6.

188. Ibrahim JG, Molenberghs G. Missing data methods in longitudinal studies: A review. Test. 2009;18:1–43.

189. Ko FWS, Tam W, Tung AHM, Ngai J, Ng SSS, Lai K, et al. A longitudinal study of serial BODE indices in predicting mortality and readmissions for COPD. Respir Med. 2011 Feb;105(2):266–73.

190. Cote CG, Celli BR. Pulmonary rehabilitation and the BODE index in COPD. Eur Respir J. 2005 Oct;26(4):630–6.

191. Verberne LDM, Leemrijse CJ, Swinkels ICS, van Dijk CE, de Bakker DH, Nielen MMJ. Overweight in patients with chronic obstructive pulmonary disease needs more attention: a cross-sectional study in general practice. npj Prim Care Respir Med [Internet]. 2017;27(1):63. Available from: http://www.nature.com/articles/s41533-017-0065-3

192. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med. 2002;

193. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease: The lung health study. Am J Respir Crit Care Med. 2000;

194. Murray RP, Anthonisen NR, Connett JE, Wise RA, Lindgren PG, Greene PG, et al. Effects of multiple attempts to quit smoking and relapses to smoking on pulmonary function. J Clin Epidemiol. 1998;

195. Simmons MS, Connett JE, Nides MA, Lindgren PG, Kleerup EC, Murray RP, et al. Smoking reduction and the rate of decline in FEV1: Results from the Lung Health Study. Eur Respir J. 2005;

196. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. European Respiratory Review. 2014.

197. Martinez FJ, Han MK, Andrei AC, Wise R, Murray S, Curtis JL, et al. Longitudinal change in the BODE index predicts mortality in severe emphysema. Am J Respir Crit Care Med. 2008;178(5):491–9.

198. Imfeld S, Bloch KE, Weder W, Russi EW. The BODE index after lung volume reduction surgery correlates with survival. Chest. 2006 Apr;129(4):873–8.

199. Thabut G, Mornex JF, Pison C, Cuvelier A, Balduyck M, Pujazon MC, et al. Performance of the BODE index in patients with a1-antitrypsin deficiency-related COPD. Eur Respir J. 2014;44(1):78–86.

200. Kontopantelis E, Stevens RJ, Helms PJ, Edwards D, Doran T, Ashcroft DM. Spatial distribution of clinical computer systems in primary care in England in 2016 and implications for primary care electronic medical record databases: A cross-sectional population study. BMJ Open. 2018;

201. Wilson DO, Rogers RM, Wright EC, Anthonisen NR. Body weight in chronic obstructive pulmonary disease: The National Institutes of Health intermittent positive-pressure breathing trial. Am Rev Respir Dis. 1989;139:1435–8.

202. Eriksson B, Backman H, Bossios A, Bjerg A, Hedman L, Lindberg A, et al. Only severe COPD is associated with being underweight: Results from a population survey. ERJ Open Res [Internet]. 2016;2(3):1–11. Available from: http://dx.doi.org/10.1183/23120541.00051-2015

203. Jung J-W, Yoon SW, Lee G-E, Shin H-G, Kim H, Shin JW, et al. Poor nutritional intake is a dominant factor for weight loss in chronic obstructive pulmonary disease. Int J Tuberc Lung Dis. 2019;23(5).

204. Donahoe M, Rogers RM, Wilson DO, Pennock BE. Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1989;140:385–91.

205. Schols AMWJ, Fredrix EWHM, Soeters PB, Westerterp KR, Wouters EFM. Resting energy expenditure in patients with chronic obstructive pulmonary disease. Am J Clin Nutr. 1991;

206. Sergi G, Coin A, Marin S, Vianello A, Manzan A, Peruzza S, et al. Body composition and resting energy expenditure in elderly male patients with chronic obstructive pulmonary disease. Respir Med. 2006;100:1918–24.

207. Franssen FME, Wouters EFM, Baarends EM, Akkermans MA, Schols AMWJ. Arm mechanical efficiency and arm exercise capacity are relatively preserved in chronic obstructive pulmonary disease. Med Sci Sports Exerc. 2002;34:1570–6.

208. Schols AMWJ, Slangen J, Volovics L, Wouters EFM. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157:1791–7.

209. Courtemanche C, Tchernis R, Ukert B. The effect of smoking on obesity: Evidence from a randomized trial. J Health Econ [Internet]. 2017;57:31–44. Available from: http://dx.doi.org/10.1016/j.jhealeco.2017.10.006

210. Wu J, Sin DD. Improved patient outcome with smoking cessation: When is it too late? Int J COPD. 2011;6(1):259–67.

211. Kwan HY, Maddocks M, Nolan CM, Jones SE, Patel S, Barker RE, et al. The prognostic significance of weight loss in chronic obstructive pulmonary disease-related cachexia: a prospective cohort study. J Cachexia Sarcopenia Muscle. 2019;10(6):1330–8.

212. Prescott E, Almdal T, Mikkelsen KL, Tofteng CL, Vestbo J, Lange P. Prognostic value of weight change in chronic obstructive pulmonary disease: Results from the Copenhagen City Heart Study. Eur Respir J. 2002;20(3):539–44.

213. Van Den Borst B, Koster A, Yu B, Gosker HR, Meibohm B, Bauer DC, et al. Is age-related decline in lean mass and physical function accelerated by obstructive lung disease or smoking? Thorax. 2011;66(11):961–9.

214. Rutten E, Calverley PMA, Casaburi R, Agusti A, Bakke P, Celli B, et al. Changes in Body Composition in Patients with Chronic Obstructive Pulmonary Disease: Do They Influence Patient-Related Outcomes? Ann Nutr Metab. 2013;63(3):239–47.

215. Caram LMDO, Ferrari R, Bertani AL, Garcia T, Mesquita CB, Knaut C, et al. Smoking and early COPD as independent predictors of body composition, exercise

capacity, and health status. PLoS One. 2016;11(10):1–12.

216. Hopkinson NS, Tennant RC, Dayer MJ, Swallow EB, Hansel TT, Moxham J, et al. A prospective study of decline in fat free mass and skeletal muscle strength in chronic obstructive pulmonary disease. Respir Res. 2007 Mar;8(25).

217. Vanfleteren LEGW, Lamprecht B, Studnicka M, Kaiser B, Gnatiuc L, Burney P, et al. Body mass index and chronic airflow limitation in a worldwide population-based study. Chron Respir Dis. 2016;13(2):90–101.

218. Subramanian A, Adderley NJ, Tracy A, Taverner T, Hanif W, Toulis KA, et al. Risk of incident obstructive sleep apnea among patients with type 2 diabetes. Diabetes Care. 2019;42(5):954–63.

219. Riley J, Antza C, Kempegowda P, Subramanian A, Chandan JS, Gokhale K, et al. Social Deprivation and Incident Diabetes-Related Foot Disease in Patients With Type 2 Diabetes: A Population-Based Cohort Study. Diabetes Care. 2021;44(3):731–9.

220. Carstairs V. Deprivation indices: their interpretation and use in relation to health. J Epidemiol Community Health. 1995;49:S3–8.

221. Madley-Dowd P, Hughes R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. J Clin Epidemiol [Internet]. 2019;110:63–73. Available from: https://doi.org/10.1016/j.jclinepi.2019.02.016

222. Fitzmaurice GM, Ravichandran C. A primer in longitudinal data analysis. Circulation. 2008;118(19):2005–10.

223. MacKinnon DP, Krull JL, Lockwood CM. Equivalence of the Mediation, Confounding and Suppression Effect. Prev Sci. 2000;1(4)(173).

224. Miller DP, Gomberg-Maitland M, Humbert M. Survivor bias and risk assessment. Eur Respir J. 2012;40(3):530–2.

225. Madigan CD, Daley AJ, Kabir E, Aveyard P, Brown W. Cluster analysis of behavioural weight management strategies and associations with weight change in young women: A longitudinal analysis. Int J Obes. 2015;39(11):1601–6.

226. Peeters A, Magliano DJ, Backholer K, Zimmet P, Shaw JE. Changes in the rates of weight and waist circumference gain in Australian adults over time: A longitudinal cohort study. BMJ Open. 2014;4(1).

227. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med. 2011;364(25):2392–404.

228. Heitmann BL, Garby L. Patterns of long-term weight changes in overweight developing Danish men and women aged between 30 and 60 years. Int J Obes. 1999;23(10):1074–8.

229. Lv J, Fan B, Wei M, Zhou G, Dayimu A, Wu Z, et al. Trajectories of early to mid-life adulthood BMI and incident diabetes: The China Health and Nutrition Survey. BMJ Open Diabetes Res Care. 2020;8(1):1–8.

230. Feldman AL, Griffin SJ, Ahern AL, Long GH, Weinehall L, Fhärm E, et al. Impact of weight maintenance and loss on diabetes risk and burden: a population-based study in 33,184 participants. BMC Public Health. 2017;17(1):1–10.

231. Divo M, Oto MM, Casanova C, Lopez CC, De-Torres J, Marin JM, et al. Somatotypes trajectories during adulthood and its association with Chronic Obstructive Pulmonary Disease (COPD) phenotypes. ERJ Open Res. 2020;(June).

232. Aars NA, Jacobsen BK. Longitudinal changes in desired body weight compared to changes in body weight: Evidence of adaptation to weight gain? BMC Obes [Internet]. 2016;3(1):1–10. Available from: http://dx.doi.org/10.1186/s40608-016-0120-6

233. Muers MF GJ. Weight loss in chronic obstructive pulmonary disease. ERJ. 1993;6(5):729–34.

234. Rawal G, Yadav S. Nutrition in chronic obstructive pulmonary disease: A review. J Transl Intern Med. 2016;3(4):151–4.

235. Di Francia M, Barbier D, Mege JL, Orehek J. Tumor necrosis factor-alpha levels and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1994;150:1453–5.

236. De Godoy I, Donahoe M, Calhoun WJ, Mancino J, Rogers RM. Elevated TNF-α production by peripheral blood monocytes of weight-losing COPD patients. Am J Respir Crit Care Med. 1996;153:633–7.

237. Maltais F, Decramer M, Casabur I, Barreiro E, Burelle Y, Debigare R, et al. An official American thoracic society/european respiratory society statement: Update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med [Internet]. 2014;189(9):E15–62. Available from: http://www.atsjournals.org/doi/pdf/10.1164/rccm.201402-0373ST

238. Wüst RCI, Degens H. Factors contributing to muscle wasting and dysfunction in COPD patients. Int J COPD. 2007;2(3):289–300.

239. Stamford BA, Matter S, Fell RD, Papanek P. Effects of smoking cessation on weight gain, metabolic rate, caloric consumption, and blood lipids. Am J Clin Nutr. 1986;43(4):486–94.

240. Rutten EPA, Spruit MA, McDonald MLN, Rennard S, Agusti A, Celli B, et al. Continuous fat-free mass decline in COPD: Fact or fiction? Eur Respir J [Internet]. 2015;46(5):1496–8. Available from: http://dx.doi.org/10.1183/13993003.00692-2015

241. Roland M, Guthrie B. Quality and Outcomes Framework: What have we learnt? BMJ [Internet]. 2016;354:1–4. Available from: http://dx.doi.org/doi:10.1136/bmj.i4060

242. Kim JH, Shim KW, Yoon YS, Lee SY, Kim SS, Oh SW. Cigarette Smoking Increases Abdominal and Visceral Obesity but Not Overall Fatness: An Observational Study. PLoS One. 2012;7(9):5–9.

243. Sanders KJC, Kneppers AEM, van de Bool C, Langen RCJ, Schols AMWJ. Cachexia in chronic obstructive pulmonary disease: New insights and therapeutic perspective. J Cachexia Sarcopenia Muscle. 2016;7(1):5–22.

244. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and

prevention. Lancet [Internet]. 2007;370(9589):786–96. Available from: http://dx.doi.org/10.1016/S0140-6736(07)61382-8

245. Dransfield MT, Kunisaki KM, Strand MJ, Anzueto A, Bhatt SP, Bowler RP, et al. Acute Exacerbations and Lung Function Loss in Smokers with and without Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2017 Feb;195(3):324–30.

246. Seemungal T a, Donaldson GC, Paul E a, Bestall JC, Jeffries DJ, Wedzicha J a. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157(5 Pt 1):1418–22.

247. Spruit MA, Gosselink R, Troosters T, Kasran A, Gayan-Ramirez G, Bogaerts P, et al. Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. Thorax [Internet]. 2003;58(9):752–6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=37094049

248. Soler-Cataluña JJ, Martínez-García MÁ, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax. 2005;60(11):925–31.

249. Snell N, Strachan D, Hubbard R, Gibson J, Gruffydd-Jones K, Jarrold I. S32 Epidemiology of chronic obstructive pulmonary disease (COPD) in the uk: findings from the british lung foundation's 'respiratory health of the nation' project. Thorax [Internet]. 2016;71(Suppl 3):A20.1-A20. Available from: http://thorax.bmj.com/lookup/doi/10.1136/thoraxjnl-2016-209333.38

250. Qureshi H, Sharafkhaneh A, Hanania NA. Chronic obstructive pulmonary disease exacerbations: Latest evidence and clinical implications. Ther Adv Chronic Dis. 2014;5(5):212–27.

251. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017 Jan;195(5):557–82.

252. Bischoff EWMA, Schermer TRJ, Bor H, Brown P, Van Weel C, Van Den Bosch WJHM. Trends in COPD prevalence and exacerbation rates in Dutch primary care. Br J Gen Pract. 2009;59(569):927–33.

253. Quint JK, Müllerova H, DiSantostefano RL, Forbes H, Eaton S, Hurst JR, et al. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). BMJ Open. 2014;4(7):1–8.

254. Taggar JS, Coleman T, Lewis S, Szatkowski L. The impact of the Quality and Outcomes Framework (QOF) on the recording of smoking targets in primary care medical records: cross-sectional analyses from The Health Improvement Network (THIN) database. BMC Public Health. 2012;12(1):1–11.

255. Barakat MF, McDonald HI, Collier TJ, Smeeth L, Nitsch D, Quint JK. Acute kidney injury in stable COPD and at exacerbation. Int J Chron Obstruct Pulmon Dis. 2015;10:2067–77.

256. Mullerova H, Shukla A, Hawkins A, Quint J. Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study. BMJ Open. 2014;4(12):e006171.

257. Wurst KE, Shukla A, Muellerova H, Davis KJ. Respiratory Pharmacotherapy Use in Patients Newly Diagnosed with Chronic Obstructive Pulmonary Disease in a Primary Care Setting in the UK: A Retrospective Cohort Study. COPD. 2014;(5):521–30.

258. Rothnie KJ, Müllerová H, Hurst JR, Smeeth L, Davis K, Thomas SL, et al. Validation of the recording of acute exacerbations of COPD in UK primary care electronic healthcare records. PLoS One. 2016;11(3).

259. Padmanabhan S. CPRD GOLD Data Specification. 2015.

260. Gershon AS, Wang C, Wilton AS, Raut R, To T. Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in Ontario, Canada, 1996 to 2007: A population-based study. Arch Intern Med. 2010;170(6):560–5.

261. Terzikhan N, Verhamme KMC, Hofman A, Stricker BH, Brusselle GG, Lahousse L. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam Study. Eur J Epidemiol. 2016;31(8):785–92.

262. De Marco R, Accordini S, Cerveri I, Corsico A, Antó JM, Künzli N, et al. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. Am J Respir Crit Care Med. 2007;175(1):32–9.

263. Langsetmo L, Platt RW, Ernst P, Bourbeau J. Underreporting exacerbation of chronic obstructive pulmonary disease in a longitudinal cohort. Am J Respir Crit Care Med. 2008;177(4):396–401.

264. Fuhrman C, Roche N, Vergnenègre A, Zureik M, Chouaid C, Delmas MC. Hospital admissions related to acute exacerbations of chronic obstructive pulmonary disease in France, 1998-2007. Respir Med. 2011;105(4):595–601.

265. Antunes FP, Costa M da CN, Paim JS, Vieira-da-Silva LM, Santos CA de ST, Cruz ÁA, et al. Trends in hospitalizations for respiratory diseases in Salvador, Bahia State, Brazil, 1998-2009. Cad Saude Publica. 2012;28(5):869–77.

266. Donaldson GC, Wedzicha JA. COPD exacerbations .1: Epidemiology. Thorax. 2006;61(2):164–8.

267. Kinnula VL, Vasankari T, Kontula E, Sovijarvi A, Saynajakangas O, Pietinalho A. The 10-year COPD programme in Finland: Effects on quality of diagnosis, smoking, prevalence, hospital admissions and mortality. Prim Care Respir J. 2011;20(2):178–83.

268. Lykkegaard J, De Pont Christensen R, Davidsen JR, Støvring H, Andersen M, Søndergaard J. Trends in the lifetime risk of COPD exacerbation requiring hospitalisation. Eur Respir J. 2013;

269. Kessler R, Ståhl E, Vogelmeier C, Haughney J, Trudeau E, Löfdahl C-G, et al. Patient Understanding, Detection, and Experience of COPD Exacerbations: An Observational, Interview-Based Study. Chest. 2006 Jul;130(1):133–42.

270. Wilkinson TMA, Donaldson GC, Hurst JR, Seemungal TAR, Wedzicha JA. Early

therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004;169(12):1298–303.

271. Rothnie KJ, Müllerová H, Thomas SL, Chandan JS, Smeeth L, Hurst JR, et al. Recording of hospitalizations for acute exacerbations of COPD in UK electronic health care records. Clin Epidemiol. 2016 Nov;8:771–82.

272. Chalmers JD, Tebboth A, Gayle A, Ternouth A, Ramscar N. Determinants of initial inhaled corticosteroid use in patients with GOLD A/B COPD: A retrospective study of UK general practice. npj Prim Care Respir Med [Internet]. 2017;27(1):1–7. Available from: http://dx.doi.org/10.1038/s41533-017-0040-z

273. Price D, West D, Brusselle G, Gruffydd-Jones K, Jones R, Miravitlles M, et al. Management of COPD in the UK primary-care setting: An analysis of real life prescribing patterns. Int J COPD. 2014;9:889–905.

274. Wisniewski D, Porzezinska M, Gruchala-Niedoszytko M, Niedoszytko M, Slominski JM, Jassem E. Factors influencing adherence to treatment in COPD patients and its relationship with disease exacerbations. Pneumonol Alergol Pol. 2014;82(2):96–104.

275. Merinopoulou E, Raluy-callado M, Ramagopalan S, Maclachlan S, Khalid JM. COPD exacerbations by disease severity in england. Int J COPD. 2016;11:697–709.

276. Gorska K, Krenke R, Korczynski P, Kosciuch J, Domagala-Kulawik J, Chazan R. Eosinophilic airway inflammation in chronic obstructive pulmonary disease and asthma. J Physiol Pharmacol. 2008;59 Suppl 6:261–70.

277. Han MK, Quibrera PM, Carretta EE, Barr RG, Bleecker ER, Bowler RP, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. Lancet Respir Med. 2017 Aug;5(8):619–26.

278. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. Eur Respir J. 2019;53(5).

279. Lindenauer PK, Stefan MS, Shieh MS, Pekow PS, Rothberg MB, Hill N. Outcomes associated with invasive and noninvasive ventilation among patients hospitalized with exacerbations of chronic obstructive pulmonary disease. JAMA Intern Med [Internet]. 2014;174(12):1982–93. Available from: http://archinte.jamanetwork.com/article.aspx?articleid=1918927

280. Groenewegen KH, Schols AM, Wouters E. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest [Internet]. 2003;124(2):459–67. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed8&NEWS=N&AN=37000120

281. Jordan R, Fitzmaurice D, Martin J, Ayres J, Cheng K, Cooper B, et al. Development of the Birmingham Lung Improvement Studies (BLISS) prognostic score for COPD patients in primary care: data from the Birmingham COPD cohort. 2019;75:OA257.

282. Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). Eur Respir J. 2008;31(4):869–73.

283. Evaluation of COPD (Chronic Obstructive Pulmonary Disease) to Longitudinally Identify Predictive Surrogate Endpoints (ECLIPSE): ClinicalTrials.gov Identifier: NCT00292552. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000. 2006. p. https://clinicaltrials.gov/ct2/show/NCT00292552.

284. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648–54.

285. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis. 1992;145(6):1321–7.

286. Jones PW, Brusselle G, Dal Negro RW, Ferrer M, Kardos P, Levye ML, et al. Properties of the COPD assessment test in a cross-sectional European study. Eur Respir J. 2011 Jul;38(1):29–35.

287. Stevens RJ, Poppe KK. Validation of clinical prediction models: what does the "calibration slope" really measure? J Clin Epidemiol [Internet]. 2020;118:93–9. Available from: https://doi.org/10.1016/j.jclinepi.2019.09.016

288. Radloff L. The Center for Epidemiologic Studies Depression Scale (CES-D) scale: A self-reported depression scale for research in the general population. Appl Psychol Meas. 1977;1:385–401.

289. Moons KGM, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A tool to assess risk of bias and applicability of prediction model studies: Explanation and elaboration. Ann Intern Med. 2019;170(1):W1–33.

290. Kappen TH, van Klei WA, van Wolfswinkel L, Kalkman CJ, Vergouwe Y, Moons KGM. Evaluating the impact of prediction models: lessons learned, challenges, and recommendations. Diagnostic Progn Res. 2018;2(1):1–11.

291. Amalakuhan B, Kiljanek L, Parvathaneni A, Hester M, Cheriyath P, Fischman D. A prediction model for COPD readmissions: catching up, catching our breath, and improving a national problem. J Community Hosp Intern Med Perspect. 2012;2(1):1–7.

292. Brusse-Keizer M, van der Palen J, van der Valk P, Hendrix R, Kerstjens H. Clinical predictors of exacerbation frequency in chronic obstructive pulmonary disease. Clin Respir J. 2011 Oct;5(4):227–34.

293. Almagro P, Barreiro B, De Echagüen AO, Quintana S, Carballeira MR, Heredia JL, et al. Risk factors for hospital readmission in patients with chronic obstructive pulmonary disease. Respiration. 2006;73(3):311–7.

294. Make BJ, Eriksson G, Calverley PM, Jenkins CR, Postma DS, Peterson S, et al. A score to predict short-term risk of COPD exacerbations (SCOPEX). Int J COPD. 2015;10:201–9.

295. Yii ACA, Loh CH, Tiew PY, Xu H, Taha AAM, Koh J, et al. A clinical prediction model for hospitalized COPD exacerbations based on "treatable traits." Int J COPD. 2019;14:719–28.

296. Annavarapu S, Goldfarb S, Gelb M, Moretz C, Renda A, Kaila S. Development and validation of a predictive model to identify patients at risk of severe COPD

exacerbations using administrative claims data. Int J COPD. 2018;13:2121–30.

297. Kerkhof M, Freeman D, Jones R, Chisholm A, Price DB. Predicting frequent COPD exacerbations using primary care data. Int J Chron Obstruct Pulmon Dis [Internet]. 2015;10:2439–50. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4644169&tool=pmcentrez&rendertype=abstract

298. Stanford RH, Nag A, Mapel DW, Lee TA, Rosiello R, Vekeman F, et al. Validation of a New Risk Measure for Chronic Obstructive Pulmonary Disease Exacerbation Using Health Insurance Claims Data. Ann Am Thorac Soc. 2016;13(7):1067–75.

299. Garcia-Aymerich J, Farrero E, Felez MA, Izquierdo J, Marrades RM, Anto JM, et al. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. Thorax. 2003 Feb;58(2):100–5.

300. Herer B, Chinet T. Acute exacerbation of COPD during pulmonary rehabilitation: outcomes and risk prediction. Int J Chron Obstruct Pulmon Dis. 2018;13:1767–74.

301. Adibi A, Sin DD, Safari A, Johnson KM, Aaron SD, FitzGerald JM, et al. The Acute COPD Exacerbation Prediction Tool (ACCEPT): a modelling study. Lancet Respir Med [Internet]. 2020;2600(19). Available from: http://dx.doi.org/10.1016/S2213-2600(19)30397-2

302. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax. 2013 Nov;68(11):1029–36.

303. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. Ann Intern Med. 1999;130(6):515–24.

304. National Institiue of Health and Clinical Excellence. Chronic obstructive pulmonary disease | Guidance and guidelines | NICE. NICE Clinical Guideline 101: Chronic Obstructive Pulmonary Disease. 2015.

305. Lõpez-Campos JL, Tan W, Soriano JB. Global burden of COPD. Respirology. 2016.

306. Siafakas N. Re-Establishing Stage 0 of COPD. Int J Pulm Respir Sci. 2017;1(5):5–6.

307. Han MLK, Agusti A, Celli BR, Criner GJ, Halpin DMG, Roche N, et al. From GOLD 0 to pre-COPD. Am J Respir Crit Care Med. 2020;203(4):414–23.

308. Ekberg-Aronsson M, Pehrsson K, Nilsson JÅ, Nilsson PM, Löfdahl CG. Mortality in GOLD stages of COPD and its dependence on symptoms of chronic bronchitis. Respir Res. 2005;6(stage 0):1–9.

309. de Oca M, Halbert RJ, Victorina Lopez M, Perez-Padilla R, Talamo C, Moreno D, et al. The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. Eur Respir J. 2012 Jul;40(1):28–36.

310. Vestbo J, Prescott E, Lange P, Jensen G, Schnohr P, Appleyard M, et al. Association of chronic mucus hypersecretion with FEV 1 decline and chronic obstructive pulmonary disease morbidity. Am J Respir Crit Care Med. 1996;153(5):1530–5.

311. Jordan RE, Adab P, Jowett S, Marsh JL, Riley RD, Enocson A, et al. TargetCOPD: A pragmatic randomised controlled trial of targeted case finding for COPD versus

routine practice in primary care: Protocol. BMC Pulm Med. 2014;14(1):1–9.

312. Houben-Wilke S, Janssen DJA, Franssen FME, Vanfleteren LEGW, Wouters EFM, Spruit MA. Contribution of individual COPD assessment test (CAT) items to CAT total score and effects of pulmonary rehabilitation on CAT scores. Health Qual Life Outcomes. 2018;16(1):1–8.

313. Jordan H, Roderick P, Martin D. The Index of Multiple Deprivation 2000 and accessibility effects on health. J Epidemiol Community Health. 2004;58(3):250–7.

314. Stenholm S, Tiainen K, Rantanen T, Sainio P, Heliövaara M, Impivaara O, et al. Long-term determinants of muscle strength decline: Prospective evidence from the 22-year Mini-Finland follow-up survey. J Am Geriatr Soc. 2012;60(1):77–85.

315. Jones PW, Adamek L, Nadeau G, Banik N. Comparisons of health status scores with MRC grades in COPD: Implications for the GOLD 2011 classification. Eur Respir J. 2013;42(3):647–54.

316. Bogart S. SankeyMATIC. D3.js. p. http://sankeymatic.com/.

317. Mirza S, Clay RD, Koslow MA, Scanlon PD. COPD Guidelines: A Review of the 2018 GOLD Report. Mayo Clinic Proceedings. 2018.

318. Singh D, D'Urzo AD, Donohue JF, Kerwin EM. Weighing the evidence for pharmacological treatment interventions in mild COPD: A narrative perspective. Respir Res. 2019;20(1):1–11.

319. Puhan MA. Chronic respiratory symptoms but normal lung function: substantial disease burden but little evidence to inform practice. Eur Respir J [Internet]. 2019;54(3). Available from: http://dx.doi.org/10.1183/13993003.01363-2019

320. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Chronic Bronchitis Before Age 50 Years Predicts Incident Airflow Limitation and Mortality Risk. Thorax. 2009;64(10):894–900.

321. Perez-Padilla R, Wehrmeister FC, De Oca MM, Lopez MV, Jardim JR, Muiño A, et al. Outcomes for symptomatic non-obstructed individuals and individuals with mild (GOLD stage 1) COPD in a population based cohort. Int J COPD. 2018;13:3549–61.

322. De Marco R, Accordini S, Cerveri I, Corsico A, Antó JM, Künzli N, et al. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. Am J Respir Crit Care Med. 2007;175(1):32–9.

323. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. The presence of chronic mucus hypersecretion across adult life in relation to chronic obstructive pulmonary disease development. Am J Respir Crit Care Med. 2016;193(6):662–72.

324. Kim V, Han MK, Vance GB, Make BJ, Newell JD, Hokanson JE, et al. The Chronic Bronchitic Phenotype of COPD An Analysis of the COPDGene Study. Chest. 2011 Sep;140(3):626–33.

325. Van Herck M, Antons J, Vercoulen JH, Goërtz YMJ, Ebadi Z, Burtin C, et al. Pulmonary Rehabilitation Reduces Subjective Fatigue in COPD: A Responder Analysis. J Clin Med. 2019;8(8):1264.

326. Gaude GS. Pulmonary manifestations of gastroesophageal reflux disease. Ann Thorac Med. 2009;4(3):115–23.

327. Nishimura M, Makita H, Nagai K, Konno S, Nasuhara Y, Hasegawa M, et al. Annual change in pulmonary function and clinical phenotype in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;185(1):44–52.

328. Godtfredsen NS, Lam TH, Hansel TT, Leon ME, Gray N, Dresler C, et al. COPD-related morbidity and mortality after smoking cessation: Status of the evidence. Eur Respir J. 2008;32(4):844–53.

329. Jones P, MitravitIles M, van der Molen T, Kulich K. Beyond Fev1 in Copd: a Review of Patient Reported Outcome. Int J Chron Obs Pulmon Dis. 2012;7:697–709.

330. Bertens LCM, Reitsma JB, Moons KGM, van Mourik Y, Lammers JWJ, Broekhuizen BDL, et al. Development and validation of a model to predict the risk of exacerbations in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2013;8:493–9.

331. Wijnant SRA, De Roos E, Kavousi M, Stricker BH, Terzikhan N, Lahousse L, et al. Trajectory and mortality of Preserved Ratio Impaired Spirometry: the Rotterdam Study. Eur Respir J. 2019;56(6).

332. Tai Joon A, Wan S, Chan Kwon P, Hyoung Kyu Y. The better explanation of COPD: the clinical role of FVC grouping. In: ERS conference abstract. 2019.

333. Celli BR, Marin JM, Cote CG, Aguirre A, Macario CC, van den Bemt L, et al. Prognostic assessment of patients with COPD (Correspondance). Lancet [Internet]. 2009;374(9705):1886. Available from: http://dx.doi.org/10.1016/S0140-6736(09)62084-5

334. Camp PG, Ramirez-Venegas A, Sansores RH, Alva LF, McDougall JE, Sin DD, et al. COPD phenotypes in biomass smokeversus tobacco smoke-exposed Mexican women. Eur Respir J. 2014;43(3):725–34.

335. Barreiro E, Jaitovich A. Muscle atrophy in chronic obstructive pulmonary disease: Molecular basis and potential therapeutic targets. J Thorac Dis. 2018;10(5):S1415–24.

336. Grabicki M, Kuźnar-Kamińska B, Rubinsztajn R, Brajer-Luftmann B, Kosacka M, Nowicka A, et al. COPD Course and Comorbidities: Are There Gender Differences? Respir Ailments Context. 2018;1113:43–51.

337. Athlin Å, Giezeman M, Hasselgren M, Montgomery S, Lisspers K, Ställberg B, et al. Prediction of mortality using different copd risk assessments – a 12-year follow-up. Int J COPD. 2021;16:665–75.

338. Siontis GCM, Tzoulaki I, Castaldi PJ, Ioannidis JPA. External validation of new risk prediction models is infrequent and reveals worse prognostic discrimination. J Clin Epidemiol [Internet]. 2015;68(1):25–34. Available from: http://dx.doi.org/10.1016/j.jclinepi.2014.09.007

339. Nambi V, Ballantyne CM, Hoogeveen RC, Agarwal SK, Panagiotakos DB, Wannamethee SG, et al. Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis. Lancet

Diabetes Endocrinol [Internet]. 2016;4(10):840–9. Available from: http://dx.doi.org/10.1016/S2213-8587(16)30196-6

340. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2016;37(29):2315–81.

341. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Vol. 140, Circulation. 2019. 596–646 p.

342. Ryder HF, McDonough CM, Tosteson ANA, Lurie JD. Decision Analysis and Cost-Effectiveness Analysis. Semin Spine Surg. 2009;21(4):216–22.

343. Tan WC, Sin DD, Bourbeau J, Hernandez P, Chapman KR, Cowie R, et al. Characteristics of COPD in never-smokers and ever-smokers in the general population: Results from the CanCOLD study. Thorax. 2015;70(9):822–9.

344. Celli BR, Agustí A. COPD: Time to improve its taxonomy? ERS Open Res [Internet]. 2018;4(1):1–8. Available from: http://dx.doi.org/10.1183/23120541.00132-2017

345. Jagana R, Bartter T, Joshi M. Delay in diagnosis of chronic obstructive pulmonary disease: Reasons and solutions. Current Opinion in Pulmonary Medicine. 2015.

346. Jiménez-Ruiz CA, Andreas S, Lewis KE, Tonnesen P, Van Schayck CP, Hajek P, et al. Statement on smoking cessation in COPD and other pulmonary diseases and in smokers with comorbidities who find it difficult to quit. Eur Respir J [Internet]. 2015;46(1):61–79. Available from: http://dx.doi.org/10.1183/09031936.00092614

347. Hoogendoorn M, Feenstra TL, Hoogenveen RT, Rutten-van Mölken MPMH. Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD. Thorax. 2010;65(8):711–8.

348. Tønnesen P. Smoking cessation and COPD. Eur Respir Rev. 2013;22(127):37–43.

349. Sahle BW, Chen W, Rawal LB, Renzaho AMN. Weight Gain after Smoking Cessation and Risk of Major Chronic Diseases and Mortality. JAMA Netw Open. 2021;4(4):1–13.

350. Cheng HG, Phillips MR. Secondary analysis of existing data: opportunities and implementation. Shanghai Arch Psychiatry. 2014;26(6):371–5.

351. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of the Health Improvement Network (THIN) database: Demographics, chronic disease prevalence and mortality rates. Inform Prim Care. 2011;19(4):251–5.

352. Idris BI, Giskes K, Borrell C, Benach J, Costa G, Federico B, et al. Higher smoking prevalence in urban compared to non-urban areas: Time trends in six European countries. Heal Place. 2007;13:702–12.

353. Benza RL, Miller DP, Foreman AJ, Frost AE, Badesch DB, Benton WW, et al. Prognostic implications of serial risk score assessments in patients with pulmonary arterial hypertension: A Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) analysis. J Hear Lung Transplant [Internet]. 2015;34(3):356–61. Available from:

http://dx.doi.org/10.1016/j.healun.2014.09.016

354. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. Pharmacoepidemiol Drug Saf. 2009;18(1):76–83.

355. Bhaskaran K, Smeeth L. What is the difference between missing completely at random and missing at random? Int J Epidemiol. 2014;43(4):1336–9.

356. Collins GS, De Groot JA, Dutton S, Omar O, Shanyinde M, Tajar A, et al. External validation of multivariable prediction models: A systematic review of methodological conduct and reporting. BMC Med Res Methodol. 2014;14(1):1–11.

357. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation. 2007;115(7):928–35.

358. Wouters EFM, Wouters BBRAF, Augustin IML, Franssen FME. Personalized medicine and chronic obstructive pulmonary disease. Current Opinion in Pulmonary Medicine. 2017.

359. Falaschetti E, Laiho J, Primatesta P, Purdon S. Prediction equations for normal and low lung function from the health survey for England. Eur Respir J. 2004;23(3):456–63.

VALORISATION ADDENDUM

Impact paragraph

This chapter describes the scientific and social impact of this thesis. Also, it highlights the impact of the created value from the gathered knowledge by making it suitable for and/or available in clinical practice and translating that information into practical services, products or tools. First, the aims and main findings of the thesis are briefly described. Next, the scientific and public relevance and its impact on clinical practice are discussed. Thereafter, target groups of this thesis are mentioned. Finally, activities and opportunities will be discussed.

Aims and main findings

While the presence of chronic respiratory symptoms and airflow limitation are the essential characteristics of chronic obstructive pulmonary disease (COPD), the disease is made up of multiple other pulmonary components and non-pulmonary features. These include the occurrence of exacerbations, alterations in body weight, unhealthy lifestyle and accelerated aging. As a result, COPD is a heterogeneous disease with many features contributing to disease burden and trajectory. Patients with a comparable degree of lung function impairment may be very different in terms of health status, functional performance and disease activity. Thus, differential treatments and follow-up are indicated based on the presence or absence of clinically relevant traits. Consequently, disease classification has been updated by including symptoms and exacerbation history and various tools for risk stratification have been developed. By assessing multiple clinically relevant components in individual patients, the variability in COPD severity and progression is accounted for in a more personalised manner and interventions can be more targeted. Also, this allows healthcare providers to more accurately predict prognosis and this can then be used for more informed treatment decisions.

Although multicomponent scores have been introduced in COPD management, many have not been adequately tested. This thesis aimed to improve multicomponent prognostication in patients with COPD, by focussing on two

multicomponent scores for the disease: the ADO (age, dyspnoea, airflow obstruction) score and the Birmingham Lung Improvement Studies (BLISS) model. While ADO was developed to predict mortality, BLISS aimed to predict respiratory hospitalisations among primary care COPD patients. In this thesis it was reported, that ADO score provides promising discrimination in predicting 3-year mortality in a primary care population including screen-detected COPD patients. If the score is used to provide risk predictions for 1- or 2-year mortality, it may need to be recalibrated. Also, in this thesis it was reported that serial assessment of the ADO score can identify patients with worsening disease and update their prognosis, especially for patients who smoke, are depressed, or have lower body weight.

Exacerbations are associated increased symptoms, reduced health status, progressive lung function decline and increased risk of hospitalisation and mortality in COPD. Therefore, preventing and treating these events are central components of disease management. Despite these efforts, this thesis reported increased rates of COPD exacerbations over the years 2005-2013 in a population-based cohort. Also, women showed a substantially higher risk of any COPD exacerbations, highlighting the need for a better understanding of sex differences in this disease. This thesis also showed that predicting exacerbations is challenging; although the BLISS score was more accurate in predicting severe exacerbations compared to another published index, the Bertens score, neither model should be used to predict moderate-to-severe exacerbations without first updating their intercepts.

Low body weight is an important prognostic factor in COPD, but the mechanisms underlying weight changes in patients with this disease remain unclear. Continuous smoking may be a contributing factor. This thesis aimed to investigate the associations between changes in body weight and smoking behaviour. It showed that among never smokers and former smokers, and within people with and without COPD, there is a similar rate of decline in weight over time. However, weight loss due to continuous smoking is accelerated if a person has COPD and quitting in those with COPD results in an accelerated weight gain compared to those without COPD. Finally, it showed that weight loss does not mediate the association between COPD-smoking and mortality.

Since not all persons with respiratory symptoms fulfill the diagnostic criteria for COPD, finally, the thesis aimed to determine factors associated with persistence of moderate-to-severe respiratory symptoms, and whether both the pattern and stability of symptom burden and the prognosis of individuals with persistent symptoms vary by whether or not they have airflow limitation. The study showed that normal spirometry may not rule out the need for further clinical investigation of

airway disease and people with pre-COPD may have unmet needs consistent with people with newly-identified COPD.

Relevance and target groups

Prediction of mortality can help clinicians better consult with patients, plan resources, and decide on pharmacologic and non-pharmacologic treatments to improve patient prognosis. Similarly, prediction of exacerbations can lead to risk-stratified respiratory treatment recommendations and improved care of COPD patients by reducing their risk of these events. However, the results of this thesis and external studies clearly show that predictions can only be accurate and inform patient care if the degree of lung function impairment is combined with other disease components into a multicomponent score. If the predicted risk of an outcome is high, it is easier for it to outweigh the risks, costs, inconveniences, and potential non-response as a consequence of treatment. The benefits of treatment must also be weighed. When clinicians communicate risk, this may motivate COPD patients suffering from certain components of prognostic scores (e.g. poor symptoms, reduced exercise tolerance and exacerbations) to improve their outcomes with self-care (e.g. smoking cessation, nutritional support in malnourished patients, self-management of exacerbations). Thus, when clinicians begin to use prognostic models to predict risk, it begins a process that leads to more objective, evidence-based clinical decisions and changes in action plans that may subsequently improve outcomes.

The development of new prognostic models for existing outcomes can contribute to confusion among clinicians and patients alike as it becomes less clear which prognostic scores to use. However, validation helps clinicians decide which scores “stand out” and can accurately predict outcomes in patient populations that they are used to providing care in. The ADO and the BLISS scores are likely to be the two best prediction models for mortality and exacerbations, respectively, and may require clinical impact studies as a next step. Thus, the scientific field benefits from the validation studies found in this thesis as only the most accurate and transportable prognostic scores can move on to this stage of prognostic score research. If COPD multicomponent models are the best way to account for COPD heterogeneity at one point in time, then they also may be the best way to represent variation in deterioration as well. Certain patients may deteriorate more rapidly than others and symptoms such as breathlessness may worsen over time while lung function remains stable. Rather than just measuring lung function over time, it may be important for clinicians to measure prognostic scores serially in COPD

patients in order to accurately update a patient's prognosis and accurately measure their rate of deterioration. This ensures that patients are well-informed on whether their disease is stable or worsening and they can also be involved in adapting their action plans. For example, reducing smoking and increasing body weight may slow disease deterioration and improve patient-related outcomes. This increases awareness in the COPD scientific community on potential avenues for the holistic treatment of COPD.

Examining factors such as persistent symptoms in symptomatic persons with normal spirometry may raise awareness of the need for clinicians to target persistent symptoms and investigate respiratory illness regardless of the level of airflow obstruction. In recent years, the scientific and clinical COPD community has de-emphasised the role of airflow limitation in the diagnosis and treatment of COPD. However, it may need to be de-emphasised even further so that persons with normal spirometry and chronic symptoms can benefit from treatments usually restricted to patients with spirometrically-defined COPD. Many patients may stand to benefit if the scientific community places GOLD stage 0 into management guidelines again. Given our results, patients may be able to use the knowledge that persistent symptoms impact their prognosis to inquire about the potential for closer investigation and monitoring of their health to prevent future exacerbations, even if they do not suffer from airflow limitation. Thus, these people may take an active role and be more involved in their care. Another example of this can be found after reflecting on our results showing the association between smoking and body weight. Patients can proactively reduce smoking behaviour to not only benefit their COPD but also raise their body weight. Also, this study asks important questions on the mechanisms between smoking and body weight in COPD patients and the phenotypes that arise from different risk factors of COPD such as smoking and biomass exposure. The scientific community can study this further and also try to answer if low body weight is a systemic effect of COPD, smoking, or both using a different patient population and adjusting for more covariates. Finally, while guidelines have recommended that clinicians give smoking cessation advice to COPD patients who continue to smoke for quite some time, our results show that this advice may need to be explicitly emphasised to patients with low body weight.

In conclusion, this thesis has an application toward personalised medicine in that it raises awareness about the heterogeneity and complexity of COPD by emphasizing components and predictors beyond airflow limitation leading to different approaches for healthcare workers and patients to make decisions together to treat COPD holistically.

Activities

The results of this thesis have led to several activities in the field of respiratory medicine and this domain of research. The results of chapters 2, 3 and 5 have been published in peer-reviewed, international journals. The following chapters were presented at the annual European Respiratory Society (ERS) congresses: chapters 2 and 3 (ERS Madrid 2019), 4 (ERS Barcelona 2021), and 5 (ERS Virtual 2020). Chapters 3 and 4 were oral presentations and were also presented at webinar for Cegedim Health Data entitled “Can research using real-world data (RWD) lead to improved patient management?” in 2021. The abstract of Chapter 3 was cited in a paper entitled: “Current developments and future directions in COPD” by Mathioudakis et al. in European Respiratory Review 2020. We will continue to publish the remaining chapters to disseminate the results to a wide audience which will include clinicians, scientists, and patients. These activities as a whole show that COPD is much more than a disease of airflow limitation and that accounting for other components, aggregating these components into a single prognostic score, and using this score in new ways should form a good basis for a future in which truly personalised COPD care can become a reality.