Imperial College London

UNDERSTANDING THE BURDEN OF COPD MORTALITY

An investigation using UK electronic healthcare record data

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Declarations

Declaration of Originality

I, Alicia Gayle herewith certify that this dissertation is my original work and that all material included which is not my own work has been properly acknowledged.

Alicia Gayle

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“Epidemiology is like a bikini: what is revealed is interesting; what is concealed is crucial.”

Prof. Peter Duesberg

Abstract

Chronic obstructive pulmonary disease (COPD) is a progressive disease largely attributed to longstanding exposure to tobacco smoking. Globally, since 2006, modelled COPD mortality rates have shown a downward trend with levels predicted to decrease by 21% into 2040, yet, few extensive patient level studies have been conducted to distinguish between those who die with COPD from those who die from COPD in the United Kingdom.

The aim of this thesis was to describe the epidemiology of mortality in patients with COPD. The objectives included:

i) to investigate COPD mortality over time in the UK population calculating all-cause and cause-specific mortality rates
ii) to understand the association between environmental exposures and COPD mortality
iii) to estimate the proportion of people with a diagnosis of COPD prior to a COPD-recorded death, and understand factors associated with missing lifetime diagnosis
iv) to ascertain the excess risk of death among patients with COPD while taking into account competing risks

This research revealed that COPD mortality rates in the UK over the last decade have been relatively stable, contrasting large declines seen in cardiovascular disease (CVD) mortality. Trend analysis described how patients with COPD were more likely to die from neoplasms or respiratory illness, but less likely to die of CVD, than they were 10 years ago. COPD mortality rates were associated with changes in temperature but not for $PM_{2.5}$,one of the most common air pollutants. Improvements in recording physician-diagnosed COPD were observed over time where as many as 96% of patients with a COPD-recorded death received a diagnosis in their lifetime, however, diagnosis is associated with significant excess risk of respiratory-related mortality compared to the general population.

Collectively, these results highlight the need to evaluate interventions that specifically reduce the mortality burden at both the population level and for patients with COPD.

Dissemination

Publications arising from this thesis

Gayle, A.V., Axson, E.L., Bloom, C.I., Navaratnam, V. and Quint, J.K., 2019. Changing causes of death for patients with chronic respiratory disease in England, 2005-2015. *Thorax*, 74(5), pp.483-491.

Gayle, A.V., Quint, J.K. and Fuertes, E.I., 2021. Understanding the relationships between environmental factors and exacerbations of COPD. Expert Review of Respiratory Medicine, 15(1), pp.39-50.

Gayle, A.V., Minelli,C., Quint,J.K.,2022. Respiratory-related death in individuals with incident asthma and COPD: a competing risk analysis. *BMC Pulmonary Medicine* 22(28).

Conference posters and oral presentations

2018 European Respiratory Society International Congress, September 2018

Gayle, A., Axson, E., Bloom, C., Navaratnam, V. and Quint, J., 2018. Changing causes of mortality for people with chronic respiratory diseases.

Gayle, A., Axson, E., Bloom, C., Navaratnam, V. and Quint, J., 2018. Mortality rates of COPD Patients in UK Electronic Health Records (Clinical Practice Research Datalink). *European Respiratory Journal* 52 (suppl 62), PA4484.

ISPE's 34th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, August 2018

Gayle, A., Axson, E., Bloom, C., Navaratnam, V. and Quint, J., 2018. Changing causes of mortality for people with chronic respiratory diseases. *Pharmacoepidemiology and Drug Safety* 27,pp. 335-335.

2019 European Respiratory Society International Congress, September 2019

Gayle, A., Minelli, C. and Quint, J., 2019. Risk of respiratory-related death in individuals with COPD and asthma: a competing risk analysis. *European Respiratory Journal* 54 (suppl 63)

2020 European Respiratory Society International Congress, September 2020

Gayle, A., Lenoir, A., Minelli, C. and Quint, J., 2020. Who are the patients who die of COPD with no evidence of prior diagnosis? A UK primary care database analysis. *European Respiratory Journal* 56, pp. 428

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List of abbreviations

ACO	Asthma – COPD Overlap Syndrome
ASMR	Age-Standardised Mortality Rate
ATS	American Thoracic Society
AUC	Area under the curve
BMI	Body Mass Index
BLF	British Lung Foundation
CAT	COPD Assessment Test
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CIF	Cumulative Incidence Function
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular disease
DALY	Disability-adjusted Life Years
DEFRA	Department for Environment, Food and Rural Affairs
EHR	Electronic Health Records
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
HES	Hospital Episode Statistics
HR	Hazard Ratio
ICD	International Classification of Disease
ICS	Inhaled Corticosteroids
IMD	Index of Multiple Deprivation
IPF	Idiopathic Pulmonary Fibrosis
IQR	Interquartile Range
ISAC	Independent Scientific Advisory Committee
LABA	Long-acting Beta-2 Agonists

LAD	Local authority district
LAMA	Long-acting Anti-Muscarinic Agent
LLN	Lower limit of normal
LSOA	Lower-layer super output area
LRTI	Lower Respiratory Tract Infection
MHRA	Medicines and Healthcare Products Regulatory Agency
mMRC	Modified Medical Research Council Dyspnoea Score
MMT	Minimum mortality temperature
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
OCS	Oral Corticosteroids
ONS	Office for National Statistics
OR	Odds Ratio
PH	Proportional hazards
PM	Particulate Matter
POP	Population
PPV	Positive predictive value
PR	Pulmonary Rehabilitation
QOF	Quality and Outcomes Framework
RCT	Randomized Controlled Trial
RR	Relative Risk
SD	Standard Deviation
TORCH	Towards a Revolution in COPD Health
T2DM	Type II Diabetes
UK	United Kingdom
US	United States
WHO	World Health Organisation

Ethics, Support and Disclosure Statement

This research was supported in part by an educational grant from AstraZeneca UK Ltd. The author also declares that at the time of writing they were an employee of AstraZeneca UK Ltd. The views expressed are those of the author and not necessarily those of AstraZeneca.

This work is based, in part, on data from the Clinical Practice Research Datalink (CPRD) obtained under license from the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA). The data are provided by patients and collected by the National Health Service (NHS) as part of their care and support. The interpretation and conclusions contained in these studies are those of the author alone.

Protocols for this research (Chapters 4-6) were approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol numbers 17_086R and 19_082) and the approved protocols were made available to the journals in which these research are published and to the reviewers during peer review. Generic ethical approval for observational research using the CPRD with approval from ISAC has been granted by a Health Research Authority Research Ethics Committee (East Midlands – Derby, REC reference number 05/MRE04/87).

Linked pseudonymised mortality data from the Office for National Statistics (ONS), socioeconomic data from the Index of Multiple Deprivation (IMD), and secondary care data from Hospital Episode Statistics (HES) were provided for these studies by CPRD for patients in England. Data were linked by NHS Digital, the statutory trusted third party for linking data, using identifiable data held only by NHS Digital. Select general practices consent to this process at a practice level, with individual patients having the right to opt-out. Use of HES and ONS data are Copyright © (2018), re-used with the permission of The Health & Social Care Information Centre, all rights reserved.

Data are available on request from the CPRD. Their provision requires the purchase of a license, and this license does not permit the authors to make them publicly available to all. The Methods sections for each Chapter have clearly specified the data selection process. To allow identical data to be obtained by others, via the purchase of a license, the code lists have been provided in the Appendices

Licenses are available from the CPRD (http://www.cprd.com): The Clinical Practice Research Datalink Group, The Medicines and Healthcare products Regulatory Agency, 10 South Colonnade, Canary Wharf, London E14 4PU.

Individual mortality data used to create the LSOA-specific daily time series were provided by the Office of National Statistics (ONS) through a specific agreement (MRP 2291/2013). These data cannot be shared by the authors and must be requested directly from ONS. Daily temperature data over the 1x1km grid were gathered from the HadUK-Grid database publicly available through the UK Meteorological Office's Integrated Data Archive System (MIDAS) stored at the Centre for Environmental Data Analysis (CEDA) archive (https://archive.ceda.ac.uk/). Information on the small-area characteristics was gathered from public sources.

1 Chapter 1: Introduction

I begin this thesis by introducing chronic obstructive pulmonary disease (COPD) and describing the epidemiology of the disease including prevalence, incidence and clinical characteristics. Although the focus of my thesis is on COPD mortality, section 1.1 provides important context for understanding the condition itself as well as a brief understanding of the magnitude of the problem. I then focus on COPD mortality in 1.2, where I describe the UK trends in COPD mortality over time. The use of electronic healthcare records (EHR) for research is introduced in 1.3 followed by the rationale for this thesis in 1.4. Finally, the chapter concludes with aims and objectives for this thesis in 1.5.

1.1 Epidemiology of COPD

COPD is a chronic lung disease in which patients develop inflammation in the small airways and progressive destruction of lung parenchyma (emphysema), resulting in a decline in lung function out of proportion to the normal decline seen with ageing (Ito and Barnes, 2009). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classified COPD as “a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases”(GOLD, 2020).

The prevalence of COPD in the general population is estimated to be between 7% and 12% globally (Landis et al., 2014) and climbs appreciably higher with age, to >10% amongst those aged ≥40 yrs. (Chapman et al., 2006). The incidence of COPD has been estimated globally as 18,721 per 1,000 person-years (95% confidence interval (CI) 18,004 – 19,456), but varies widely by country; while the rate in European countries has declined, incidence in other continents has increased (Vos, 2015). In the UK ~115,000 people are diagnosed with COPD each year, and between 2004 and 2012, the incidence of COPD decreased among both males and females (**Figure 1.1**) (BLF, 2016b). Within the UK, COPD prevalence, incidence, and mortality rates are highest in Scotland and the north of England, and are over twice as great in the most deprived population quintile than in the least (Snell et al., 2016).

COPD typically presents with three key signs or symptoms, a chronic cough that may be intermittent or unproductive, chronic sputum production and persistent dyspnoea (difficulty breathing) (Viegi et al., 2007). A clinical diagnosis then requires confirmation with spirometry showing evidence of airflow obstruction; a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ≤0.7 confirms the presence of airflow limitation that is not fully reversible (GOLD, 2020). In addition, where the FEV_1/FVC ratio is below the lower fifth percentile of a large healthy reference group (the statistically defined lower limit of normal (LLN)) airflow obstruction is also confirmatory of chronic obstruction (Quanjer et al., 1993). COPD can be classified with respect to severity of airflow limitation, by symptoms, or through a combination of these with consideration of medical history. It

is a heterogeneous disease, and the natural history varies greatly from person to person with respect to lung pathology, trajectory of the disease, and comorbidity. Traditionally, the severity of this disease is graded using either level of airflow limitation (FEV_1) or a combined assessment using the modified Medical Research Council (mMRC) dyspnoea grade, current health status assessed by the COPD Assessment Test (CAT) and future risk based on exacerbation history (GOLD Stage – See **Appendix 9.1.1**) (Vestbo J et al., 2017).

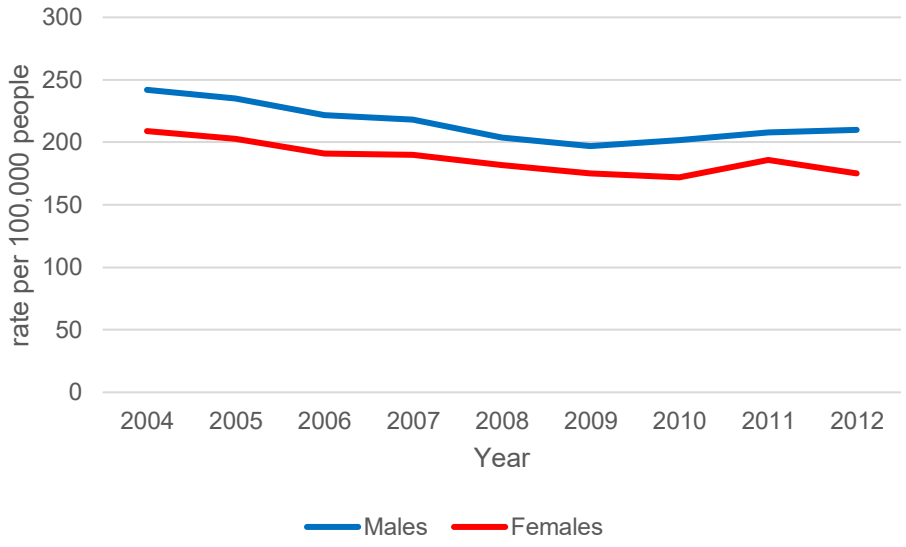


FIGURE 1-1 NUMBER OF NEWLY DIAGNOSED COPD PER 100,000 PEOPLE EACH YEAR IN THE UK, 2004–12

Reproduced from the British Lung Foundation report 2016 (BLF, 2016b)

Many patients with COPD experience exacerbations over the course of their disease, these are a sustained worsening of a patient's condition that is acute in onset and may warrant additional treatment in a patient with underlying COPD (Burge and Wedzicha, 2003, Price et al., 2010, GOLD, 2015). Exacerbations are characterised by increased inflammation of the airways and worsening airway obstruction resulting in increased dyspnoea, sputum purulence and sputum volume (Donaldson and Wedzicha, 2006). Although there is no agreed classification of exacerbations, they can be defined using respiratory symptoms alone or symptoms plus an event such as hospital admission. The American Thoracic Society/European Respiratory Society (ATS/ERS) 2004 guidelines classified exacerbations into three

categories: mild exacerbations (normally managed at home by the patient), moderate exacerbations (requiring consultation with primary care physicians) and severe exacerbations (needing hospitalisation)(ATS and ERS, 2004).

1.2 COPD mortality

Population mortality figures are probably the most reliably recorded data for examining long-term trends in COPD prognosis as they are the most universally recorded healthcare statistic along with births and population figures. Although diagnostic codes have changed frequently (Marks and Burney, 1997), true rates are probably under-recorded (Mannino et al., 1997), and COPD is frequently also present in patients who are recorded as dying from ischemic heart disease or lung cancer. Chronic bronchitis and emphysema were first described in Western Europe in the early nineteenth century. Repeated attacks of bronchial infection ending in oedematous heart failure caused more than 5% of all deaths in middle and old age in the UK in the middle of the nineteenth century. However, at that time, bronchiectasis, unrecognized tuberculosis, and other chronic lung diseases might have also been included (Marks and Burney, 1997).

COPD represents an increasing burden worldwide with most deaths from COPD occurring in low-income regions including East, South and South-East Asia and central Africa, where age-standardised rates are also higher (**Figure 1.2**), this has important implications for health-care providers from a clinical and cost point of view (Anto et al., 2001). According to the 2010 Global Burden of Disease study, COPD was responsible for about 5% of disability-adjusted life years (DALYs) globally (76.7 million) – and 5% of total deaths (2.9 million) (Lozano et al., 2012, Murray et al., 2012). Discouragingly, it is projected to jump to the fourth leading cause of death worldwide by 2040 (Foreman et al., 2018).

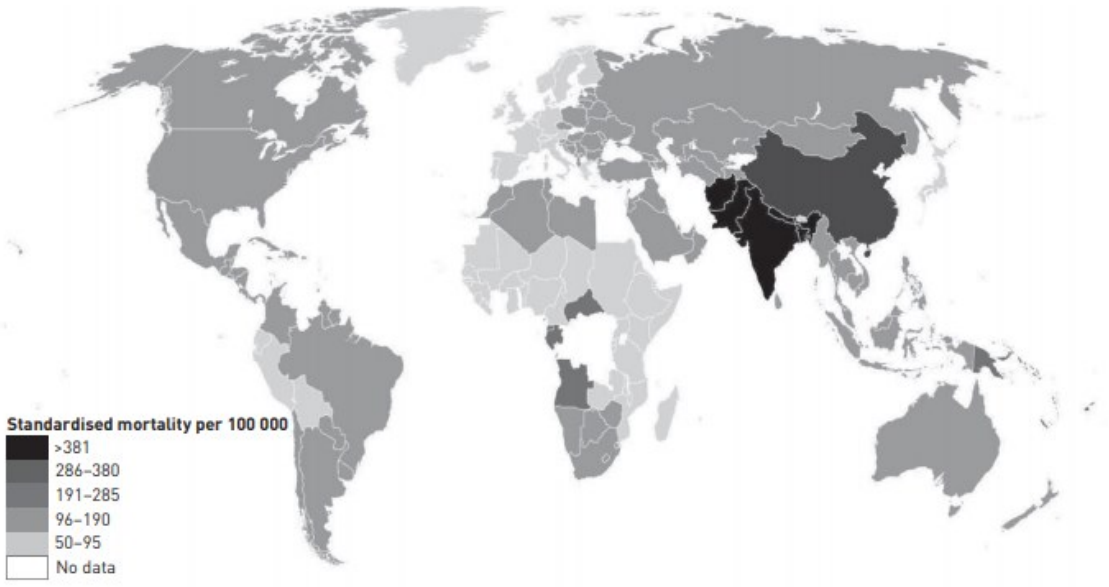


FIGURE 1-2 AGE- AND SEX-ADJUSTED CHRONIC OBSTRUCTIVE PULMONARY DISEASE MORTALITY IN 2010

Reproduced from Burney et al 2015 (Figure 1) (Burney et al., 2015)

Reasonably consistent estimates of COPD mortality in the UK have been available since 1930 (Royal College of Physicians, 1971). At that time, the disease was largely associated with lower socioeconomic demographic groups (Goodman et al., 1953). Deaths amongst women classified as “bronchitis” were about 60% lower than the rate observed amongst men; and as rates declined between 1930-1970, lung cancer was steadily rising. In men, bronchitis mortality was broadly constant or slightly rising from 1930 to 1970, and, by 1970, mortality was about 5 times that in women. In the early 1960s, mortality from “bronchitis” in the UK was 30 times that recorded in the US, prompting systematic transatlantic investigations (Reid and Fletcher, 1971). These investigations identified some differences in clinical definition, such as the more common diagnosis of “emphysema” in the US, but for a given smoking history, breathlessness and impaired spirometry were more common in the UK. Pooling all possible diagnoses, COPD mortality seemed to be about 4 times more common in the UK than in US men.

Previous literature had suggested a steady and continuing decline in COPD mortality in men but an increase in mortality in women (Peto et al., 1994). During the 1990s, there was a 25% fall in male mortality but a 33% rise in female mortality so that in

1999 women accounted for 44% of the total deaths attributed to COPD. In both men and women, there has been a dramatic increase in the age at diagnosis and death from COPD (Mannino and Kiri, 2006). In a previous large study of general practitioners' records in the UK, the mean age at diagnosis was 67 years and at death was 76 years (Soriano et al., 2000); this could have lingering implications for the male: female ratio for total mortality now, as women currently account for 55% of the total population over 65 years in the UK (ONS, 2020a).

Despite a clear dichotomy in gender-specific mortality dynamics, overall mortality rates from COPD have reported to have been increasing steadily over the past few decades. This trend is the opposite to that of the trend for cardiovascular diseases (CVD); for example, although WHO estimates suggest that ischaemic heart disease and stroke will remain ranked first and second leading causes of death worldwide in 2030, there is also evidence that the increase in CVD mortality is slowing substantially relative to the increase in COPD mortality (Mathers and Loncar, 2006).

1.2.1 Prognostic Risk Factors

Among the diagnosed COPD population, several clinical and demographic factors have been previously identified to classify patients at higher risk of death and serve as prediction tools. These include information that can be easily observed or obtained using medical records (including smoking status, disease severity, frequency of exacerbations, presence of comorbidities, and symptom burden). The evidence base for identification of patient factors to risk-stratify COPD is extensive; in the following sections, I describe some key factors and their association with mortality.

Smoking

The increased risk of death in patients with COPD is most pronounced in current smokers, irrespective of disease severity (Shavelle et al., 2009). A study using a model based on the National Health and Nutrition Examination Survey (NHANES) III data estimated mortality risk and found that COPD was associated with a modest reduction in life expectancy for people who never smoked, and a very large reduction in current or former smokers (**Figure 1.3** (Shavelle et al., 2009). However, smoking status is often not included in composite risk scores, possibly because patients with

more severe disease are more likely to quit, confounding the relationship of current smoking and mortality in study populations enriched for patients with COPD.

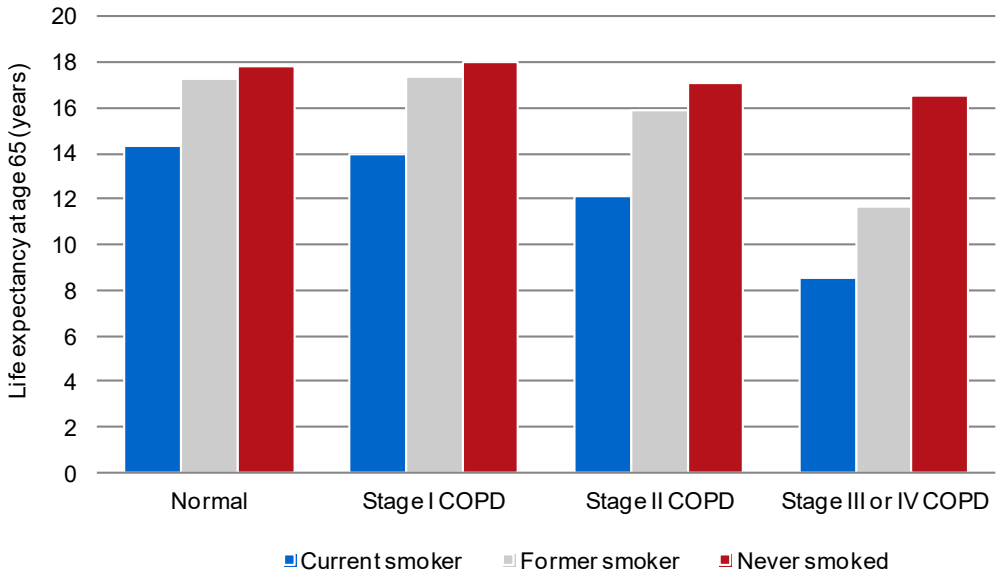


FIGURE 1-3 LIFE EXPECTANCIES FOR OTHERWISE HEALTHY 65-YEAR-OLD CAUCASIAN MALES

*Reproduced from Shavelle et al 2009 (Figure 6) (Shavelle et al., 2009); COPD stage refers to GOLD 2008 classification (See **Appendix 9.1.1**)*

COPD severity

Several studies found the mortality associated with COPD increased with increasing severity of COPD. A study of more than 15,000 adults in the US aged between 43 and 66 years stratified COPD-related deaths by disease severity according to the GOLD criteria (GOLD, 2006) (See **Appendix 9.1.1**). Mortality in patients classified as GOLD 3 or 4 was more than twice that of patients classified as GOLD 2 (34.0% and 15.6%, respectively; **Table 1.1)**. The death rate was also considerably higher in patients classified as GOLD 3 or 4 compared with patients classified as GOLD 1.

TABLE 1-1 RATE OF COPD-RELATED DEATHS BY GOLD SPIROMETRIC CATEGORY IN PATIENTS AGED 43-66 YEARS OLD

GOLD Category	Patients *n*	Deaths *n* (%)	Death rate/ 1,000 person years
GOLD 3 or 4	271	92 (34.0)	42.9
GOLD 2	1484	232 (15.6)	18.1
GOLD 1	1679	137 (8.1)	9.1
GOLD 0	2244	204 (9.1)	10.1
Restricted	1101	150 (13.6)	15.6
Normal	8661	427 (4.9)	5.4

*Adapted from the GOLD 2006 report (GOLD, 2006), See **Appendix 9.1.1** for GOLD stages*

Similarly, a study using a model based on NHANES III survey data found higher lung function impairment was associated with an increased risk of death compared with less or no lung impairment (Mild COPD relative risk (RR) of death=1.2; Severe COPD RR of death=1.7) (Shavelle et al., 2009). These held even when considering change in GOLD stage over time. Patients whose severity stage (GOLD ABCD criteria - See **Appendix 9.1.1**) worsens have worse outcomes with a "dose effect" present such that worse outcomes are seen in those whose severity stage deteriorates by more than one step, for example A to D, when compared to those whose severity stage only worsens by one stage, for example A to B, or B to C, or A to BC[1]) (Flynn et al., 2018).

Although GOLD is aimed at the management and classification of the disease, the way in which it was developed has resulted in many studies attempting to establish the prognostic capacity of the composite ABCD classification when compared to FEV_1 alone (See **Appendix 9.1.1**). Lange et al. previously pooled data from two similar prospective, population studies conducted in Copenhagen (2001 to 2003 and 2003 to 2010; *n*=6,628) (Lange et al., 2012). In both studies, patients were monitored for an average 4.3 year follow-up and the studies recorded all COPD exacerbations, hospital admissions, and all-cause mortality occurring during that timeframe. Worse survival was reported in patients categorised as GOLD B (low risk, more symptoms) than in patients categorised as GOLD C (high risk, fewer symptoms; **Figure 1.4**) (Lange et al., 2012). Conversely, when patients were classified according to the airflow limitation stratification system (using FEV_1 alone) the risk of mortality increased with increasing GOLD group. Therefore, the presence

[1] GOLD stages B and C are the least common classification and their association with poor outcomes has overlapped in previous cohorts therefore the analysis by Flynn et al. combined these 2 groups.

of more symptoms, in particular, dyspnoea, increased the risk of mortality even in individuals with preserved lung function (as assessed by FEV_1)(Lange et al., 2012). In the ABCD classification (based only on symptoms and exacerbation and not on spirometry), less of a dose-response gradient has been observed, other research has corroborated this conclusion that the ABCD assessment may not be a better predictor of mortality than the spirometric grades alone (Menezes et al., 2017).

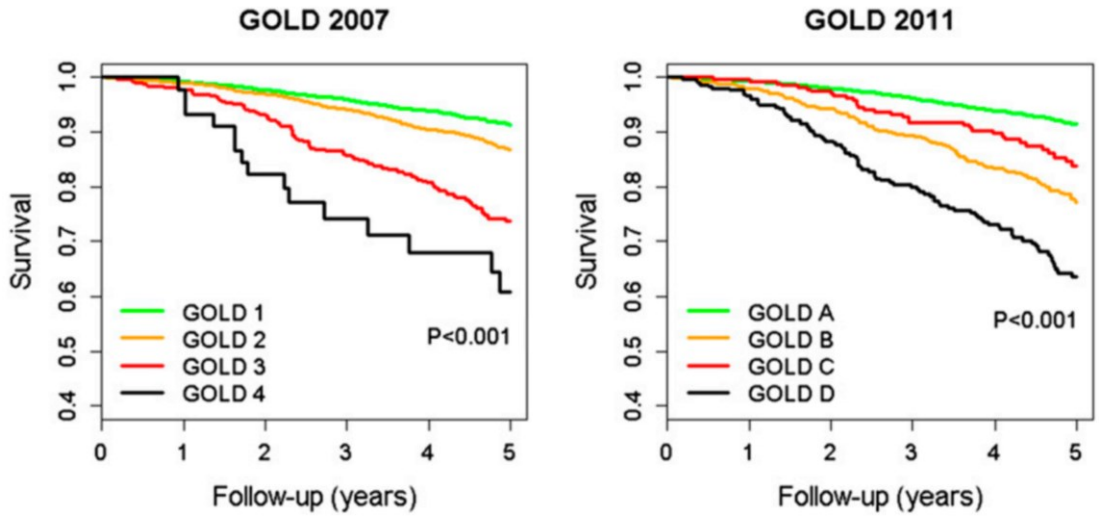


FIGURE 1-4 KAPLAN-MEIER SURVIVAL CURVES ACCORDING TO THE 2007 GOLD 1 TO 4 AND 2011 GOLD A TO D CLASSIFICATIONS

Reproduced from Lange et al 2012 (Figure 2) (Lange et al., 2012)

Exacerbations

Severe exacerbations requiring hospitalisation are independently associated with all-cause mortality in patients with COPD. A prospective study of 304 male patients with stable COPD investigated the effect of severe acute exacerbations on survival (Soler-Cataluna et al.). Patients with very frequent exacerbations (≥3 exacerbations) had a significantly higher mortality rate than patients with no hospitalisations (*P*<0.001; **Figure 1.5**) (Soler-Cataluna et al.). The risk of death in very frequent exacerbators was 4.30 times higher (95% CI, 2.62 to 7.02) compared with non-exacerbators. Furthermore, patients with infrequent exacerbations (1 to 2 exacerbations) also showed significant differences in survival compared with patients with no hospitalisations (Hazard Ratio (HR) 2.20; 95% CI, 1.45 to 3.33; *P*<0.0002; **Figure 1.5**).

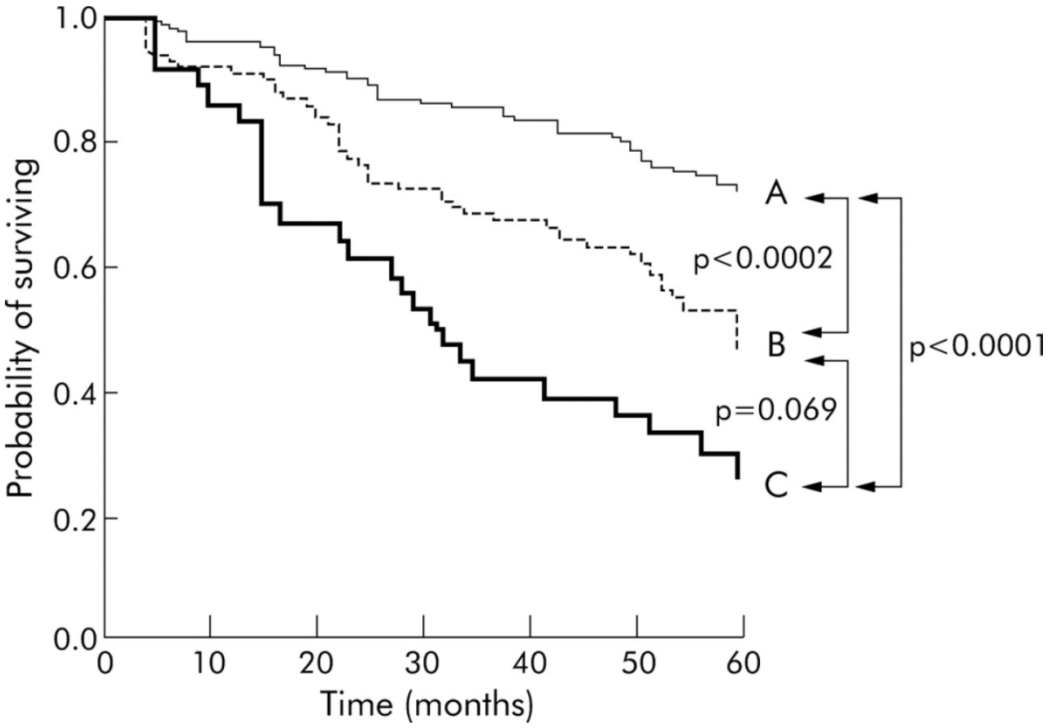


FIGURE 1-5 KAPLAN-MEIER SURVIVAL CURVES BY FREQUENCY OF EXACERBATIONS IN PATIENTS WITH COPD

Reproduced from Soler-Cataluna et al 2005 (Figure 1) (Soler-Cataluna et al.)

Studies have also reported a high mortality rate after admission to hospital with acute exacerbations of COPD. An in-hospital mortality rate of 11% in patients with acute hypercapnic respiratory failure was observed in a prospective cohort study of 1,016 patients (Connors Jr et al., 1996). During follow-up, patients who initially survived the hospital admission had mortality rates of 43% and 49% after 1 and 2 years, respectively. Steer et al. corroborated these findings, demonstrating an in-hospital mortality rate for exacerbation of COPD between 2.5 and 25% (Steer et al., 2010). A Spanish prospective cohort study found that mortality at 180 days, 1 year, and 2 years following hospitalisation for acute exacerbation of COPD was 13.4%, 22%, and 35.6%, respectively (Almagro et al., 2002). In this study, lower quality of life, being unmarried, depressive symptoms, more comorbid conditions, and hospital readmission were also associated with an overall poor prognosis (Almagro et al., 2002).

Comorbidities

COPD is associated with many comorbidities, particularly those related to cardiovascular, endocrine, bone and smoking-related conditions, in addition to conditions that would occur due to the patients' advanced age and due to shared risk factors. All these diseases worsen the burden of COPD, and can frequently cause death, independently of respiratory failure.

An analysis of the US National Hospital Discharge Survey evaluated all COPD-related hospital discharges that occurred in the US from 1979 to 2001 in adults >25 years of age(Holguin, 2005). A hospital diagnosis of COPD was associated with a higher rate of age-adjusted, in-hospital mortality for pneumonia, hypertension, heart failure, ventilator failure and thoracic malignancies compared with hospital discharges that did not mention COPD (**Figure 1.6**) (Holguin, 2005).

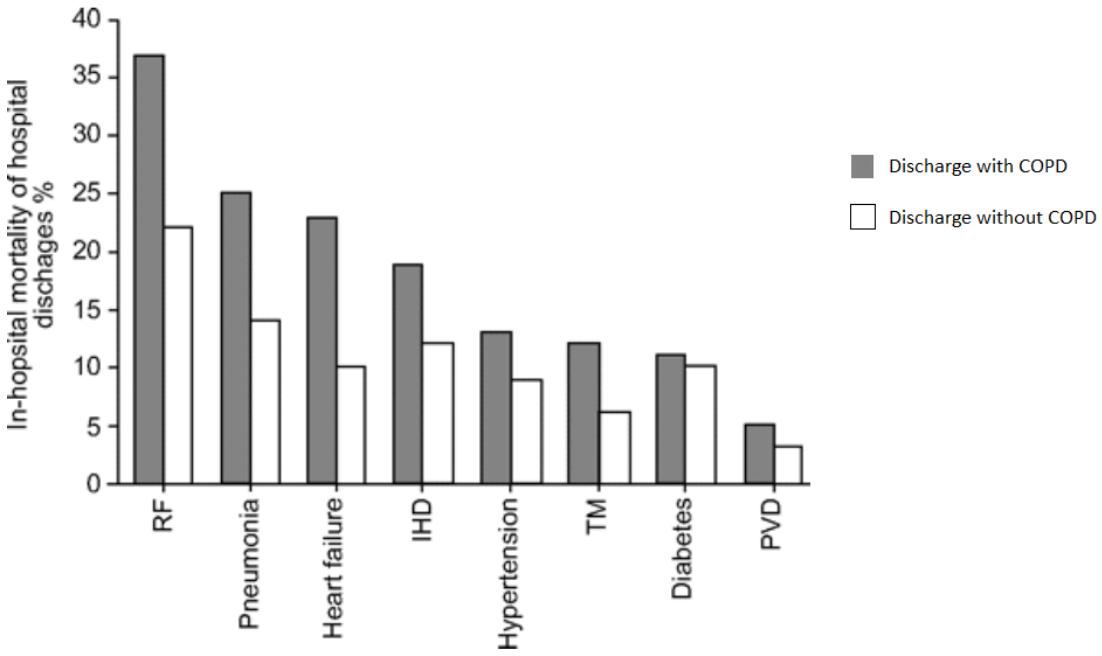


FIGURE 1-6 AGE-ADJUSTED MORTALITY OF COPD-RELATED HOSPITAL DISCHARGES ASSOCIATED WITH SELECTED COMORBID CONDITIONS

Reproduced from Holguin 2005 (Figure 3) (Holguin, 2005); IHD = ischaemic heart disease; PVD = pulmonary vascular disease; RF = respiratory failure; TM = thoracic malignancy

Coronary heart disease and COPD share the same main risk factor, smoking. The presence of symptoms of chronic bronchitis increases the risk of death due to a coronary event by 50%; and for every 10% decrease in FEV_1, all-cause mortality increases by 14%, cardiovascular mortality increases by 28%, and the frequency of

non-fatal coronary events increases by 20%. The link between COPD and coronary heart disease is independent of any other confounding cardiovascular risk factors, namely smoking status, cholesterol, systemic hypertension and body mass index (BMI) (Cavaillès et al., 2013).

Obesity is hypothesized to have a protective effect in relation to all-cause mortality, with an increased risk in those who are considered underweight, and in COPD, such an obesity paradox may be present (Spelta et al., 2018). Several studies investigated the relationship between weight and mortality in COPD patients, and a meta-analysis by Guo et. al found the lowest risk of mortality is for a BMI of 30 kg/m^2 (Guo et al., 2016). However, there is conflicting evidence for patients considered morbidly obese (BMI ≥40 kg/m^2). Jordan et al. reported a significant increase in deaths due to respiratory disease in COPD patients with a BMI ≥40 kg/m^2 (HR 5.78, 95% CI 1.09–30.61) (Jordan Jr and Mann, 2010), whereas overweight (BMI 25.0-39.9 kg/m^2) participants in clinical trial settings have a significantly lower risk of all-cause mortality versus normal-weight participants (HR 0.74, 95% CI 0.64–0.86) (Putcha et al., 2021).

Type II diabetes (T2DM) is one of the most common comorbidities in obese COPD patients; incidence of T2DM in COPD has been increasing in the UK in recent decades (Gayle et al., 2019a) and affects the prognosis of COPD (i.e. time to first hospitalisation and 5-year mortality rate) (Mannino et al., 2008). According to the Emerging Risk Factors Collaboration, the HR for COPD-related death was 1.27 compared to subjects without diabetes (Rao Kondapally Seshasai S, 2011).

Not only are asthma and COPD frequently encountered in clinical practice, but they often coexist. Based on the most commonly used definition of asthma COPD overlap (ACO), the syndrome is estimated to be present in 15 to 45% of the population with obstructive airway disease, and the prevalence increases with age (Hosseini et al., 2019). Higher rates of comorbid conditions have been demonstrated in the ACO population and the suggestion is that ACO patients have worse prognosis compared to asthma or COPD alone. However, in a recent study of 214 patients with an exacerbation of COPD with and without asthma, Peltola et al. found that survival in ACO patients was significantly higher than in COPD patients (4.7 vs. 1.7 years, $p = 0.001$) (Peltola et al., 2020). The authors discuss some possible explanatory

factors. Patient characteristics such as younger age (67 years in the ACO group vs. 70 years in the COPD group, $p < 0.05$), female sex (34% for ACO vs. 22% for COPD) or smaller number of pack-years (39 pack-years for ACO vs. 44 pack-years for COPD, $p = 0.05$), as seen in the study population may explain the differences observed. The lung function (based on FEV_1 and diffusing capacity of carbon dioxide, corrected for haemoglobin) of the ACO patients wasn't better compared to COPD patients, but the variability of airway obstruction and inflammation in asthma might have, for example, resulted in better response to medication than in COPD. The use of ICS has been shown to prevent the decline of lung function in asthma patients by preventing severe exacerbations and the authors hypothesize that this might have been reflected in ACO patients, too. Finally, they suggest that the protective factors could also be unrelated to asthma itself, such as the obesity paradox.

Risk Scores

Identification of validated risk scores to help predict all-cause mortality are clearly desirable, but not necessarily straightforward, reflecting the range of comorbidities, clinical presentation and complexity of underlying pathophysiological mechanisms associated with COPD. Several indices have been proposed based on comorbidities in order to improve the prediction of mortality, including, the COTE index (COPD specific comorbidity test) developed by Divo et al., and the CODEX index (comorbidity, obstruction, dyspnoea and previous severe exacerbations) developed by Almagro and colleagues. Previously Divo et al. identified 12 comorbidities (included in the 25-point score COTE index) closely related to mortality, including cardiovascular disease (atrial fibrillation, heart failure and coronary artery disease) and anxiety (Divo et al., 2012). Increases in the COTE index were associated with an increased risk of death from COPD-related (HR 1.13; 95% CI:1.08-1.18) and non-COPD-related (HR 1.18; 95% CI:1.15-1.21) causes, and was able to predict mortality with an area under the curve (AUC) of 0.62 (95% CI 0.57–0.68) (Divo et al., 2012). Similarly, the CODEX index, including comorbidities from the Charlson index, was independently associated with 1-year all-cause mortality (AUC 0.68; 95% CI:0.65-0.71) (Almagro et al., 2014). Whilst these scores have demonstrated some association with mortality outcomes, recent studies have not replicated these results. Morales et al. validated the use of comorbidity-based scores against simpler indices

and found that the ADO score combined with the COTE score outperformed both COTE alone as well as CODEX (Morales et al., 2018).

In addition to comorbidity-weighted indices, numerous prognostic models have been developed to provide a single score/index to predict mortality among patients with COPD. The ADO and BODE scores have shown the best discriminatory performance for predicting COPD mortality (Guerra et al., 2018). BODE includes severity of airflow obstruction (FEV_1), nutritional status (BMI), exercise capacity using the 6-min walk test and severity of dyspnoea (mMRC), and it predicts mortality better than the FEV_1 alone (AUC of 0.74) (Celli et al., 2004) and has been endorsed in clinical guidance (GOLD, 2020). The ADO score combines three types of easily accessible information, age, dyspnoea, and airflow obstruction (FEV_1 % predicted), and it accurately predicts 3-year mortality (Puhan et al., 2012).

1.2.2 Environmental Risk Factors

The principal environmental factor in COPD is well known, exposure to cigarette smoke, and it can be modified. However, although smoking is the best-studied external COPD risk factor, it is not only one. Air pollution, climate, and exposure to dusts and noxious chemicals whether through occupation or otherwise can also influence COPD mortality, either directly or indirectly, when the exposures are sufficiently intense or prolonged. In this section I will briefly discuss air pollution, climate and their association with COPD mortality.

Air pollution

Ambient air pollutants, such as particulate matter (PM) of various sizes (diameter < 10 μg (PM_{10}) and < 2.5 μg ($PM_{2.5}$)), sulphur dioxide (SO_2), nitrogen dioxide (NO_2) and ozone (O_3), can cause acute inflammatory injury of the respiratory tract, alveolar epithelial damage and changes in chemical composition of lung lavage fluids, which can exacerbate COPD (Lopez-Campos et al., 2016).

$PM_{2.5}$ is the most widely studied air pollutant and is composed of metals, elementary carbon, organic carbon, and chemical components. $PM_{2.5}$ has a small diameter but large surface area and is therefore capable of carrying several various toxic components. Due to its small size and easy transportation, $PM_{2.5}$ can be inhaled deep into the airway and deposited in lung tissue, especially alveolar regions,

causing damage in the lung. Furthermore, particulate matter may disrupt the lung endothelial cell barrier integrity via enhanced oxidative stress, thereby inducing lung dysfunction and causing adverse cardiopulmonary outcomes (Wang et al., 2010). Previous cohort studies have found associations between long-term ambient outdoor air pollution exposure and adverse effects on human health, in particular respiratory mortality. In a cohort of US Medicare beneficiaries, Pun et al. found an association between long-term $PM_{2.5}$ exposure and respiratory mortality (RR 1.24, 95% CI:1.23, 1.25) (Pun et al., 2017). An increase in $PM_{2.5}$ was also significantly associated with an increase in the risks of pneumonia and COPD mortality, with RRs of 1.60 (95% CI: 1.57, 1.63) and 1.10 (95% CI:1.08, 1.12), respectively, between 2000 and 2008 (Pun et al., 2017). Moreover, in a recent systematic review and meta-analysis Zhu et al. found an increased risk of COPD mortality associated with a 10-μg/m³ increase in $PM_{2.5}$ (RR 1.02, 95% CI:1.01-1.02) (Zhu et al., 2020).

Temperature

The relationship between COPD mortality and temperature is well known (Anderson et al., 1997). Extremes of temperature, including both extremes of hot and cold, have also been linked to excessive morbidity and mortality among individuals with COPD (Hansel et al., 2016). Bennett et al. identified 921,288 cardiorespiratory deaths in May–September of 2001–2010 (47% of all deaths in England and Wales over this period) and found that in the most vulnerable districts (areas in which effect sizes were larger than the national average), which were those in London and south/southeast England, the odds of dying from cardiorespiratory causes increased by more than 10% for 1 °C warmer temperature, compared with virtually no effect in the most resilient districts, which were in the far north (Bennett et al., 2014).

As global temperatures rise and there is slow progress in substantially reducing air pollution levels, the need to understand the mechanisms between environmental factors and their association with COPD mortality is growing in importance. Furthermore, the anticipated effects of climate change also include overall warmer temperatures as well as increases in temperature variability and extreme weather conditions, which will impact the frequency of exacerbations and all-cause mortality.

1.2.3 Interventions

Clearly, the mortality burden of COPD can be reduced by preventing at-risk individuals from developing the disease. This can be achieved by screening for COPD in susceptible people and involves taking detailed patient history to assess risk factor exposure (e.g., tobacco smoke), medical and family history, and presence of genetic risk factors or comorbid conditions. Early identification and prevention of COPD progression, e.g., by reducing exposure to tobacco smoke, occupational substances, and air pollution, would reduce the burden of COPD mortality.

Once the disease is established, a variety of effective treatments exists for COPD. Several studies report the impact of management and therapies on COPD, although survival is rarely the primary endpoint of such studies. Data for the impact of interventions on COPD survival are reviewed below, considering some non-pharmacological and pharmacological options.

Smoking Cessation

Smoking cessation is of ultimate importance in arresting the process of lung-function decline in COPD and should be the emphasis of any program that aims to intervene in COPD at an early stage. The Lung Health Study followed smokers with mild obstruction who were randomized to intensive smoking cessation with or without an inhaled bronchodilator compared with smokers in whom no intervention was used (Anthonisen et al., 1994). They found that patients who ceased smoking had a markedly reduced decline in FEV_1 over a 5-year period compared with those who did not. In contrast, treatment with a bronchodilator did not significantly affect the decline in lung function over time. Similarly, multiple large trials from the 1990s and 2000s failed to show any disease-modifying effect from medical therapy (EUROSCOP, Copenhagen Heart, ISOLDE, BRONCUS) (Decramer et al., 2011). Further, data from the Seven Countries Study show that there is a mortality benefit to smoking cessation, regardless of severity of lung disease (Pelkonen et al., 2000). This benefit is most likely driven by a reduction in cardiovascular mortality rather than an effect on respiratory-related mortality; however, the benefit to the patients remains the same.

The few large observational studies with a long follow-up period suggest that smoking cessation decreases the relative risk (relative to continued smoking) of

incident COPD and hospital admission with a COPD exacerbation. The risk reduction varies with duration of smoking cessation and cumulative tobacco exposure (pack-years of smoking) (Anthonisen et al., 2005).

In earlier studies, mortality rates due to COPD were paradoxically elevated in ex-smokers compared with current smokers for up to 10 years after smoking cessation but decreased thereafter. Many recent studies have not been of sufficient size or strength to clarify this issue, and reverse causality can also lead to underestimation of the benefits of cessation, even in studies that have shown some benefits. The available data show a permanently increased risk of morbidity and mortality due to COPD in ex-smokers compared with never-smokers.

Pharmacotherapy

Wide ranges of pharmacological therapies have been used to treat patients with COPD. These include short-acting bronchodilators (including β2-agonists [SABA] and anticholinergics), long-acting bronchodilators (including β2-agonists [LABA], and muscarinic antagonists [LAMA] such as tiotropium), inhaled corticosteroids (ICS), oral steroids, oral theophylline, antibiotics, and influenza and pneumococcal vaccines. As treatments have so far been shown to not to significantly reduce the progression or suppress the inflammation of COPD (Barnes, 2008) their main focus is on minimizing risk factors, improving symptoms, and preventing exacerbations; no treatment has convincingly been shown to significantly reduce mortality.

Earlier trials have been conducted evaluating the safety and efficacy of steroid therapy with results suggest a potential survival benefit associated with ICS therapy versus placebo (**Table 1.2**). Further to this, the TORCH (Towards a Revolution in COPD Health) trial, treatment with salmeterol plus fluticasone over 3 years showed a decrease in mortality that almost reached statistical significance and re-raised the possibility that pharmacotherapy could affect survival (Calverley et al., 2007). Among the observational cohorts, studies have demonstrated a potential reduction in risk with ICS, given alone or in combination with a LABA (**Table 1.2**). Given the borderline RCT results and heterogeneity of observational research, which have been criticised as subject to immortal-time bias (Suissa, 2004), there is a need to robustly synthesize the current evidence to understand the true survival benefit of inhaled steroid therapy.

Limited evidence has evaluated the survival benefit of treatment with bronchodilators. A meta-analysis (Sin et al., 2003) of nine randomised, placebo-controlled trials of LABA treatment, did not show any significant improvement in all-cause mortality with active treatment (RR=0.76; 95% CI: 0.39, 1.48). Most recently the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trial reported that tiotropium 18 µg once daily administered for up to 4 years in patients with COPD was associated with decreased mortality (Celli et al., 2009) suggesting that among a larger cohort of patients there may be an additional benefit of bronchodilation among patients with COPD.

TABLE1-2 SUMMARY OF DATA FROM RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIALS AND OBSERVATIONAL COHORT STUDIES INVESTIGATING THE EFFECT OF PHARMACOTHERAPY ON MORTALITY IN COPD PATIENTS

Source of data	Comparison	RR[a] (95% CI) of mortality	Statistical Significance
Clinical Trials for ICS			
(Burge et al., 2000)	FP vs placebo	0.77 (0.54, 1.11)	NS
(van der Valk et al., 2002)	FP vs placebo	0.98 (0.06, 15.55)	NS
(Wise et al., 2000)	Triamcinolone vs placebo	0.79 (0.40, 1.53)	NS
(Vestbo et al., 1999)	Budesonide vs placebo	0.80 (0.22, 2.92)	NS
(Pauwels et al., 1999)	Budesonide vs placebo	0.81 (0.22, 2.04)	NS
(Sin et al., 2003)	ICS vs placebo	0.78 (0.58, 1.05)	NS
(Sin and Man, 2005)	ICS vs placebo	0.73 (0.55, 0.96)	Significant
Clinical trials for LABA + ICS			
(Szafranski et al., 2003)	Budesonide+formoterol vs placebo	0.66 (0.24, 1.81)	NS

Source of data	Comparison	RR[a] (95% CI) of mortality	Statistical Significance
(Mahler et al., 2002)	FP+salmeterol vs placebo	0.16 (0.01, 3.01)	NS
Pooled summary (n=1,486) (Sin et al., 2003)	ICS+LABA vs placebo	0.52 (0.20, 1.34)	NS
(Calverley et al., 2007)	ICS + LABA vs placebo	0.83 (0.68,1.00)	NS
Observational Studies			
(Sin and Tu, 2001)	ICS vs no ICS	0.71 (0.65, 0.78)	Significant
(Soriano et al., 2002)	FP + salmeterol vs no ICS or LABA	0.48 (0.31, 0.73)	Significant
	FP alone vs no ICS or LABA	0.62 (0.45, 0.85)	Significant
	Salmeterol alone vs no ICS or LABA	0.79 (0.58, 1.07)	Significant
(Sin and Man, 2003)	ICS vs no ICS	0.75 (0.68, 0.82)	Significant
	Low-dose[b] ICS vs no ICS	0.77 (0.69, 0.86)	
	Medium-dose[b] ICS vs no ICS	0.48 (0.37, 0.63)	
	High-dose[b] ICS vs no ICS	0.55 (0.44, 0.69)	
(Suissa, 2003)	ICS vs no ICS Time fixed adjusted rate	0.69 (0.55, 0.86)	NS after controlling for time dependence
	ICS vs no ICS Time dependent rate	1.00 (0.79, 1.26)	
(Suissa, 2004)	ICS vs bronchodilators	0.66 (0.57, 0.76)	NS

Source of data	Comparison	RR[a] (95% CI) of mortality	Statistical Significance
(Fan et al., 2003)	Low-dose ICS vs no ICS	0.75 (0.53, 1.05)	NS
	Medium-/high-dose ICS vs no ICS	0.91 (0.73, 1.13)	
(Kiri et al., 2005)	ICS vs no ICS propensity scores	0.69 (0.052, 0.93)	Significant
	ICS vs no ICS nested case control	0.71 (0.56, 0.90)	
(Gershon et al., 2014)	ICS + LABA vs LABA Propensity score regression	0.92 (0.87,0.97)	Significant

[a]Hazard ratio. [b]Dose was converted to beclomethasone equivalents and classified as low (≤ 500 µg/day), medium (501–1000 µg/day), and high (>1000 µg/day).NS = Not statistically significant. FP = Fluticasone Propionate, ICS = Inhaled Corticosteroid, LABA = long acting beta-agonist, LAMA = long –acting anti-muscarinic antagonist. *Adapted from Mannino and Kiri 2006 Table 3* (Mannino and Kiri, 2006)

1.3 Electronic healthcare records

Broadly defined, EHRs represent longitudinal data (in electronic format) that are collected during routine delivery of health care. EHRs generally contain demographic, vital statistics, administrative, claims (medical and pharmacy), clinical, and patient-centred (e.g., originating from health-related quality-of-life instruments, home-monitoring devices, and frailty or caregiver assessments) data.

Utilisation of EHR has greatly increased over time and continues to enhance the ability to conduct epidemiological and clinical research. Usage of EHR present a number of advantages: (Menachemi and Collum, 2011)

- availability of data, studies are less costly and more timely than traditional data collection approaches e.g. prospective cohorts, RCTs
- size of data available, enabling researchers to evaluate multiple risk factors and/or outcomes simultaneously, to test associations in subpopulations, and to study rare outcomes
- broader population inclusion, increasing generalisability beyond that of RCT participants
- potential for wide data element coverage through linkages e.g. primary care medical records linked with secondary care inpatient data
- length and/or depth of available follow up, while traditional prospective studies must re-contact participants and may face difficulties with maintaining study samples

The scope of EHRs vary widely across the world. In the United Kingdom, routinely collected primary care data, anonymized at source, can be made available through the General Practice Research Database (now CPRD, Clinical Practice Research Datalink (Herrett et al., 2015b)). In addition to CPRD, other data providers also collate and provide primary care data for research purposes, QResearch (http://www.qresearch.org) and The Healthcare Improvement Network (THIN)(Blak et al., 2011)) are other examples. A similar development has taken place in the Netherlands, where, in the early 1990s, the Netherlands Institute for Health Services Research (NIVEL) developed its Netherlands Information Network of General Practice, now named NIVEL Primary Care Database (NIVEL-PCD) (Schweikardt et al., 2016). In the United States, administrative claims data like IBM's MarketScan

(Butler et al., 2021) and Medicare for adults over the age of 65 are widely used for epidemiological research (Verheij et al., 2018).

Although easier to obtain, EHR data present unique challenges to epidemiological research. The EHR may reflect single components of care (e.g., primary care, emergency department, and intensive care unit) or data from an integrated hospital-wide or inter-hospital linked system. EHRs may also change over time, reflecting evolving technology capabilities or external influences (e.g., changes in type of data collected related to coding, guidelines, or reimbursement practices). The main consideration of using EHR data is that the data are not collected for research purposes and are generated as part of standard clinical practice or for financial purposes (e.g.health insurance payments). Repurposing these data for research creates the potential for information bias, related to misclassification, mismeasurement, or non-random missingness of data used to characterize a population. As such, efforts are made to increase reliability and mitigate the limitations, for example validation of key clinical diagnostic definitions is possible and frequently performed for prevalent chronic diseases like COPD (Nissen et al., 2019, Quint et al., 2014b).

1.3.1 Use of EHR to describe COPD mortality

Mortality data can be reported in many ways, for different purposes. Absolute death counts are useful to clinicians and for local use; crude mortality rates allow comparisons with other conditions and are useful for regional healthcare planning. Finally, standardised mortality rates are valuable for comparison between countries and/or period by adjusting for differences in the demographic composition.

Previous studies describing COPD mortality have relied on population death statistics and in-hospital data, and while these data sources are widely used to compare across countries, they often underestimate the true disease-specific mortality, as many patients remain undiagnosed. Further, COPD as a cause of death may be cited as a contributory, rather than an underlying cause, or may not be cited at all on death certificates. For example, in an epidemiological study of causes of death among a cohort of diagnosed COPD patients in England and Wales between 1993–1999, obstructive lung disease was mentioned on 8.0% of death certificates and in 59.8% of these, the underlying cause of death was attributed to obstructive

lung disease (Hansell et al., 2003a). In the TORCH trial, the first international trial of patients with moderate to severe COPD maintenance therapy that defined all-cause mortality as a primary outcome (McGarvey et al., 2007), among 395 adjudicated deaths that also had informative death certificates, COPD was mentioned on only 58% of the certificates. Even among those patients whose adjudicated cause of death was a COPD exacerbation (n = 127), COPD was underreported: COPD was not listed as the main cause of death in 34% and was not mentioned at all in 21% of these death certificates (Drummond et al., 2010).

Further, few clinical trials focus on mortality as a primary endpoint, historically pharmacotherapy trials in COPD have investigated mortality endpoints as drug safety related events or in post-hoc analysis and are often underpowered (Han et al., 2018, Chen et al., 2020, Beeh et al., 2013). Another key limitation of the larger COPD trials has been their ability to follow patients long-term. The TORCH trial followed patients for 3 years (McGarvey et al., 2007). Similarly, the SUMMIT ("Study to Understand Mortality and Morbidity in COPD") trial also followed patients between 5-44 months to evaluate all-cause mortality (Vestbo et al., 2013). The UPLIFT trial followed patients for 4-years (Celli et al., 2009).

To advance scientific knowledge in this field, my research utilises large datasets of routinely collected data, with longitudinal information about diagnoses, investigations, prescriptions, hospitalisations, mortality, and from both the general population and a large sample of people with physician-recorded diagnosis of COPD. After carefully considering various possible sources of data, such as prospectively collected cohort or trial data, EHR data appeared as the most appropriate data source that could provide the richness, breadth and long-term perspective required for this research.

1.4 Rationale

COPD represents an important and growing healthcare concern as a leading cause of morbidity worldwide. Particularly worrying is the marked increase in deaths due to COPD over the past couple of decades, a trend that is predicted to continue. In addition, cause for concern is the dramatic rise in COPD mortality seen in women in many countries. Improved treatment of COPD, and the ability of targeted interventions to improve survival, therefore represents an important goal.

Of all the descriptive epidemiological data available for COPD, mortality data are the most readily accessible and can provide reliable trends in disease burden. Historically, the impact of COPD had been underestimated due to a lack of accurate epidemiologic data, misdiagnosis, and inconsistent use of clinical codes when reporting COPD as a cause of death. However, in recent decades the approach of using the single term COPD has been championed in global and national guidelines, to improve awareness, simplify the coding and, ultimately, lead to greater accuracy in death certification for COPD.

If COPD patients at highest risk of specific causes of death can be identified using routinely collected data, then healthcare practitioners can ensure that they are targeted for interventions and trials of treatments; this in turn will potentially reduce excess deaths in a greater proportion of the COPD population.

1.5 Aims and objectives

The overall aim of this thesis was to describe the mortality burden associated with a diagnosis of COPD in the UK. It is hoped that the findings presented here provide a contemporary understanding of COPD mortality epidemiology, and further evidence to shape change in clinical practice by defining outcome measures for evaluation of preventative strategies and can ultimately help to prevent excess deaths.

This thesis includes four overarching aims with more specific sub aims, all of which contribute to understanding the mortality burden associated with COPD. **Figure 1.7** depicts the structure of these aims to illustrate how they contribute to the thesis overall aim.

AIM 1 To investigate COPD mortality in the UK

AIM 1.1 Describe COPD mortality rates in the UK over the last 10 years among the general population

Global and regional trends in COPD mortality have been well-documented (Burney et al., 2015). With increasing average life expectancy in Western populations and decreasing prevalence of smoking, there is a need to understand the contemporary trends of COPD mortality in the UK, a country which has the highest respiratory-related mortality in Europe (Salciccioli et al., 2018). This aim sets the context for the preceding aims by describing the trends in COPD mortality among the general population in the UK and providing a comprehensive overview of COPD mortality using population statistics that are frequently cited in government reports and clinical guidelines.

AIM 1.2 Determine the impact of environmental factors such as geographic area, season, pollutants, and temperature on COPD mortality in the UK

Globally, the level of tobacco smoking has decreased by 27.5% in the past 30 years. Concurrently, indoor particulate matter pollution from solid fuels (PM_{10} & $PM_{2.5}$) has decreased by 45.8%, while the level of exposure to ambient $PM_{2.5}$ has increased by 41.2% giving rise to speculation that exposure to ambient $PM_{2.5}$ might become a greater cause of COPD morbidity (Yang et al., 2021). Numerous studies have reported associations between $PM_{2.5}$ and COPD hospitalizations and mortality in cities worldwide (Zhu et al., 2020). Therefore, for this second part of aim 1 I have

focused on the relationship between $PM_{2.5}$ and daily temperature and explored how these relate to COPD-recorded mortality. This is the first study to combine population data in England and Wales at a granular geographic area level to understand the impact of pollution and temperature on COPD mortality.

AIM 2 To estimate the proportion of people with a diagnosis of COPD prior to COPD-recorded death and understand factors associated with missing lifetime COPD diagnosis

Although evidence has shown that there are significant delays in COPD diagnosis in the UK and potential for millions of patients to be missed, there is little contemporary evidence describing the impact of missed COPD diagnosis with respect to COPD related mortality. In this study, I identify people whose underlying cause of death is recorded as COPD and retrospectively interrogate medical records for a prior diagnosis of COPD.

AIM 3 To calculate all-cause and cause-specific mortality rates for COPD

AIM 3.1 Describe the current mortality trends among those with a diagnosis of COPD

Many studies have investigated respiratory deaths reported on death certificates; (BLF, 2016a, Hansell et al., 2003b, Soriano et al., 2017); however, relying on death certificates alone means that a large number of COPD patients are missed. Previous studies have found that anywhere between 6 and 82% of patients with a chronic respiratory disease have their diagnosis listed anywhere on their death certificate. (Drummond et al., 2010, Higgins and Keller, 1989, Hutchinson et al., 2014, Konietzko et al., 1969). Therefore, the first part of this aim is to describe mortality rates of people with a diagnosis of COPD. This is first and largest observational study to estimate mortality rates using a nationally representative cohort of patients with physician diagnosed COPD.

AIM 3.2 Determine the major underlying causes of death among COPD patients and changes over time

Previous studies have reported that globally approximately 1/3 of COPD patients die of respiratory disease, 1/3 of cardiovascular disease and 1/3 of lung cancer (Mathers and Loncar, 2006). However, these studies are dated and whether there have been shifts in causes of mortality over the last 10 years in COPD patients has not been studied. Management of cardiovascular disease has improved significantly over the past 10 years, and it is possible that fewer COPD patients are dying of cardiovascular disease, and more are dying of lung cancer, or that COPD patients are dying of different things now compared to 10 years ago. If this is the case, perhaps management efforts should be reconsidered. In this aim, I highlight the leading causes of death among COPD patients and how these have changed over the last 10 years.

AIM 4 To estimate the excess risk of death among patients with COPD while taking into account competing risks

Following the previous aim 3.2, I set out to quantify and explain excess mortality attributed to each cause of death and to assess which cause fundamentally drives excess mortality among COPD patients when compared to the general population.

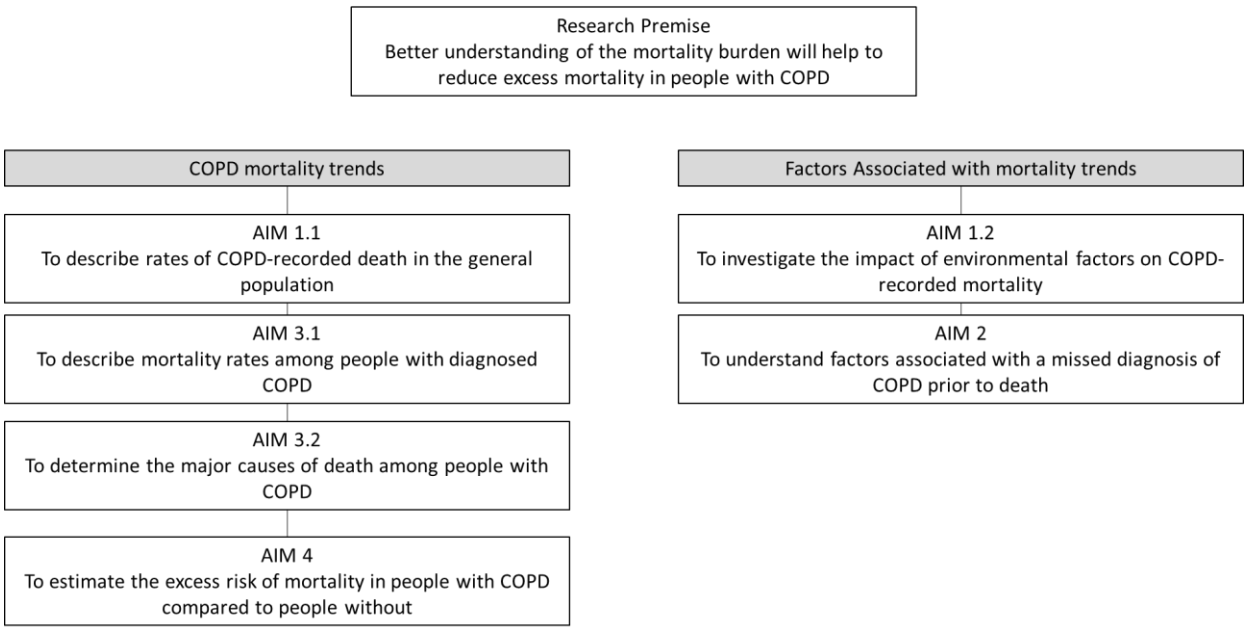


FIGURE 1-7 THESIS STRUCTURE

2 Chapter 2: Data Sources

In this chapter, I describe the data sources and methods of data extraction, generalisability, strengths and limitations of the individual datasets. More specific details pertaining to methods and statistical analysis are provided within each chapter.

2.1 Background

This thesis will primarily utilise existing data from routinely collected data, including data from UK primary care electronic health records (Clinical Practice Research Datalink - CPRD), hospital episode statistics (HES), mortality data (Office of National Statistics - ONS) and deprivation data (Index of Multiple Deprivation- IMD), pollution data from the Department for Environment, Food and Rural Affairs (DEFRA), and temperature data from the UK Meteorological Office (Met Office). **Table 2.1** outlines the data sources used for each research aim.

TABLE 2-1 DATA SOURCES USED FOR SPECIFIC AIMS

AIM	Data Sources used	Topic
1.1 1.2	ONS, DEFRA, Met Office	COPD mortality rates in the general population and environmental factors
2	CPRD (GOLD & Aurum), HES, IMD, ONS	Factors associated with a missed diagnosis of COPD
3.1 3.2	CPRD (GOLD), HES, IMD, ONS	Mortality rates among those with a diagnosis of COPD
4	CPRD (GOLD), IMD, ONS	Excess risk of death among those with COPD compared to the general population

2.2 Office for National Statistics

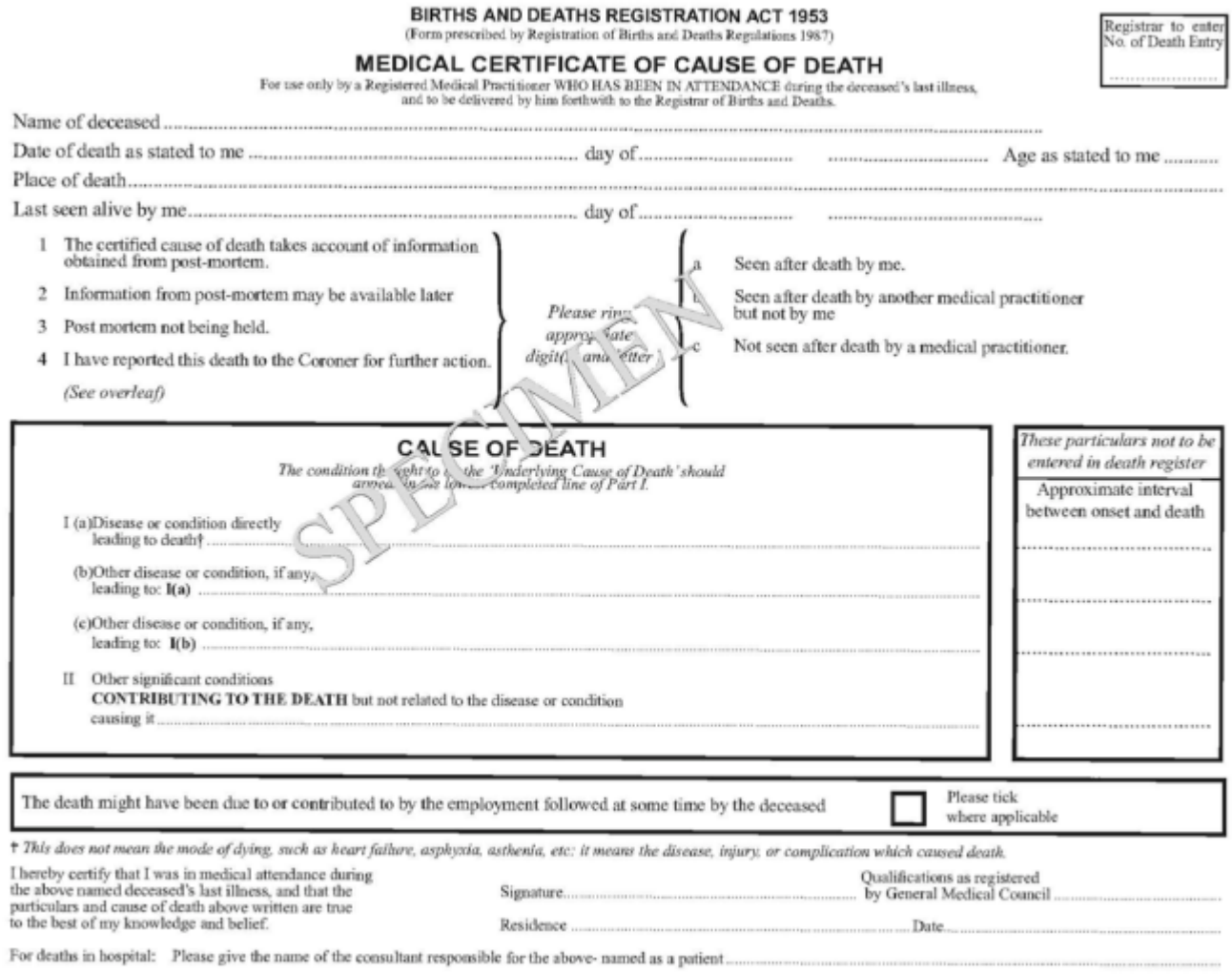
The Office for National Statistic (ONS) is a UK government agency that collects, analyses and disseminates statistics about the UK's economy, society and population. For the purposes of this thesis I obtained mortality data and population size estimates, both of which are open access to the public (ONS, 2020a, ONS, 2020b). Death registration data includes information on the official date and causes of death, available at https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths . In addition, current and historic population estimates (by age, sex, country and region) are available at https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates.

2.2.1 Death registration

The Births and Deaths Registration Act (1836) made it a legal requirement for all deaths to be registered from 1 July 1837. Historically, only the underlying cause of death on death certificates had been routinely coded and analysed in most countries including England. Rules for the selection of the underlying cause of death changed in England in 1984 and 1993, with substantial impact on mortality rates for pneumonia, and a lesser but still important impact on some other diseases (Brock et al., 2006).

Data collection

ONS mortality statistics are based on information recorded when deaths are certified and registered. A medical practitioner, using the Medical Certificate of Cause of Death (MCCD) (**Figure 2.1**), certifies most deaths. An informant – usually a near relative of the deceased, takes this certificate to a registrar. Before submitting a death registration through the Registration Online (RON) system, the registrar will verify that all the information provided has been entered accurately. There are some automatic validation checks within RON to help the registrar with this process. The cause of death reported represents the final underlying cause of death. This takes account of additional information received from medical practitioners or coroners after the death has been registered; around 40% of deaths are referred to the coroner.



BIRTHS AND DEATHS REGISTRATION ACT 1953

(Form prescribed by Registration of Births and Deaths Regulations 1987)

Registrar to enter No. of Death Entry

MEDICAL CERTIFICATE OF CAUSE OF DEATH

For use only by a Registered Medical Practitioner WHO HAS BEEN IN ATTENDANCE during the deceased's last illness, and to be delivered by him forthwith to the Registrar of Births and Deaths.

Name of deceased .....

Date of death as stated to me ..... day of .... Age as stated to me .....

Place of death .....

Last seen alive by me ..... day of ....

1 The certified cause of death takes account of information obtained from post-mortem.

2 Information from post-mortem may be available later

3 Post mortem not being held.

4 I have reported this death to the Coroner for further action.

(See overleaf)

Please ring appropriate digit(s) and letter

a Seen after death by me.

b Seen after death by another medical practitioner but not by me

c Not seen after death by a medical practitioner.

SPECIMEN

CAUSE OF DEATH

The condition thought to be the 'Underlying Cause of Death' should be entered on the lowest completed line of Part I.

I (a) Disease or condition directly leading to death† .....

(b) Other disease or condition, if any, leading to: I(a) .....

(c) Other disease or condition, if any, leading to: I(b) .....

II Other significant conditions CONTRIBUTING TO THE DEATH but not related to the disease or condition causing it .....

These particulars not to be entered in death register

Approximate interval between onset and death

The death might have been due to or contributed to by the employment followed at some time by the deceased ☐ Please tick where applicable

† This does not mean the mode of dying, such as heart failure, asphyxia, asthenia, etc: it means the disease, injury, or complication which caused death.

I hereby certify that I was in medical attendance during the above named deceased's last illness, and that the particulars and cause of death above written are true to the best of my knowledge and belief.

Signature ..... Qualifications as registered by General Medical Council .....

Residence ..... Date .....

For deaths in hospital: Please give the name of the consultant responsible for the above- named as a patient .....

FIGURE 2-1 MEDICAL CERTIFICATE OF CAUSE OF DEATH

Reproduced from the Office For National Statistics 2020 (ONS, 2020b)

Cause of death coding

The ONS code cause of death using the World Health Organization's (WHO) International Classification of Diseases, Tenth Revision (ICD-10). Most deaths (around 80%) have the underlying cause of death coded automatically using coding software. Experienced coders code the remainder manually. Manual coding is necessary for deaths involving a coroner's inquest. Using an automated coding tool improves the international and temporal comparability of mortality statistics. Periodical reports on persistent coding problems are referred to a medical epidemiologist and to international forums (Coleman and Aylin, 2000).

ICD-10 was introduced in England and Wales in January 2001. Until December 2010, ONS used the Mortality Medical Data System (MMDS) ICD-10 version 2001.2 software provided by the United States National Centre for Health Statistics (NCHS) to code cause of death. In January 2011, this was updated to version 2010, which incorporated most of the WHO amendments authorised up to 2009. On 1 January 2014, ONS changed the software used to code cause of death to a package called IRIS (version 2013)(Wells, 2014). Multiple-cause coding was introduced as standard practice in England from 1993, but English national information about multiple-cause mortality for longer-term trends is unavailable. Also worth noting, that as well as the coding changes, there have been changes in clinical terminology in the past 25 years that will have affected statistics for chronic bronchitis and other obstructive lung diseases (Goldacre et al., 2004).

2.2.2 Linking mortality data to other data sets

The General Register Office must report every death in the UK and information is recorded by the ONS. A medical certificate is required upon death which lists the cause (or causes) of death. The certificate must be signed by a doctor and delivered to the general register office. All information recorded on death certificates is captured by ONS, which makes ONS more detailed than the death information recorded in EHR. ONS contains the date of death recorded by the general register office, the underlying cause of death, and up to 15 contributory causes of death. ONS mortality data is considered the “gold standard” in recorded death data in the UK. More than 50% of deaths in the UK do not occur in hospital and therefore cannot be captured in hospital administrative data (Gallagher et al., 2019); therefore, studies that include death as a main outcome should link EHR with ONS (Delmestri and Prieto-Alhambra, 2020). Interestingly, a study investigating the accuracy of death recording in CPRD, one of the largest EHR databases available in the UK, compared with ONS found that 69.7% of deaths were recorded on the same day in both databases (Gallagher et al., 2019).

2.3 The Clinical Practice Research Datalink

The CPRD provide primary care databases of anonymised medical records from general practitioners from 1987 to the present day, with coverage of over 60 million patients from over 2,000 practices in the UK (CPRD, 2021). With 13 million active (alive, currently registered) patients meeting quality criteria, approximately 20%[2] of the UK population are included and patients are broadly representative of the UK general population in terms of age, sex and ethnicity. General practitioners are the gatekeepers of primary care and specialist referrals in the UK. The CPRD primary care databases are therefore rich sources of health data for research, including data on demographics, symptoms, tests, diagnoses, therapies, health-related behaviours and referrals to secondary care. CPRD data are very widely used internationally for epidemiological research and have been used to produce over 1,000 research studies, published in peer-reviewed journals across a broad range of health outcomes (Herrett et al., 2015a, Tate et al., 2014).

CPRD provide two databases; CPRD GOLD and CPRD Aurum based on different software systems used to collect data at GP practices. The number of GPs using Vision software (the basis of CPRD GOLD) has been declining in recent years and now represents less than 5% of all GP software market share in England, while EMIS (the basis for CPRD Aurum) has over 56% of the GP software market share. In October 2017, CPRD launched its second database based on a different general practice data collection software in England only; CPRD Aurum. Like CPRD GOLD, CPRD Aurum contains electronic healthcare records recorded by GPs to facilitate clinical care using a different GP patient management software, EMIS. Unlike the Vision software that supports CPRD GOLD, EMIS was not developed with the intent to provide data for medical research. To date, patients included in CPRD Aurum are representative of the general UK population in terms of geographical spread, socioeconomic deprivation, age, and gender (Wolf et al., 2019).

2.3.1 Structure and organisation of CPRD data

One of the core challenges of using the CPRD for research is that the EHR data are not in a format appropriate for analysis. The structure of the database reflects the primary purpose of data collection, which is essentially administrative and clinical.

[2] Source: June 2021 – CPRD Aurum Release Notes

Data are present in a longitudinal format across different tables within and across data sources and need to be combined appropriately to create a single flat file that can be used for analysis. This process is complex and requires careful evaluation of variable definitions, linkage eligibility, and relational keys but also of the varying levels of detail and specificity within and between health care settings or health care providers.

CPRD GOLD data is available as ten structured text files linked by a patient, practice or staff identifier. **Figure 2.2** depicts the relational structure of the GOLD data. Data are supplied in a format that can be imported into standard statistical software to enable code searching, merging of records and building of analytical cohorts.

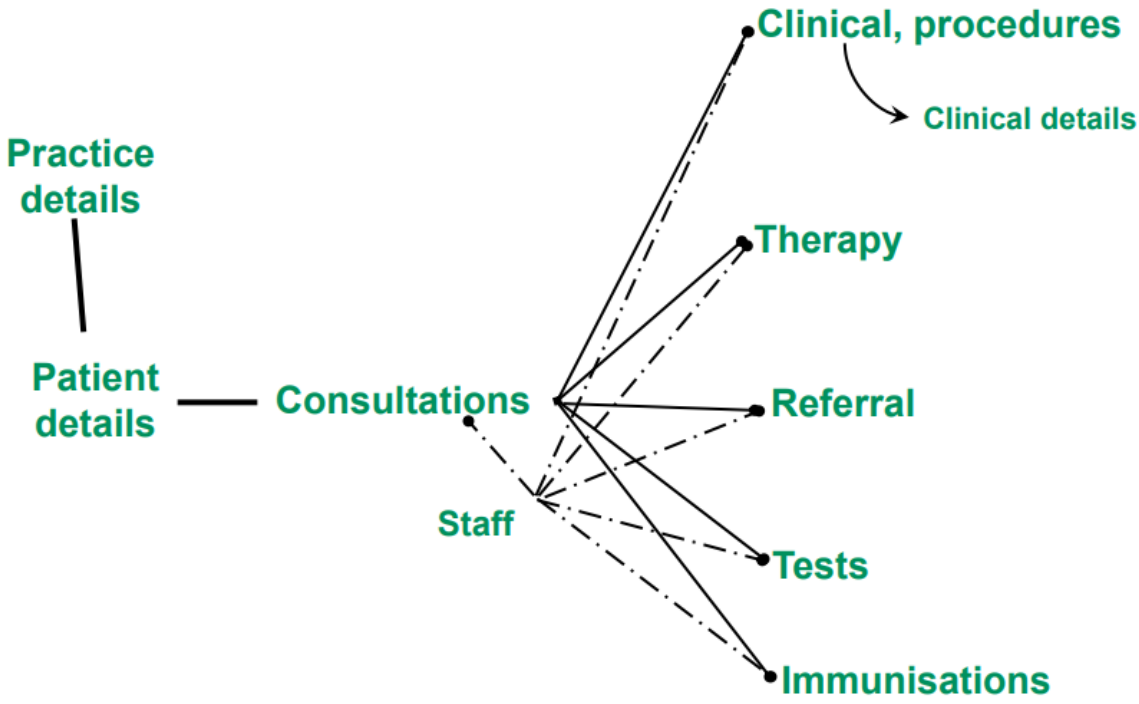


FIGURE 2-2 CPRD GOLD STRUCTURE[3]

Similarly, CPRD Aurum is available to researchers as eight files in text format as representation in (**Figure 2.3**). A number of GP practices that previously contributed data to CPRD GOLD, when using InPS Vision software, transitioned to EMIS software and agreed to contribute data to CPRD Aurum. In this situation, CPRD holds duplicate historical data for such practices in the CPRD GOLD and CPRD Aurum databases. Combination of data from both databases for a study is possible with a migrators file to identify the overlapping practices and dates:

[3] Source: CPRD GOLD eLearning

"VisionToEmisMigrators.txt". This migrators file is refreshed every month with the CPRD Aurum monthly build. For the purposes of this thesis, migrating practices were removed from the CPRD GOLD data. Further information on the compilation of the study cohort is available in **Section 4.3**.

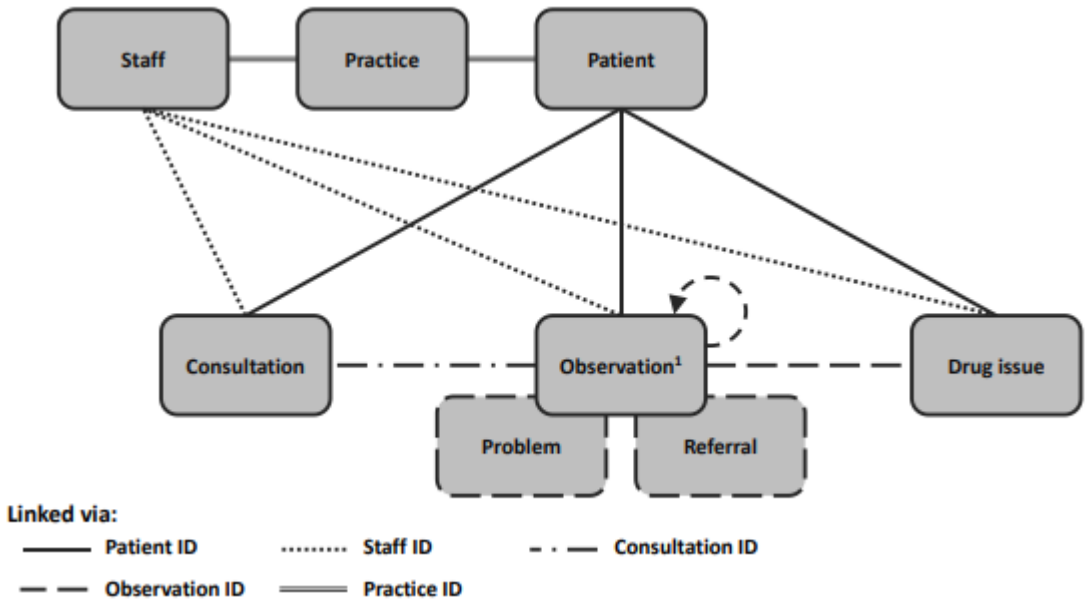


FIGURE 2-3 CPRD AURUM DATASET STRUCTURE[4]

2.3.2 Coding

The structured coding system used across EHR data facilitates operations, ensures data integrity, avoids duplication, and reduces required storage space. More complex clinical concepts, such as symptoms, diagnoses, procedures, are also coded, and these typically present with a very large breadth of codes and descriptors. In the CPRD data are captured by GPs using the Vision or EMIS patient management software platform, clinical concepts are represented by 'Read' or 'SNOMED' codes (both are then mapped to unique 'medcodes'), prescriptions are coded using the British National Formulary (BNF) and the Dictionary of Medicines and Devices (dm+d) codes, a subset of the SNOMED CT terminology, and have been assigned a "ProdCode.", and in secondary care settings (including HES and ONS data linked to CPRD), ICD-10 codes are used.

[4] Source: CPRD Aurum eLearning

2.3.3 Quality and completeness

Data from practices that have consented to contribute data to CPRD are regularly uploaded to the CPRD servers. Data are then processed and go through quality checks before being pseudonymised and made available for research (Wolf et al., 2019).

CPRD creates a new version of the CPRD databases on a monthly basis; each new monthly "build" of the database contains:

- all the data from the previous version of the database; plus
- all the patient data collections that have been processed since the previous version was created.

If a patient leaves a participating GP practice or dies, their medical records are kept in all future monthly versions of the database. If, however, a practice decides to opt out, then records from that practice will not be included in future monthly builds. The same is true of individual patients from participating GP practices who declare their wish to opt out of the scheme: their records will no longer be included in subsequent monthly versions of the database. It is for these reasons that it is recommended that researchers use the same CPRD database build for any given piece of analysis, and not attempt to append data from different versions.

CPRD carry out, before the data are released to researcher's, two quality assurance processes. These generate a number of data quality markers (variables) which are added to the dataset before it is released to users. These quality indicators are designed to reassure users that flagged data meet the following quality criteria:

- there is logical consistency in patient data (e.g. the patient has a date of birth that predates their registration date at a GP practice);
- longitudinal information is continuous, with no gaps in the recording at either the individual patient or the practice level; and
- practice level data are complete and plausible.

The quality markers are defined as:

- an acceptability flag which is used at the individual patient level; and
- the "up-to-standard" (UTS) date which is used at the practice level

In order to meet the data quality assurance criterion at the patient level and be flagged as “acceptable” patients must pass all the following checks:

- they must have a valid gender and birth date;
- their registration dates must be logically consistent and valid;
- patients who have transferred out of a practice must also have a transfer-out reason and vice versa; and
- they must have at least one valid, non-missing event date.

Practices are deemed to be UTS if they have no meaningful gaps in data recording (i.e. there are no periods during which time the practice appears to be recording an unusually low number of weekly events compared with its five-week average) and if their rate of deaths is close to the expected level. Data from each practice can be used for research after the UTS date.

2.3.4 Governance

CPRD is joint venture from the Medicines and Healthcare Regulatory Agency (MHRA) and the National Institute for Health Research (NIHR). It is owned by the UK Department of Health and operates within the MHRA. CPRD itself has National Research Ethics Service Committee (NRES) ethics approval for the collection and supply of CPRD data and established linked databases for observational research. CPRD must meet UK and European laws of confidentiality to protect patient identities because patient consent has not been given. Therefore, patient identifiers are kept separate from any clinical data so that CPRD and researchers are unable to identify patients from the data. Prior to extracting CPRD data, approval from an Independent Scientific Advisory Committee (ISAC) is required. Approval is needed because patient level data is being requested. To do this an ISAC form must be submitted. The form describes the research project, the funding source for the study, specific details on how and where the data will be accessed and processed and data linkages that will be required.

2.4 EHR Linkages

Use of EHR for research purposes requires sound knowledge of the data resource. Each resource must be considered and evaluated according to the validity of each data element, the reason the data are recorded, and types of data available (inpatient, outpatient, lab data, etc.). Often the scope of one dataset is insufficient to cover the continuum of care that patients receive; therefore, linking data sets is required to increase visibility of patients' interactions with the healthcare system.

CPRD can link their two databases, CPRD GOLD and CPRD Aurum, to other databases. Data linkage in England is carried out by the Trusted Third Party, NHS Digital (Padmanabhan et al., 2019). CPRD operates a general practice 'opt-in' and patient 'opt-out' system. GP practices choose to contribute de-identified patient data to CPRD for all patients, except for those who have opted-out from the sharing of their patient record with CPRD or NHS Digital. General practice software suppliers submit personal identifiers (NHS number, gender, date of birth and postcode) to NHS Digital, alongside system patient and practice identifiers. Data custodians for external datasets also send patient identifiers to NHS Digital. NHS Digital uses identifiers to link the datasets using an 8-stage deterministic methodology. CPRD subsequently receives a de-identified linked cohort file and provides researchers with anonymised linked data and metadata detailing the linkage process. In the dataset provided by CPRD for use in this thesis, linkage was available for 75% of English practices covering approximately 50% of all patients in CPRD.

The databases that can be linked with CPRD used in this research include Hospital Episode Statistics (HES), a secondary care database, the Office of National Statistics (ONS), mortality data (detailed earlier in **Section 2.2**), and the Index of Multiple deprivation (IMD), socioeconomic deprivation data.

2.4.1 Hospital Episode Statistics

Hospital Episode Statistics (HES) is a data warehouse containing details of all admissions to NHS hospitals in England. It includes private patients treated in NHS hospitals, patients who were resident outside of England and care delivered by treatment centres (including those in the independent sector) funded by the NHS. HES also contains details of all NHS outpatient appointments in England. HES contains over 200 million records. Admitted patient care data is available from 1989

onwards, with more than 18 million new inpatient records with over 350 data items per record added each year. Outpatient attendance data has been collected since 2003, with more than 90 million new records added each year. HES data covers all NHS Clinical Commissioning Groups (CCGs) in England, including:

- private patients treated in NHS hospitals
- patients resident outside of England
- care delivered by treatment centres (including those in the independent sector) funded by the NHS

Each HES record contains a wide range of information about an individual patient admitted to an NHS hospital. For example:

- clinical information about diagnoses and operations
- information about the patient, such as age group, gender and ethnic category
- administrative information, such as time waited and date of admission
- geographical information on where the patient was treated and the area in which they lived

2.4.2 Indices of Multiple Deprivation

The Indices of Multiple Deprivation (IMD) provides a measure of a patient's socioeconomic status in relation to their postcode (Evans et al., 2016) and is based on seven domains of deprivation. The domains are combined using the following weights to produce the overall IMD:

- Income Deprivation (22.5%)
- Employment Deprivation (22.5%)
- Education, Skills and Training Deprivation (13.5%)
- Health Deprivation and Disability (13.5%)
- Crime (9.3%)
- Barriers to Housing and Services (9.3%)
- Living Environment Deprivation (9.3%)

The IMD is based on LSOA (Lower-layer Super Output Areas), small areas designed to be of a similar population size, with an average of approximately 1,500 residents or 650 households. There are 32,844 LSOAs in England. The Office produced them for National Statistics for the reporting of small area statistics.

IMD measures of relative deprivation can be linked to CPRD data through the patient and/or practice postcode. This measure can be used as a proxy for socio-demographic and socio-economic data, which are generally poorly recorded in the primary care data, as they do not directly relate to a patient's care. Data are provided as quintiles or deciles of the deprivation score or rank to prevent disclosure of patient or practice area. The postcode of the practice or patient residence is mapped to LSOA using their postcodes.

2.5 Environmental data

In addition to patient health data, in collaboration with researchers at the London School of Hygiene and Tropical Medicine, I was able to conduct research using data on pollution and temperature in order to understand how these factors relate to COPD mortality among the general population.

2.5.1 Pollution data: The Department for Environment, Food and Rural Affairs

In the UK, land surface pollutant observations are recorded by the Department for Environment, Food and Rural Affairs (DEFRA) Automatic Urban and Rural Network (AURN), with a network of ~ 600 hourly measuring sensors.

Daily PM_{10} and $PM_{2.5}$ ($\mu g/m^3$) measurements are available from five monitoring network sources through the Openair project (Carslaw and Ropkins, 2012) and the related R package openair (Carslaw and Ropkins, 2015): AURN, Air Quality England, King's College London, Scotland Air Quality Network, and Wales Air Quality Network . These data, while being constant in time, are defined at a very high spatial resolution given by the LSOA geography. **Figure 2.4** shows the location of the monitors across Great Britain.

Schneider et al. compiled daily concentrations of $PM_{2.5}$ over all 234.429 1 km grid-cells across Great Britain in the period 2008–2018 using a four-stage satellite-based machine learning model (Schneider et al., 2020). Stage-1 applied a random forest (RF) algorithm to predict $PM_{2.5}$ concentrations in monitors with only PM_{10} records. Stage-2 used RF models to impute missing satellite aerosol optical depth (AOD) from Terra and Aqua satellites, using modelled-AOD from the Copernicus Atmosphere Monitoring Service reanalysis provided by the European Centre for Medium-Range Weather Forecasts (Bozzo et al., 2017). Stage-3 combined the output from Stage-1 and Stage-2 with a list of spatial and spatio-temporal synchronised predictors to estimate $PM_{2.5}$ concentrations at the locations of the monitors. Stage-4 used the Stage-3 model to predict daily $PM_{2.5}$ across the whole of the UK.

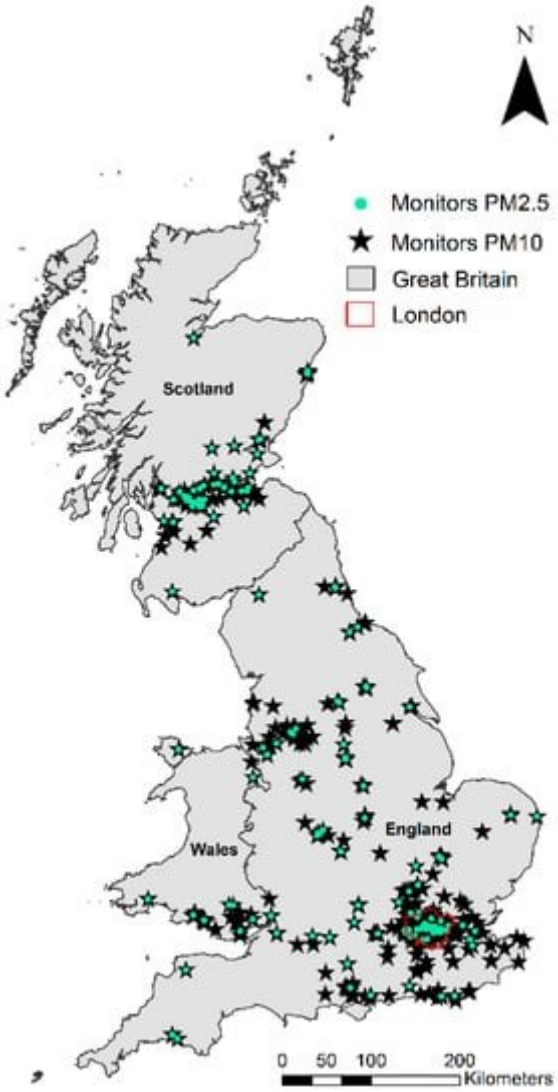


FIGURE 2-4 SPATIAL DISTRIBUTION OF 581 PM_{10} AND $PM_{2.5}$ MONITORS ACROSS GREAT BRITAIN BETWEEN 2008-2018

Reproduced from Schneider et al 2020 (Figure 1) (Schneider et al., 2020)

2.5.2 Temperature data: The UK Meteorological Office

The UK Meteorological Office (Met Office) has a network of ~ 200 hourly measuring meteorological stations distributed across the country as part of the Met Office Integrated Data System (MIDAS). Daily minimum and maximum temperatures by 1x1km grid are compiled into HadUK-Grid which is stored at the Centre for Environmental Data Analysis archive (http://archive.ceda.ac.uk/).

Gasparrini et al. extracted a daily series of air temperature between 2000 and 2018 in England and Wales at LSOA (Gasparrini et al., 2021). The average daily

temperature time series in °C, were then derived by computing the area-weighted average of the values of all the grid cells intersecting the LSOA boundaries, with weights proportional to the intersection areas.

3 Chapter 3: Mortality rates and environmental factors

This chapter describes the first piece of analysis, the aim of which was to describe the trends in COPD mortality among the general population and understand the role of environmental factors, in particular air pollution and changes in temperature. This work benefitted from the input of collaborators at the London School of Hygiene and Tropical Medicine. My role consisted of conducting the mortality rate analyses associated with aim 1.1 and providing the mortality definitions for aim 1.2.

Parts of the research presented in this chapter has been previously published at Gayle, A.V., Quint, J.K. and Fuertes, E.I., 2021. Understanding the relationships between environmental factors and exacerbations of COPD. *Expert Review of Respiratory Medicine*, 15(1), pp.39-50.

3.1 Background

Over the 20th century in the UK, mortality rates fell in both sexes, at all ages. In more recent decades, improvements in cardiovascular disease mortality through a combination of health care improvements, reductions in smoking and occupational changes have helped improve the proportion of people reaching older ages, with the majority of further improvements in survival rates for younger people anticipated to continue at older ages in future. However, since 2010–2011, mortality improvements have significantly slowed or completely stalled, raising questions about where progress can be made among the underlying causes of death (Marshall et al., 2019). Respiratory diseases are reported to be responsible for 20% of all deaths in the UK, mostly due to lung cancer, COPD, and pneumonia (BLF, 2016a). With the prevalence of smoking declining (Cornish et al., 2019), it's not known whether the stagnant overall mortality rates are similar for respiratory disease.

There has been increased attention to the anticipated effects of climate change, including overall warmer temperatures as well as temperature variability and extreme weather conditions; these have been shown to impact people living with underlying cardiac and respiratory diseases, including COPD, who are at increased risk for adverse health effects of extreme heat and cold exposure (Hansel et al., 2016). Studies have shown an association between change in seasons and risk of COPD mortality. A study across 12 U.S. cities estimated that the effect of hot temperatures during summertime can increase the risk of death attributable to COPD by as much as 25% (Braga et al., 2002). Ryti et al. previously conducted a systematic review and meta-analysis on the association between cold spells and mortality from respiratory diseases, revealing positive associations (RR 1.21; 95%CI: 0.97-1.51) across 9 studies (Ryti et al., 2016). Previously Gasparrini et al conducted an assessment of temperature-related mortality in England and Wales concluding that on average an excess of 801 and 57,803 deaths occur every year due to exposure to heat and cold, respectively, corresponding to a standardised rate of 1.46 and 102.88 deaths per 100,000 person-years(Gasparrini et al., 2021). However, it is unknown whether these relationships hold true in relation to COPD-related mortality.

The annual mortality burden in the UK from exposure to outdoor air pollution is estimated at around 40,000 deaths per year (Holgate et al., 2016). $PM_{2.5}$ is the most

widely studied air pollutant and is composed of metals, elementary carbon, organic carbon, and chemical components. It is of particular importance because its high size to weight ratio allows binding of various toxic compounds, which can then be transported to the lower regions of the lung because of $PM_{2.5}$'s small size. Previous studies have shown that $PM_{2.5}$ is strongly associated with mortality due to respiratory diseases. In a meta-analysis including 37 studies, Devries et al. found an increased risk of COPD mortality associated with exposure to $PM_{2.5}$ (RR = 1.048, 95% CI 1.019–1.078 per 10μg/m^3 increase in pollutant concentration) (DeVries et al., 2017). However, this estimate does not include data from the UK. Further, the UK in 2019 was ranked 21st out of countries with the lowest levels of $PM_{2.5}$ nationally on IQAir's World's Most Polluted Countries 2019 report, with an annual average concentration of 10.5 μg/m^3 (IQAir, 2020). Despite low levels of pollution, elevated risks for respiratory-related mortality are still observed in countries with similarly low levels of pollution (Hales et al., 2021). This association may also hold for respiratory mortality in the UK.

The exposure reduction target for $PM_{2.5}$ (an annual mean of 25 μg m^{-3} and a target to reduce population-weighted average concentrations by 15% between 2010 and 2020) by The UK Committee on the Medical Effects of Air Pollutants (COMEAP) marked the first recommendation to legislate an aim to improve overall population health burden rather than solely to attain a particular target pollutant concentration (COMEAP, 2009). This call was further echoed in response to the report "Prevention of Future Deaths" (following the inquest into the death of Ella Adoo-Kissi-Debrah), which recently prompted the Royal College of Physicians to urge the UK government to "set legally binding targets for $PM_{2.5}$ based on WHO guidelines to reduce the number of deaths from air pollution in the UK" (RCP, 2021). With heightened focus on air pollution levels, the continued calls globally to tackle the effects of climate change on human health, and the heterogeneity of evidence on air pollution and respiratory outcomes, there is a need to understand the impact of temperature and pollution levels of COPD mortality.

3.2 Study aims and objectives

Therefore, this study aims to understand the impact of air pollution and temperature on COPD mortality in the UK. This is achieved through the specific objectives below:

1.1 Describe the respiratory and COPD mortality rates in the general population over time

1.2 Determine the association between respiratory mortality in the general population and pollution controlling for temperature and season

3.3 Methods

3.3.1 Study design

This study was an ecological study spanning the period 2008 to 2018.

3.3.2 Data source

This study utilised publicly available data on population size and mortality obtained from the Office for National Statistics. ONS data was linked with pollution data from DEFRA and Met Office (See Section **2.5**) temperature data at the LSOA level.

3.3.3 Exposure

$PM_{2.5}$ Levels

Pollution data from the national network of monitors were obtained from previously derived monitor data to estimate daily average $PM_{2.5}$ ($\mu g/m^3$) levels at LSOA (Schneider et al., 2020). The spatial distribution of annual average $PM_{2.5}$ concentrations for 2008, 2013, and 2018 are shown in **Figure 3.1**, revealing a decrease of pollution levels in recent years across the UK, although slightly stronger in England. The maps also display the corresponding annual average of $PM_{2.5}$ levels in London. The maps show local hotspots of high pollution, with a spatial distribution that changes along the study period.

Temperature

Temperature data was available from previously derived time series (See section **2.5**). Temperature measures were defined as daily averages in °C.

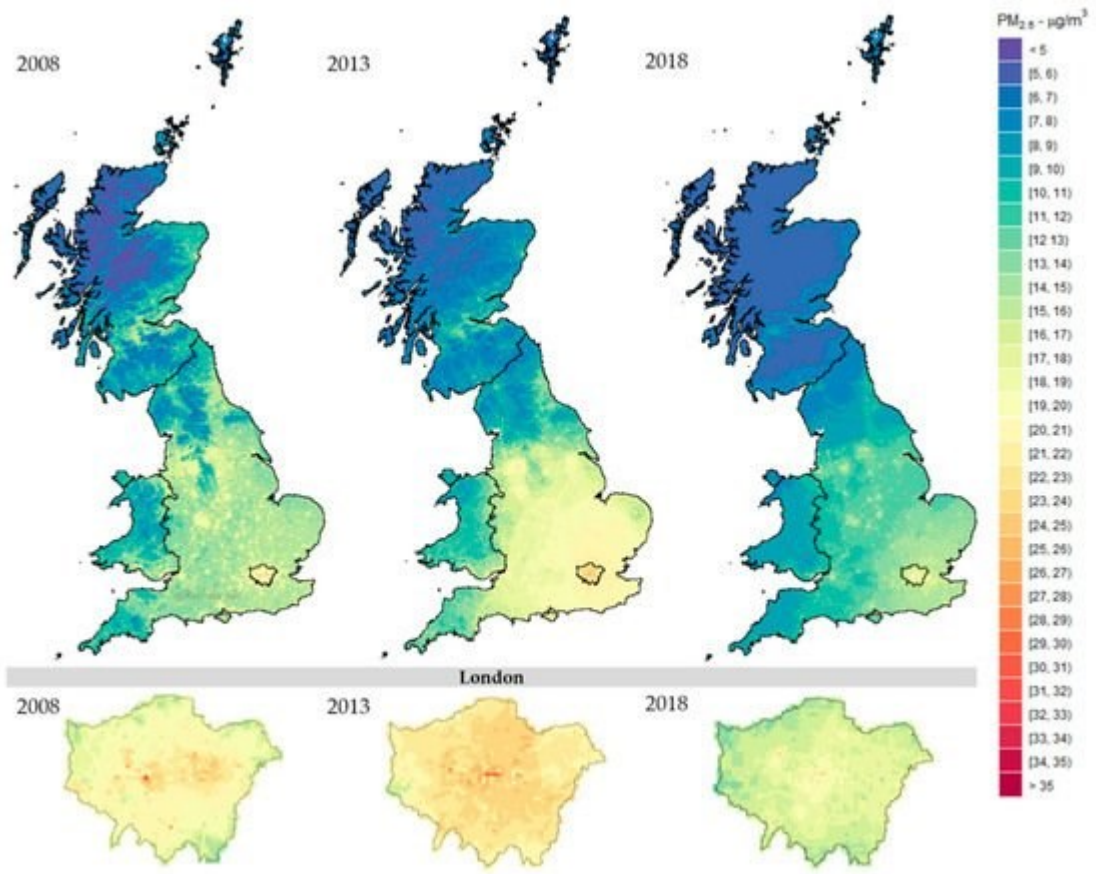


FIGURE 3-1 $PM_{2.5}$ CONCENTRATIONS ACROSS ENGLAND, SCOTLAND, WALES AND LONDON FOR 2008, 2013, AND 2018 AGGREGATED BY ANNUAL MEANS.

Reproduced from Schneider et al 2020, (Figure 3) (Schneider et al., 2020), All plots were built under the same colour scale.

3.3.4 Outcomes

Aggregate mortality data with LSOA identifiers were provided by ONS and aggregated as LSOA-specific daily series of mortality counts.

Outcomes were defined using ICD-10 codes and grouped as:

- All-cause mortality (excludes accidents and other external causes, ICD10: V01-Y98)
- Respiratory-related mortality (See **Appendix 9.3: Table B**)
- COPD-related mortality (ICD-10: J43-J44, See **Appendix 9.3: Table E**)

3.3.5 Statistical Analysis

Age standardised mortality rates (ASMR) per 100,000 population (2013 European standard population) were presented between 2008 and 2018 for men and women separately in England and Wales. COPD-related ASMR's were described together with cardiovascular deaths and cancer deaths to allow for comparison to other common causes in the general population.

Air pollution, Temperature and mortality outcomes

The association between air pollution, temperature and mortality outcomes (all-cause, respiratory and COPD) were estimated using a case time series design, to model data collected at small area level, in which the outcome event was a count of cause-specific mortality on a given day (the unit of analysis) aggregated by LSOA, associated with area-level daily average $PM_{2.5}$ and daily average temperature (Gasparrini, 2021). The data were fitted using a conditional poisson regression adjusted for overdispersion (Armstrong et al., 2014), where the expected counts of deaths on any given day in each LSOA were modelled within a local authority district (LAD). This model definition was selected in previous mortality studies (Gasparrini et al., 2015) and was used because of its flexibility in allowing the application of sophisticated time series techniques such as smoothing and distributed lag models at small-area level, using multiple series of high-resolution data defined at LSOA and enabling a fine control for underlying exposure trends. The models were adjusted for age (years), sex (male, female) and season.

To understand the impact of the choice of lag days for exposure classification, the model was run for both warmer and colder daily temperature exposure estimates extending from 0 up to lag 20. **Appendix 9.1.3** illustrates the RR of mortality associated with warmer or colder daily temperatures from lag 0 – 20 for all causes of death. The final models were based on lag 3 days for $PM_{2.5}$ and temperature as these are consistent with previous studies (Armstrong, 2006) and represented the strongest RR with mortality outcomes.

The temperature-mortality relationship has been described as a J- or U-shaped curve, where the minimum is the temperature at which the risk of mortality is lowest (Tobías et al., 2021). Consequently, the minimum mortality temperature (MMT) is an

important indicator to characterize associations between temperature and health, in particular regarding long-term adaptation to climate. The MMT was identified from each estimated spline curve representing the overall cumulative exposure-response (the net effect summed across lags), together with an approximate parametric bootstrap estimator of its confidence interval and standard error.

All statistical analyses were performed in R software (version 3.6.2).

3.4 Results

3.4.1 Respiratory mortality in England and Wales

The all-cause mortality rate in England and Wales decreased between 2008 and 2018 from 1,292 per 100,000 to 1,121 per 100,000 among men, and from 943 per 100,000 to 838 per 100,000 among women.

Between 2008 and 2018 the COPD (ICD-10: J40-J44), the ASMR decreased slightly from 70 - 62 per 100,000 people among males, and increased slightly from 43 –45 per 100,000 among females (**Figure 3.2**).

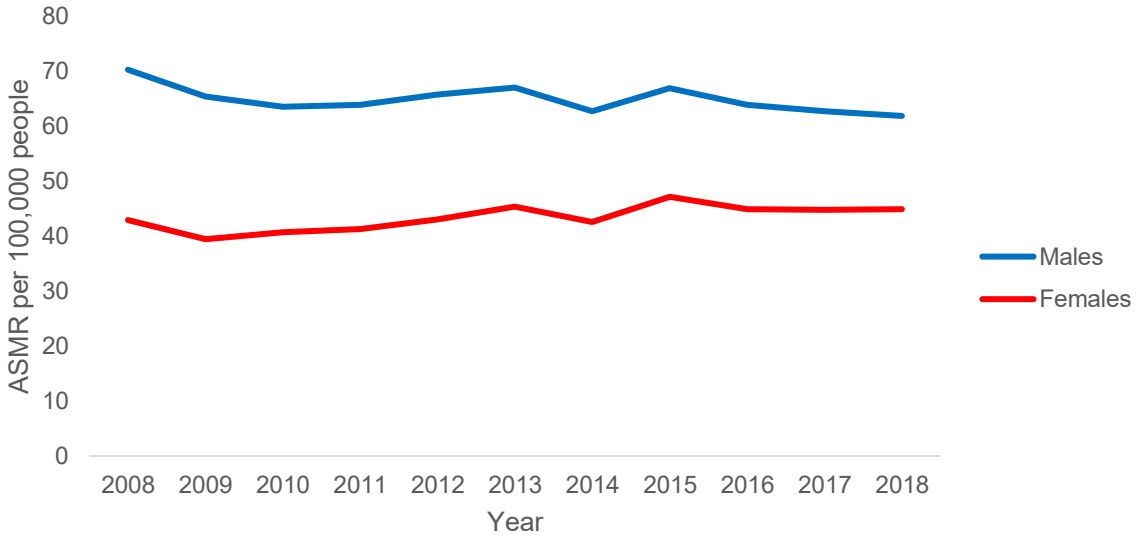


FIGURE 3-2 ASMR OF COPD DEATHS IN ENGLAND AND WALES BETWEEN 2008 AND 2018

This was different for other leading causes of death. Between 2008 and 2018, the ASMR decreased among males and females for both ischaemic heart disease (ICD-10: I20-I25) and all types of cancer (ICD-10: C00-D49) (**Figure 3.3)**.

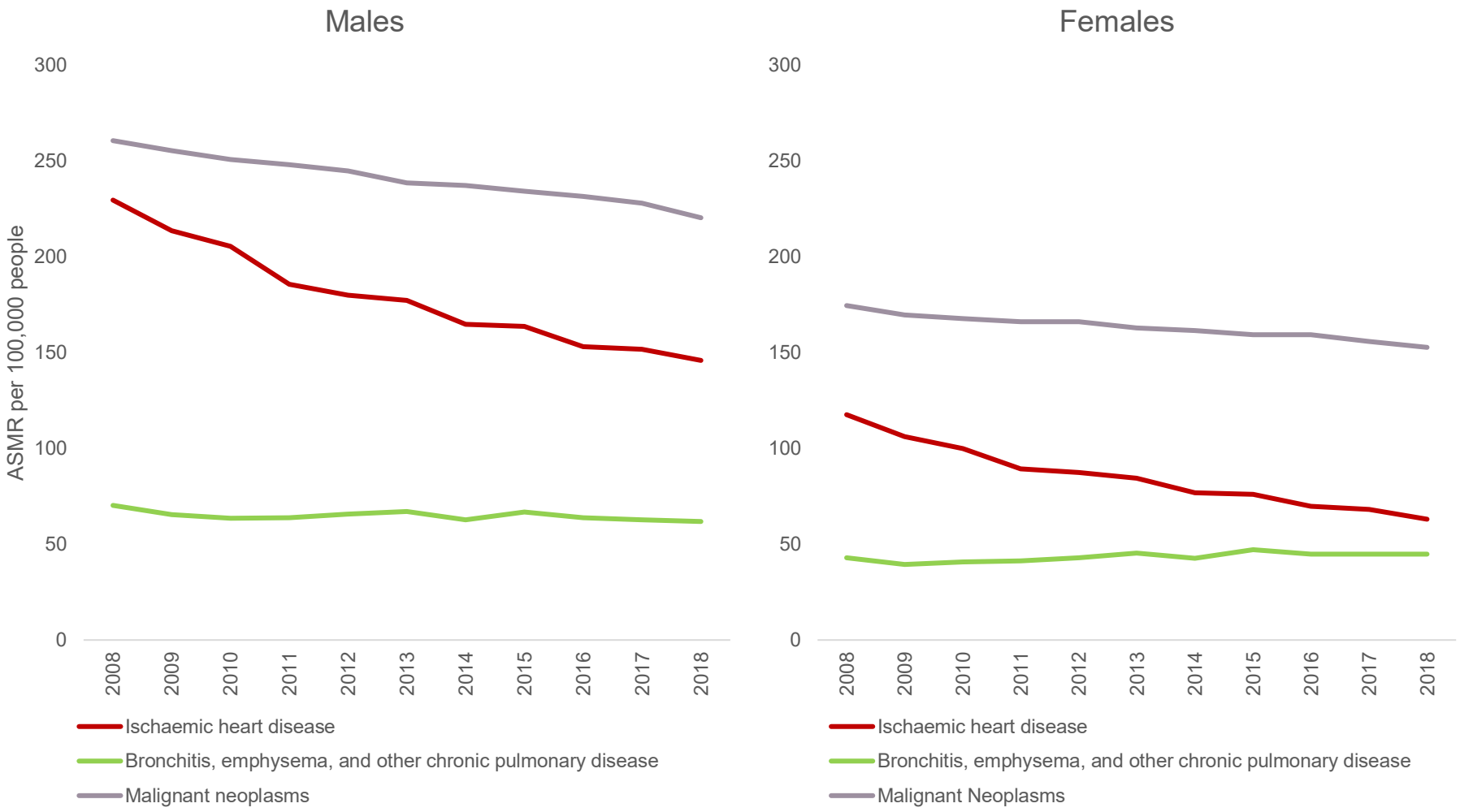


FIGURE 3-3 ASMR FOR LEADING CAUSES OF DEATH IN ENGLAND AND WALES BETWEEN 2008 AND 2018 AMONG MALES AND FEMALES

Mortality, pollution and temperature data

Between 2008 and 2018, over 5 million deaths were observed across 348 local authority districts and 34,752 lower super output areas (**Table 3.1**). Of these, 774,067 were attributed to any respiratory disease and 286,123 were attributed to COPD.

TABLE 3-1 NUMBER OF DEATHS BY CAUSE AND AREA, 2008-2018

Cause	Deaths	LAD	LSOA
All-Cause	5,316,484	348	34,752
Respiratory	774,067	348	34,674
COPD	286,123	348	34,066

LAD: Local Authority District, LSOA: Lower super output area

3.4.2 Pollution

Exposure to $PM_{2.5}$ after controlling for temperature and calendar time was not associated with a significant increased risk of all-cause mortality (**Table 3.2**). Similarly, for respiratory causes of death and COPD-related mortality there were no significant increased risks. A modest percentage increase risk in average $PM_{2.5}$ level was suggested for respiratory deaths (RR 0.57% (95%CI 0.08 – 1.05)).

TABLE 3-2 RR OF CAUSE SPECIFIC MORTALITY ASSOCIATED WITH $PM_{2.5}$

Cause	RR (95%CI) $PM_{2.5}$
All-Cause	0.15% (-0.05% to 0.34%)
Respiratory	0.57% (0.08% to 1.05%)
COPD	0.07% (-0.72% to 0.87%)

3.4.3 Temperature

Taking pollution and time into account, temperature was associated with increased risks of mortality at both extremes. Coldest days and hottest days were associated with increased risks of all-cause, respiratory and COPD-mortality (**Table 3.3**). Figures **3.4,3.5 & 3.6** visualise the non-linear relationship between change in temperature and RR of cause specific mortality at lag 3. There were clear increased mortality risks seen in the hottest temperatures (above 20˚C) and for the coldest temperatures (below -2˚C) for both respiratory causes of death as well as for COPD.

TABLE 3-3 RR OF DEATH ASSOCIATED WITH COLD AND HOT TEMPERATURES AT LAG 3 DAYS

Cause	MMT	RR (95%CI) cold	RR (95%CI) heat
All-cause	16.2	1.08 (1.07 to 1.09)	1.08 (1.08 to 1.09)
Respiratory	15.7	1.09 (1.06 to 1.11)	1.19 (1.17 to 1.22)
COPD	15.5	1.04 (1.00 to 1.08)	1.21 (1.16 to 1.26)

MMT: Minimum mortality temperature

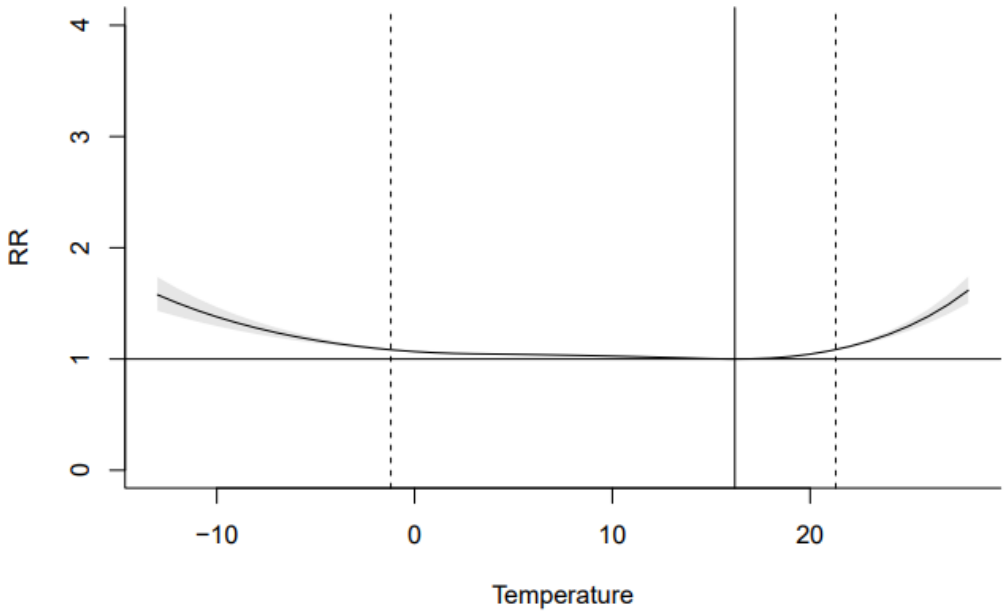


FIGURE 3-4 RELATIONSHIP BETWEEN TEMPERATURE AND ALL-CAUSE MORTALITY AT LAG 3 DAYS, EXPRESSED AS RELATIVE RISK (RR) AND BANDS CORRESPONDING TO THE 95% CONFIDENCE INTERVALS[5]

[5] MMT expressed as a solid vertical line with corresponding 95% confidence intervals as dashed vertical lines

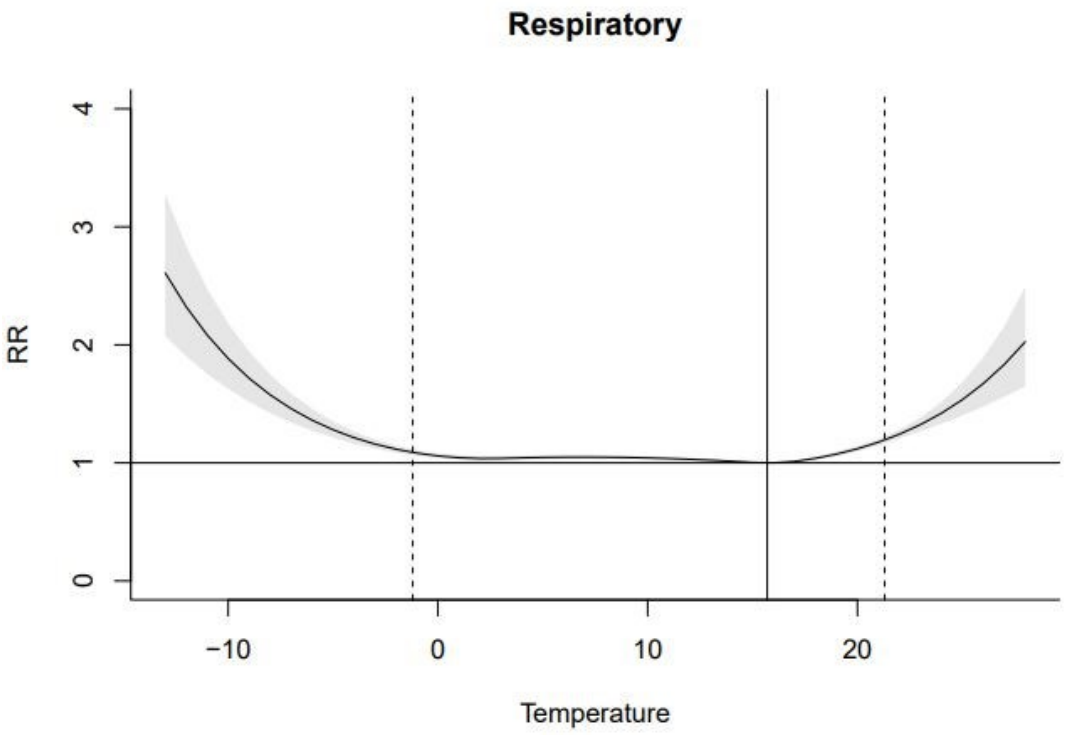


FIGURE 3-5 RELATIONSHIP BETWEEN TEMPERATURE AND RESPIRATORY MORTALITY AT LAG 3 DAYS, EXPRESSED AS RELATIVE RISK (RR) AND BANDS CORRESPONDING TO THE 95% CONFIDENCE INTERVALS

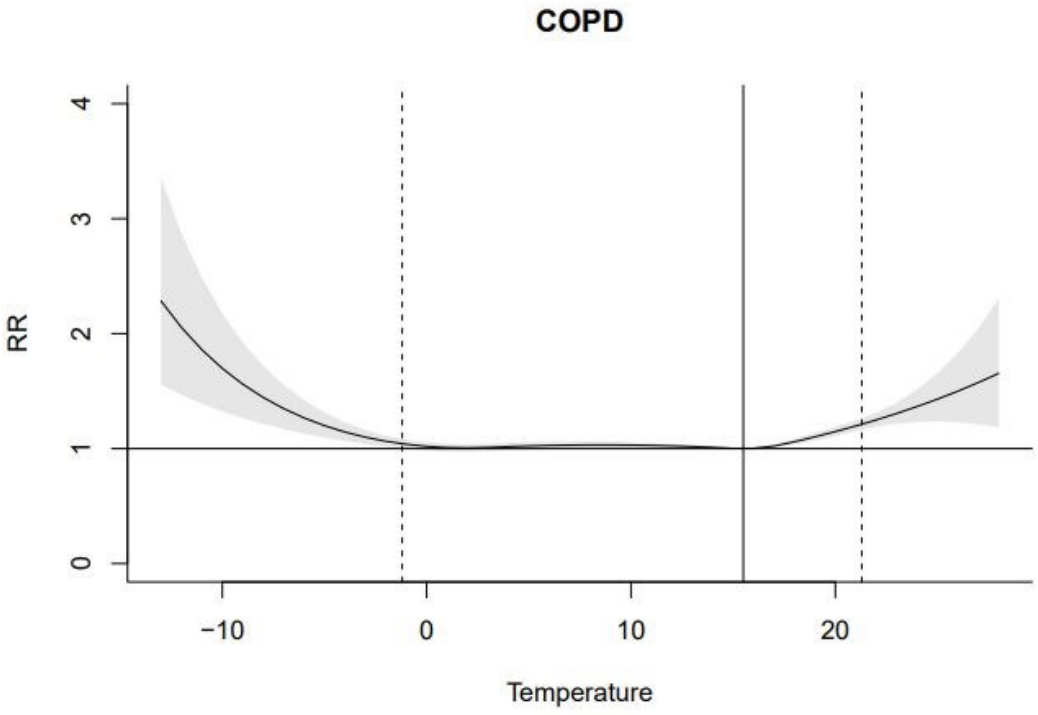


FIGURE 3-6 RELATIONSHIP BETWEEN TEMPERATURE AND COPD MORTALITY AT LAG 3 DAYS, EXPRESSED AS RELATIVE RISK (RR) AND BANDS CORRESPONDING TO THE 95% CONFIDENCE INTERVALS

3.5 Discussion

3.5.1 Summary of Main findings

From 2008 to 2018, the ASMR of COPD mortality among men only decreased from 70 to 62 per 100,000 people, and among women increased slightly from 43 to 45 per 100,000 people, appearing stable when compared with other common causes of death. During this time period there were no significant associations found between exposure to the air pollutant $PM_{2.5}$ and COPD mortality. However, an association of average daily temperature with mortality from all-cause, respiratory and COPD causes was found in extreme hot and cold days of the year.

3.5.2 Comparison to Similar work

Globally, the number of COPD deaths has been estimated to have increased by 97.44% from 3.52×10^5 to 6.95×10^5 between 1990 and 2019, while the ASMR has decreased from 10.19 to 8.95 per 100,000 (Yang et al., 2021). The British Lung Foundations' 'Respiratory Health of the Nation' project outlined key metrics for COPD in the UK; Snell et. al estimated that between 2004 and 2012, approximately 30,000 people were dying each year of COPD in the UK, making UK COPD mortality rank third in Europe (Snell et al., 2016). The present study shows similar ASMR trends to previous estimates and demonstrates that COPD mortality remains high with rates remaining higher among men compared with women. This disparity might be partly explained by differences in smoking habits and the related higher life expectancy among women.

Overall, the body of epidemiological evidence linking exposure to short-term air pollutants and exacerbation rates is rather large, and includes studies from different regions of the world, on several air pollutants emitted from different sources with varying compositions (Donaldson et al., 2018, Annesi-Maesano, 2017, Ji et al., 2011). I found that $PM_{2.5}$ concentrations were not associated with significantly increased risks of COPD deaths in England. This contradicts some earlier findings. Zhu et al. conducted a systematic literature review and meta-analysis and found that a 10-$\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 1.5% (95% CI: 0.9-2.2%) increase in COPD mortality, with an OR of 1.015 (95% CI: 1.009-1.022) (Zhu et al., 2020). While statistically significant positive associations between respiratory mortality and $PM_{2.5}$ level were found in the Canadian Community Health Survey and

the Japanese Three-Prefecture cohort study (with hazard ratios ranging from 1.11 to 1.54) (Pinault et al., 2016, Katanoda et al., 2011), other studies have shown null associations(Pun et al., 2017). Positive but non-statistically significant associations, for instance, were reported in the California Teachers Study (Ostro et al., 2010, Lipsett et al., 2011) and the National Institutes of Health's Diet and Health Study (Thurston et al., 2016). The null findings from these previous US and European studies and from the current study suggest that the evidence linking $PM_{2.5}$ exposure to increased risk of COPD mortality is not fully conclusive and may be more nuanced. One important consideration is that the biological mechanisms linking long-term $PM_{2.5}$ exposure to lung function decline are not well defined. While short-term exposure to high-concentration $PM_{2.5}$ can lead to a burst of inflammation and oxidative stress in the lungs, as well as the ciliary dysfunction in the upper airway (Wang et al., 2020), long-term exposure has not been shown to increase emphysema progression when assessed by CT scan (Wang et al., 2019). However, the likely explanation for the discrepancy observed in this study compared with the literature is that $PM_{2.5}$ levels in the UK declined between 2008 and 2018 (**Figure 3.1**) whilst COPD mortality rates remained relatively constant over the same time period (**Figure 3.2**), demonstrating that there may be unmeasured confounding factors. These are likely to be best characterised at the individual person-level and may include factors such as individual exposure to outdoor pollutants, occupational exposure and pre-existing medical history. A further study with more focus on individual patient exposure and measured lung function decline or COPD-related mortality is therefore suggested.

This is the most contemporary study to date to systematically evaluate the effect of extreme and moderate ambient temperatures on cause-specific respiratory mortality in the UK. The observed non-linear relationship between daily temperature illustrated that both heat and cold effects have adverse impact on respiratory mortality, especially COPD, and is consistent with previous studies. Hansel et al. reviewed the strong association that has previously been observed for periods of heat waves (Hansel et al., 2016) and similarly discussed how the literature suggests that daily changes in temperature are associated with increased mortality risk. In a recent US nationwide study, Zhan et al. investigated temperature change and occurrence of cause-specific deaths(Zhan et al., 2017). Compared to people dying from

cardiovascular causes, decedents from respiratory disease showed an increased risk of dying on extremely positive days (those in which temperature increase from the previous day was greater than 0˚C), with a relative risk of 1.31 (95% CI, 1.08–1.58). A rapid temperature increase lead to the dehydration, salt depletion, and increased surface blood circulation, which the authors hypothesize might induce the occurrence of death (Zhan et al., 2017). For extreme cold, the literature is conclusive as to the increased risk of respiratory-related mortality in colder periods (McCormack et al., 2017) and a number of hypotheses are proposed to explain the relationship between colder seasons and increased respiratory mortality. Bacterial and viral co-infections are more common in colder months as temperature change and could reduce the resistance of the immune system to respiratory infections as well as affecting physiological changes in the circulatory system.

3.5.3 Strengths and Limitations

This study provides a countrywide evaluation of the health impact of air pollution and temperature, with a comprehensive assessment of mortality risks across the 37,453 small census areas of England and Wales and has several advantages. The study design uses high resolution measurements assigned at small-area level capturing the localised geographical patterns of the pollutants, but also ensuring adequate confounding and spatial autocorrelation adjustment. Most of the previous studies on environmental exposure and mortality associations are based on time series analyses of largely aggregated data, or alternatively, small-area assessments limited to single cities.

However, a key limitation of this study is the use of an ecological population-level approach. Available outdoor air pollution measurements from fixed monitoring stations were used to assess relationships between daily deaths and short-term changes in air pollutant exposures. Therefore there is a risk of exposure misclassification and by design, I did not consider individual-level confounders, such as smoking, activity levels and differences in time-activity patterns and microenvironments (Quint, 2017). In addition, socioeconomic variables and area characteristics (such as area level deprivation or proportion of greenspace), which have previously been shown to modify the associations between pollution and mortality (Milojevic et al., 2014, Bixby et al., 2015), were not included. Furthermore, this study does not account for population mobility during 2008–2018 and assumed

constant residence and thus levels of exposure to air-pollution. While this is a limitation, it may have a minimal impact on the results given that the majority of COPD deaths occur in people 60 years or older, a population which is less likely to move.

3.6 Conclusion

Rates of COPD mortality in the general population have shown mild decreases but appear relatively stable in comparison to other major causes of death. Changes in temperature are associated with both respiratory and COPD-related mortality. At the area level, changes in $PM_{2.5}$ levels is associated with modest increases in respiratory-related but not COPD-related mortality. Patient-level exposure data are needed to confirm these associations.

4 Chapter 4: Changes over time in COPD diagnosis among those with a COPD recorded death

This chapter estimates the proportion of the population with a COPD-recorded death who receive a clinician recorded diagnosis of COPD during their lifetime and factors associated with potentially having a missed diagnosis.

4.1 Background

The true prevalence of COPD in the UK has been speculated (Diab et al., 2018), with a suggestion that there are a large proportion of patients who do not receive a diagnosis at all. The prevalence of COPD in England for people 15 years of age or older using Quality and Outcomes Framework (QOF) data is 1.37%; however, Nacul et al. estimate this to be 3.58% of the English population, suggesting that there is considerable underreporting of patients with diagnosed COPD or that there may be a large number of people who are undiagnosed (Nacul et al., 2011).

The British Lung Foundation previously estimated that 2.2 million symptomatic but undiagnosed people with COPD live in the UK (BLF, 2007). Opportunities for diagnosis are missed in 85% of patients up to 5 years before diagnosis (Jones et al., 2014). People sometimes have mild or infrequent symptoms, making it difficult to be diagnosed. Clinicians may attribute respiratory symptoms to other diseases where symptoms overlap, including heart failure, asthma, and other chronic lung conditions. Another potential issue may be that spirometry, the essential test to detect airway obstruction, may not be available or is misinterpreted by lack of recognition of poor quality or use of inappropriate reference values (Rothnie et al., 2017).

NICE guidelines [NG115] recommend that diagnosis of COPD is established based on confirmation of airflow obstruction, defined as $FEV_1/FVC < 0.7$ (NICE, 2018). While spirometry can be performed in primary care, often diagnostics are conducted in secondary care settings where results may or may not be shared with GPs or. when shared, may not be coded and entered into the medical record in a way that is easily accessible to clinicians or researchers. Quint et al. previously validated COPD diagnosis in primary care data, concluding that using COPD codes alone has a PPV of 86.5% (77.5–92.3%), and using them in combination with recorded spirometry and prescription of specific COPD medications has a PPV of 89.4% (80.7–94.5%) accurately identifies the majority of COPD patients in medical records (Quint et al., 2014a).

Although evidence has shown that there are significant delays in COPD diagnosis in the UK and the potential for millions of patients to be missed (Roberts and Gaduzo, 2013), there is little real-world evidence describing the impact of missed diagnosis

with respect to COPD related mortality, and thus there is a need to investigate this further.

4.2 Study aims and objectives

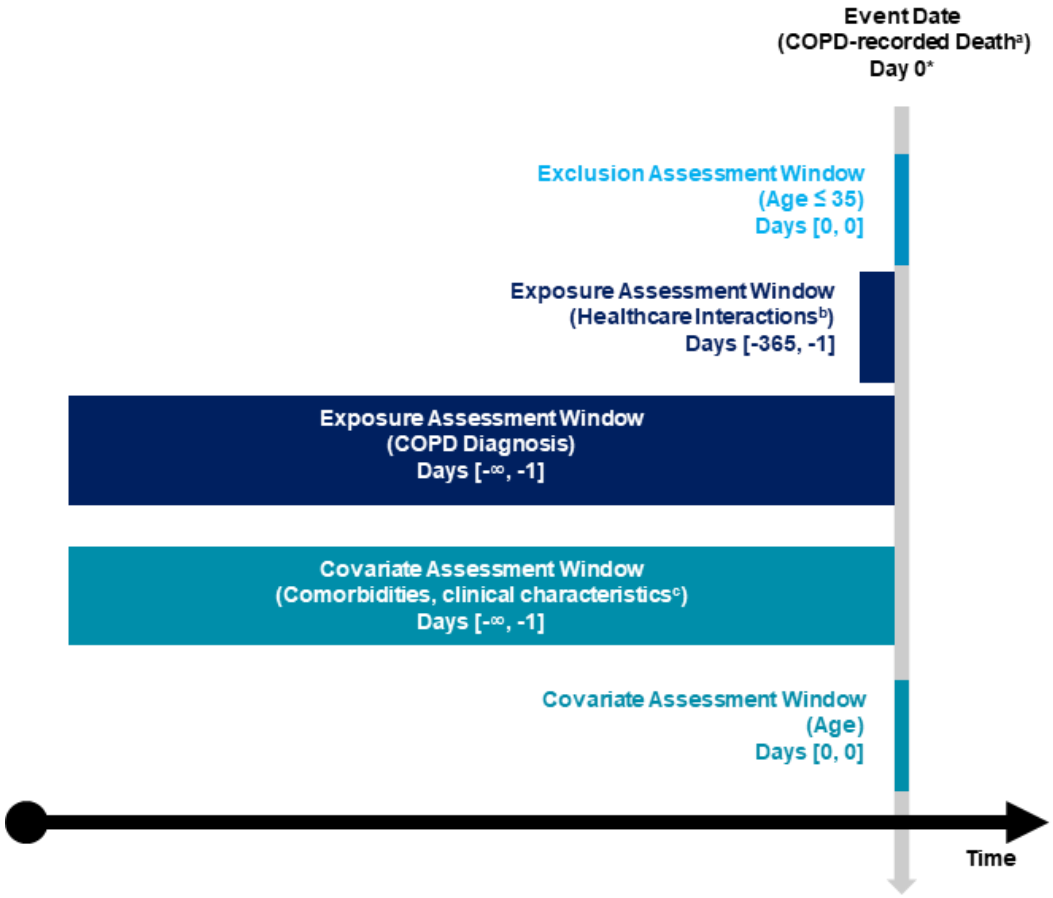
This chapter aims to measure the proportion of patients with a diagnosis of COPD prior to death (assuming a COPD recorded death as the gold standard), using a range of diagnostic definitions found to have high sensitivity and specificity in primary care data. Specifically, I will:

- Estimate the proportion of people with a COPD recorded death with evidence of diagnosis in their medical record
- Describe the changes in the proportion of COPD deaths with evidence of diagnosis over time
- Assess factors associated with missed diagnosis

4.3 Methods

4.3.1 Study Design

This study utilised a cohort design, with details illustrated in **Figure 4.1**.



[a] COPD (ICD-10 J43-J44) as the underlying cause of death or in the first position on the death certificate
*Death date between 2000 and 2017
[b] Includes: asthma, flu, pneumonia and medications prescribed
[c] Includes: sex, deprivation, region, ethnicity, BMI, smoking status, heart failure, asthma, bronchiectasis, interstitial lung disease, respiratory symptoms of cough, sputum production and breathlessness
∞ denotes all available records

FIGURE 4-1 STUDY DESIGN

4.3.2 Data Source

The May 2019 build of the CPRD GOLD and Aurum datasets were used for this analysis (See **Section 2.3.1**). Primary care data from practices using CPRD GOLD and Aurum were combined. Patients who belonged to practices that migrated from Vision to EMIS software (GOLD to Aurum) were removed from the GOLD data set to avoid duplication. Linked IMD, HES and ONS mortality data was obtained for patients belonging to practices that were eligible for linkage (linkage set 17). The

approval for this study was published at https://www.cprd.com/protocol/describing-characteristics-patients-who-die-copd-no-evidence-prior-diagnosis.

4.3.3 Study Population

All patients who died in England between 2000 – 2017 whose underlying cause of death or first position cause of death on the death certificate was COPD (ICD-10 Codes J43-J44) were included (See **Appendix 9.3: Table E**). Patients with at least one year of "research standard" CPRD registration before death were included; practices are designated as 'up to standard' in CPRD from the date that they met specified data entry quality criteria, which may have occurred before or after a patient registered with the practice. Patients were excluded if they were 35 years or under at the time of death (**Figure 4.1**).

Cause of death was used to identify the cohort using information derived by ONS to determine the terminal event, as well as the underlying cause of death code from ONS data, which has been derived using standardized guidelines from information available on death certificates (Devis and Rooney, 1999a). Additionally, all causes mentioned on the death certificate (proposed causes) were obtained, the cause in the first position was also used to define the cohort as previous studies have shown that there may be issues surrounding the accuracy of the underlying cause which is a derived variable (Sinha et al., 2008a).

4.3.4 Outcomes

I retrospectively looked for evidence of COPD diagnosis based on interpretations of the NICE diagnostic guidelines (NICE, 2018) and previously validated CPRD diagnostic algorithms (Quint et al., 2014a). The definitions used to diagnose COPD, presented in **Table 4.1**, range from loose definitions to the strictest.

TABLE 4-1 COPD DEFINITIONS

Group	Definition
A	Specific COPD code only: Diagnostic COPD code or record of acute exacerbation of COPD in either primary care or secondary care data using previously validated Read/SNOMED-CT/ICD-10 codes (Quint et al., 2014a) (see **Appendix 9.3: Tables C - E, and K- M** for codes used to identify COPD and COPD exacerbations using SNOMED-CT codes).
B	Specific COPD code and record of spirometry: Record of spirometry being performed at any time in a patients' medical history
C	Specific COPD code and medication prescribed within 4 weeks of a diagnostic code
D	Specific COPD code, presence of spirometry and medication prescribed within 4 weeks of a diagnostic code
E	Specific COPD code with spirometry confirmed obstruction (FEV_1/FVC <0.7)
F	Specific COPD code with spirometry confirmed obstruction FEV_1/FVC<Lower Limit of Normal (LLN)

4.3.5 Exposures

Patient demographics and clinical characteristics were described using information across the entire medical history and in the year prior to death. Demographics included:

- Age
- Sex
- Patient-level deprivation, as defined by the index of multiple deprivation (IMD)
- ethnicity
- Region (North England and South England)

Comorbid conditions with similar symptom presentation as COPD were considered; they were defined as a recorded diagnosis, at any point in the medical record, for heart failure (**Appendix 9.3: Tables X,Y & Z**), interstitial lung disease (ILD) (**Appendix 9.3: Tables R,S & T**), bronchiectasis (**Appendix 9.3: Tables U,V & W**), and asthma (**Appendix 9.3: Tables F,G & H**), as defined by Read/SNOMED-CT and ICD-10 codes. For asthma, I considered diagnosis both at any point in the medical history and in the year prior to death, to distinguish between historic and current comorbid asthma. Mild flu or pneumonia was defined by presence of a Read/SNOMED-CT code in primary care records (**Appendix 9.3: Tables BB,CC,EE,FF**), while severe flu or pneumonia was defined by presence of an ICD-10 code in hospital records (**Appendix 9.3: Tables DD,GG**). Last recorded body mass index in kg/m^2 (BMI) was obtained from test records. Smoking status was defined using presence of Read/SNOMED-CT codes relating to smoking; codes closest to date of death were then used to categorize patients into “current smoker”, “former smokers”, “non-smokers”, while absence of any smoking record was grouped into “not recorded” (**Appendix 9.3: Tables I & J**).

For COPD symptoms, I considered cough, sputum production and breathlessness, as defined by Read/SNOMED-CT and ICD-10 codes (**Appendix 9.3: Tables HH-PP**). Spirometry tests were identified in patient test records and results closest to death date were used. In the 3 months prior to death, prescriptions of NICE guideline recommended COPD-related medications were described, and they were grouped by drug class (**Appendix 9.3: Tables P & Q)**. Evidence of a flu vaccination was defined using medication codes (**Appendix 9.3: Tables QQ, RR**).

4.3.6 Statistical Analysis

To illustrate the impact of the choice of diagnostic criteria (**Table 4.1**), and for ease of comparison, I compared the loosest criteria (A - COPD code only) with the strictest (E - COPD code and confirmation of airflow obstruction). I then considered definition B (COPD code and presence of spirometry) as the main definition for the purposes of further analysis, as this was the most robust definition according to NICE guidelines (NICE, 2018).

Patient clinical and demographic characteristics were described using summary statistics (N and % for binary and categorical variables; median and interquartile range for continuous non-normally distributed variables and ordinal variables). The proportion of patients diagnosed over time was evaluated using the Cochrane-Armitage test for trend. Differences in the specified covariates between those with and those without a diagnosis of COPD were tested using Wilcoxon rank sum tests for continuous variables, and Chi-squared tests for categorical variables. Factors independently associated with missed COPD diagnosis were identified using a two-level mixed effect logistic regression model with random intercept by GP practice to account for the multi-level nature of the data. The model was adjusted for age (year of birth), sex, smoking status (current/former/non-smoker/unknown), BMI (underweight, normal weight, overweight, obese, unknown), year of death, IMD, ethnicity and comorbid respiratory diseases (asthma ever, ILD, and bronchiectasis).

As a sensitivity analysis, the analysis was repeated after excluding patients with any recorded asthma diagnosis, as the overlap between COPD and asthma may have biased the proportion of patients who do not receive a diagnosis of COPD prior to death; previous research has shown that a large proportion of diagnosed asthma patients later have COPD listed as their underlying cause of death (Nissen et al., 2018, Gayle et al., 2019b).

All statistical analyses were performed in STATA version 15 (StataCorp LP, College Station, Texas, US).

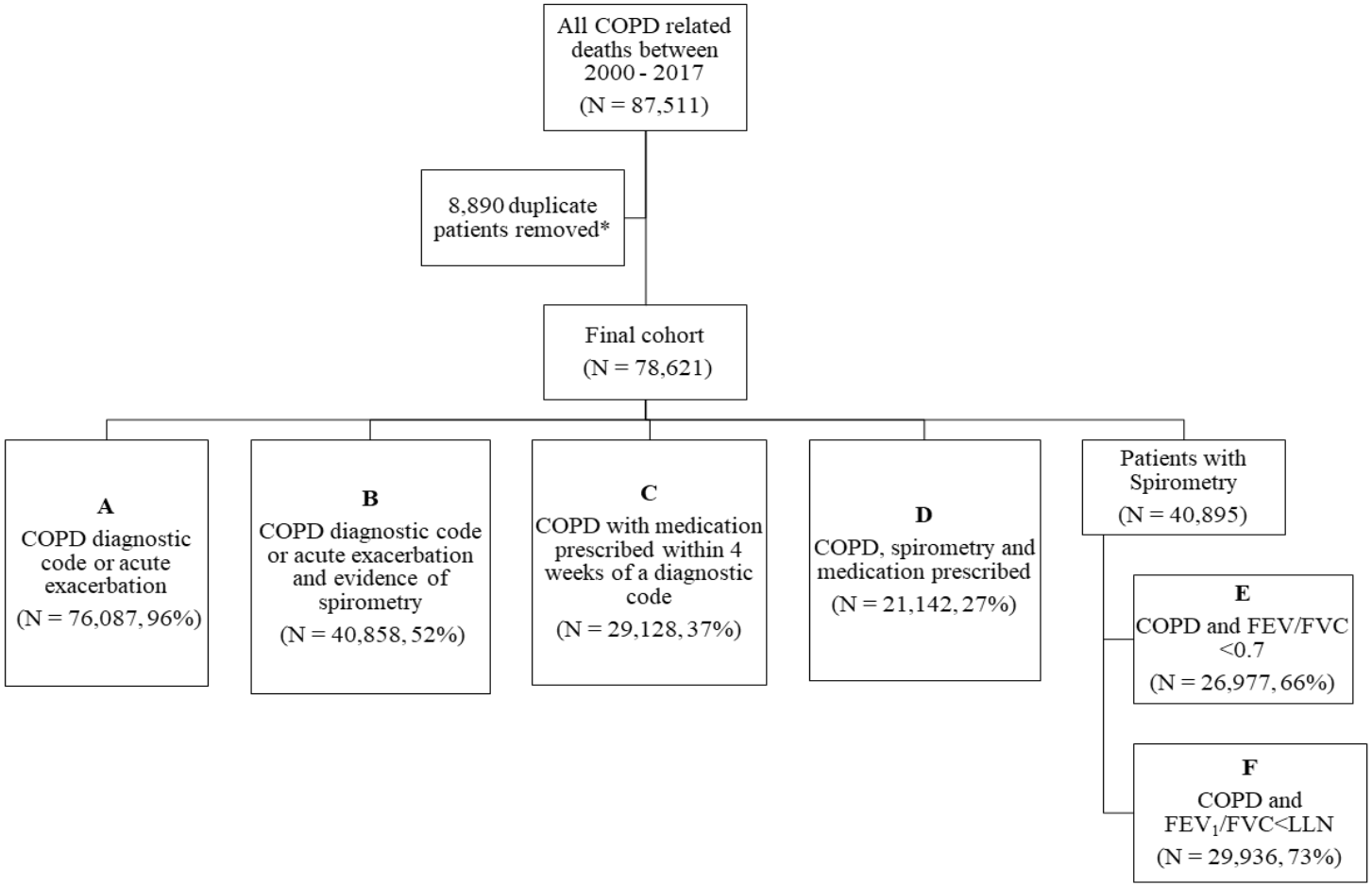
4.4 Results

4.4.1 Cohort characteristics

87,511 patients with COPD as the main cause of death were identified. Among them 18,945 patients belonged to practices included in GOLD and 59,676 in Aurum, resulting in a cohort of 78,621 patients (after removing duplicates) (**Figure 4.2**). Depending on the definition of COPD used (**Table 4.1**), as many as 96% or as few as 27% of patients had evidence of a COPD diagnosis in their medical records (**Figure 4.2**). Just over half of patients (52%, N = 40,895) had evidence of spirometry in their medical records; when considering criteria including spirometric evidence of airflow obstruction, the proportion of patients with missed COPD diagnosis was estimated between 34% using definition E and 27% using definition F (**Figure 4.2**).

Comparing the loosest criteria (A - COPD code only) with the strictest (E - COPD code and confirmation of airflow obstruction), the proportion of patients with missed COPD diagnosis decreased over the study period from 17% in 2000 to 0% in 2017 (p-trend <0.001) using definition A (**Figure 4.3**) and from 100% in 2000 to 25% in 2017 (p-trend <0.001) using definition E (**Figure 4.4**).

Table 4.2 describes patient characteristics between those with and without a diagnosis according to definitions A (loosest) and E (strictest). Using the loosest definition, the majority of patients with COPD death were identified using medical records (N = 2,543, 4% missed). Patients who were missed tended to have higher proportions of unrecorded clinical and demographic information compared with those with a diagnosis. Using the strictest definition, a greater proportion were missed (N = 13,918, 44%).



*patients belonging to GP practices that migrated from Vision (GOLD) to EMIS (Aurum)
A– Specific COPD code only; B – Specific COPD code and presence of spirometry; C - Specific COPD code and medication prescribed within 4 weeks of a diagnostic code; D - Specific COPD code, presence of spirometry and medication prescribed within 4 weeks of a diagnostic code; E - Specific COPD code with spirometry confirmed obstruction (FEV1/FVC <0.7); F - Specific COPD code with spirometry confirmed obstruction (FEV1/FVC<LLN)

FIGURE 4-2 COHORT ATTRITION AND NUMBER OF PEOPLE WITH EVIDENCE OF COPD DIAGNOSIS BY DEFINITION

TABLE 4-2 CHARACTERISTICS OF PATIENTS WITH MISSED LIFETIME COPD DIAGNOSIS COMPARED TO THOSE WITH AND WITHOUT A DIAGNOSIS OF COPD BEFORE DEATH, ACCORDING TO DEFINITIONS A AND E IN TABLE 4.1.

		Definition A		Definition E*	
		Missed COPD diagnosis	**COPD diagnosis**	**Missed COPD diagnosis**	**COPD diagnosis**
		N=2,534	**N=76,087**	**N=13,918**	**N = 26,977**
Age at Death		79 (70-86)	80 (72-86)	80 (73-86)	79 (72-85)
Sex	Male	1,529 (60.3%)	39,846 (52.4%)	6,944 (49.9%)	15,035 (55.7%)
	Female	1,005 (39.7%)	36,241 (47.6%)	6,974 (50.1%)	11,942 (44.3%)
IMD	1 - least deprived	363 (14.3%)	10,993 (14.4%)	1,983 (14.2%)	3,836 (14.2%)
	2	447 (17.6%)	13,282 (17.5%)	2,447 (17.6%)	4,786 (17.7%)
	3	451 (17.8%)	14,772 (19.4%)	2,709 (19.5%)	5,263 (19.5%)
	4	606 (23.9%)	16,687 (21.9%)	3,096 (22.2%)	5,997 (22.2%)
	5 - most deprived	636 (25.1%)	20,043 (26.3%)	3,651 (26.2%)	7,048 (26.1%)
	Missing	31 (1.2%)	310 (0.4%)	32 (0.2%)	47 (0.2%)
Region	South of England	1,383 (54.6%)	39,607 (52.1%)	7,455 (53.6%)	13,398 (49.7%)
	North of England	1,151 (45.4%)	36,480 (47.9%)	6,463 (46.4%)	13,579 (50.3%)
Ethnicity	White	1,395 (55.1%)	68,147 (89.6%)	12,753 (91.6%)	25,219 (93.5%)
	Asian	22 (0.9%)	437 (0.6%)	95 (0.7%)	129 (0.5%)
	Black	18 (0.7%)	265 (0.3%)	46 (0.3%)	75 (0.3%)
	Mixed/Other	17 (0.7%)	436 (0.6%)	80 (0.6%)	120 (0.4%)
	Missing	1,082 (42.7%)	6,802 (8.9%)	944 (6.8%)	1,434 (5.3%)
BMI (kg/m^2)	Underweight (<18.5)	129 (5.1%)	9,308 (12.2%)	1,878 (13.5%)	4,558 (16.9%)
	Healthy Weight (18.5-24.9)	680 (26.8%)	28,378 (37.3%)	5,316 (38.2%)	12,063 (44.7%)
	Overweight (25.0-39.9)	293 (11.6%)	13,708 (18.0%)	2,885 (20.7%)	5,393 (20.0%)
	Obese (>40)	114 (4.5%)	8,904 (11.7%)	2,201 (15.8%)	3,422 (12.7%)
	Missing	1,318 (52.0%)	15,789 (20.8%)	1,638 (11.8%)	1,541 (5.7%)
Comorbid Conditions	Heart Failure	303 (12.0%)	31,414 (41.3%)	6,211 (44.6%)	10,797 (40.0%)
	Asthma [ever]	406 (16.0%)	40,085 (52.7%)	8,267 (59.4%)	16,595 (61.5%)
	Asthma [year prior]	80 (3.2%)	7,145 (9.4%)	1,722 (12.4%)	2,598 (9.6%)
	Bronchiectasis	30 (1.2%)	7,166 (9.4%)	1,546 (11.1%)	3,326 (12.3%)

		Definition A		Definition E*	
		Missed COPD diagnosis	**COPD diagnosis**	**Missed COPD diagnosis**	**COPD diagnosis**
		N=2,534	**N=76,087**	**N=13,918**	**N = 26,977**
	Interstitial Lung Disease	49 (1.9%)	4,432 (5.8%)	1,125 (8.1%)	1,675 (6.2%)
COPD symptoms	Cough symptoms	132 (5.2%)	41,164 (54.1%)	9,173 (65.9%)	18,677 (69.2%)
	Sputum production	36 (1.4%)	25,602 (33.6%)	5,788 (41.6%)	13,099 (48.6%)
	Breathlessness	1,485 (58.6%)	64,045 (84.2%)	10,610 (76.2%)	23,409 (86.8%)
Smoking Status	Current smoker	809 (31.9%)	25,464 (33.5%)	4,343 (31.2%)	8,740 (32.4%)
	Former smoker	281 (11.1%)	32,563 (42.8%)	7,500 (53.9%)	15,885 (58.9%)
	Non smoker	355 (14.0%)	8,116 (10.7%)	1,490 (10.7%)	1,923 (7.1%)
	Missing smoking status	1089 (43.0%)	9,944 (13.1%)	585 (4.2%)	429 (1.6%)

A: COPD code E: COPD code with confirmed airflow obstruction, *Groups E N = 40,895 with record of spirometry, IMD: Index of Multiple Deprivation (patient level), BMI: Body Mass Index, Data are presented as n (%) for categorical measures, Median and IQR for numerical variables. Comorbidities assessed as occurring at any point in medical record prior to death unless otherwise stated

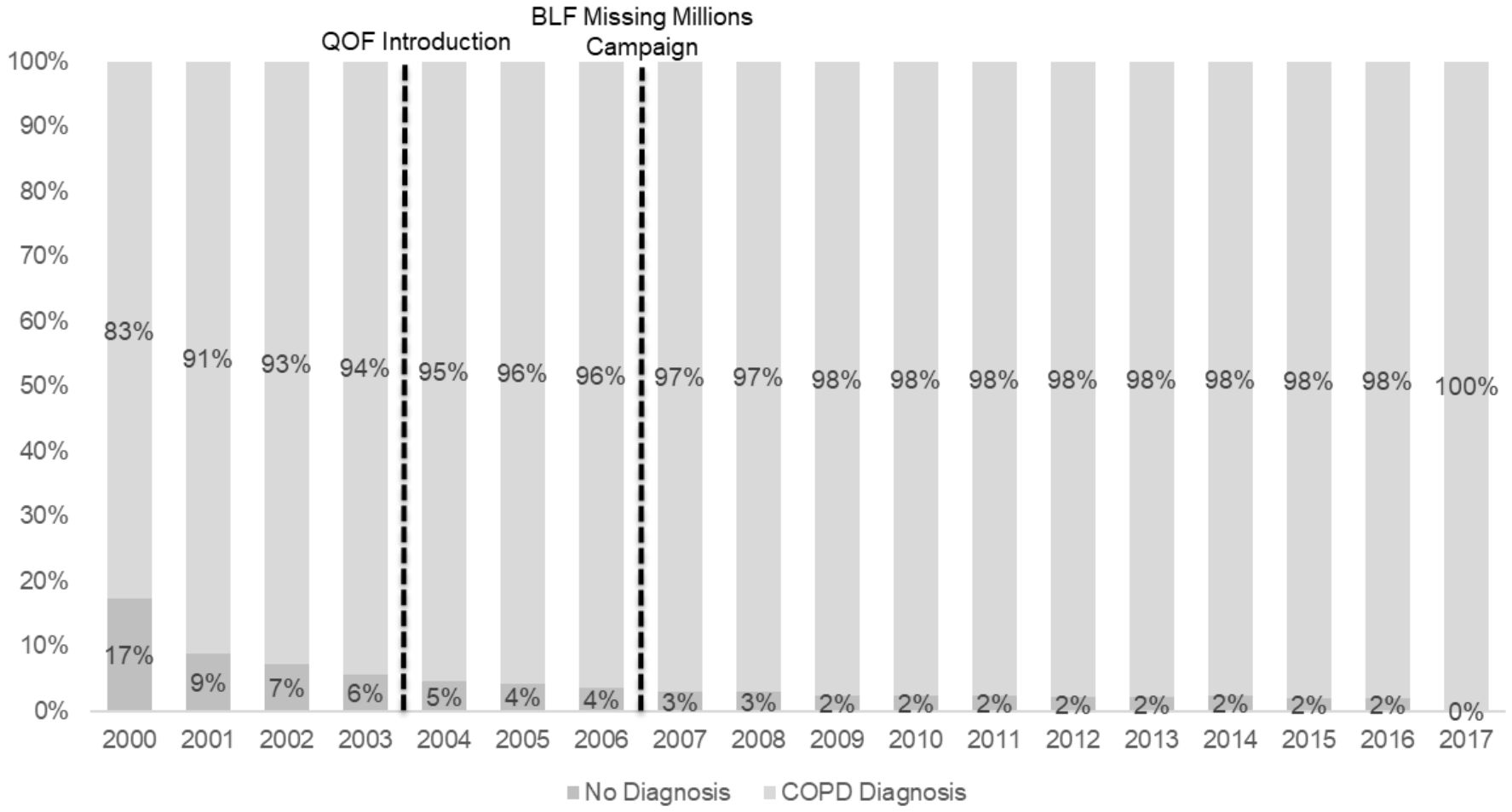


FIGURE 4-3 PROPORTION OF PATIENTS WITH A MISSED COPD DIAGNOSIS BY YEAR OF DEATH [DEFINITION A]

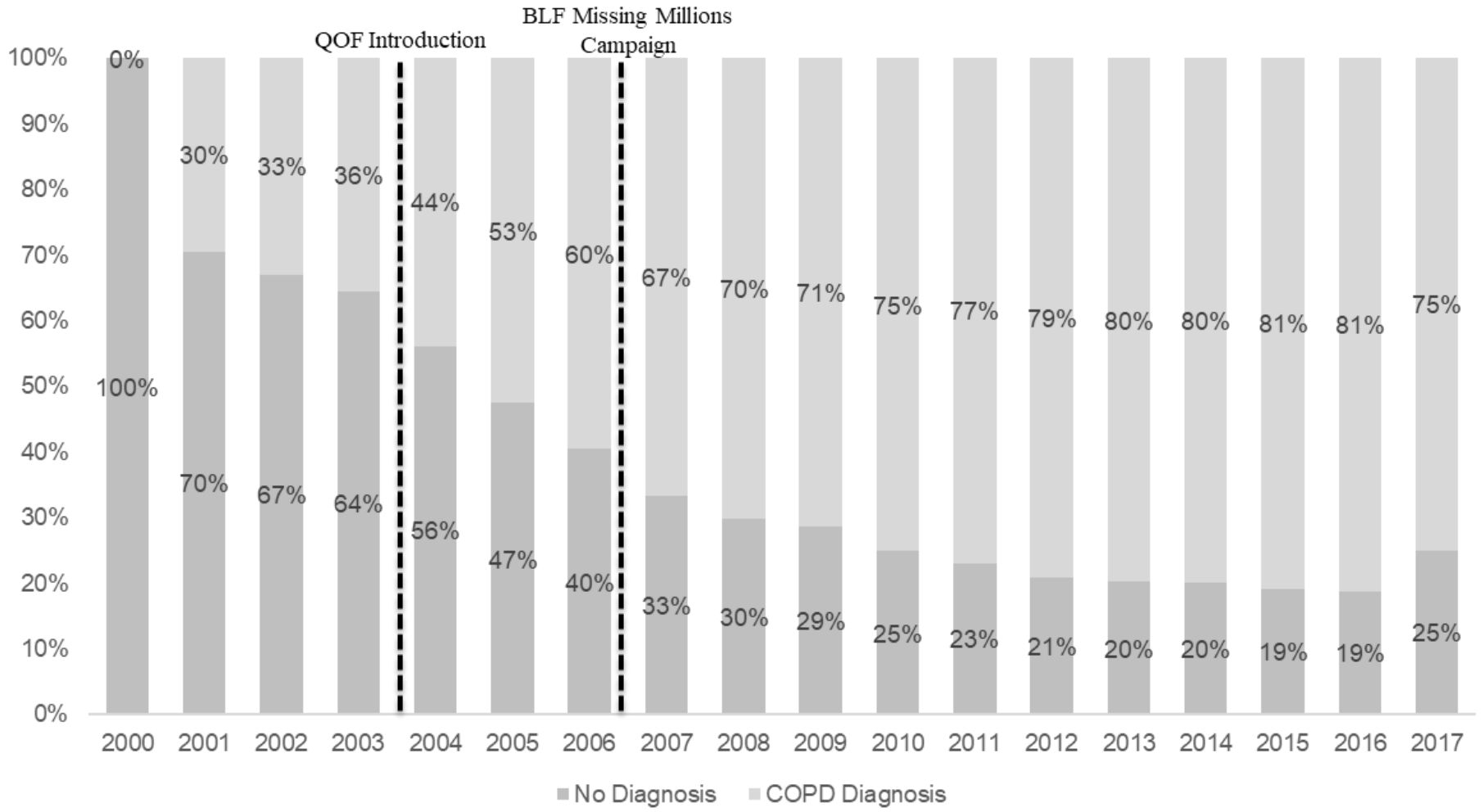


FIGURE 4-4 PROPORTION OF PATIENTS WITH A MISSED COPD DIAGNOSIS BY YEAR OF DEATH [DEFINITION E]

Using the main definition (B - COPD code and presence of spirometry), just over half, 40,858 (52%) had evidence of COPD diagnosis in their medical records, and the proportion of patients with missed COPD diagnosis decreased over the study period from 91% in 2000 to 31% in 2017. **Table 4.3** describes patient characteristics comparing those with and without a COPD diagnosis in their lifetime, using this definition. Among the 37,763 (48%) patients with a missed COPD diagnosis, 10,023 (26.5%) had no smoking information recorded, under half had an asthma diagnosis at any point in their medical history (N = 15,645; 41%), and while patients reported little or no respiratory symptoms (N = 13,453; 35.6%) reporting cough), a large proportion had reported feeling breathless at least once in their medical history (N = 27,351; 72%). Among those with evidence of COPD diagnosis, only 1,010 (2.5%) had missing smoking information, the prevalence of asthma was higher (N= 24,846; 61%), and the majority presented with cough (N = 27,843; 68.1%) and reported feeling breathless (N= 38,179; 93%).

Clinical characteristics were different between those with and without evidence of diagnosis of COPD. Spirometry was performed in 37 patients who did not have a COPD diagnostic code or exacerbation record, where the median FEV_1% predicted was 76% (IQR 72-88), and only 10 people (27% of those tested) had confirmed obstruction ($FEV_1/FVC < 0.7$) on at least one occasion in their medical history. The most prescribed pharmacotherapies in the three months prior to death among those without evidence of diagnosis were short-acting beta agonists (27% N = 10,193), oral corticosteroids (15% N=5,691) and inhaled corticosteroids (13% N=5,079). After excluding patients with evidence of asthma in their medical records, these proportions were reduced (**Figure 4.5**). 52% (N = 4,809) of patients with a diagnosis of COPD received a long-acting bronchodilator (in monotherapy, dual or triple combination) in the three months prior to death, whereas this was 18% (N = 1,682) among those without a diagnosis.

TABLE 4-3 PATIENT CHARACTERISTICS (USING THE MAIN DEFINITION: B - COPD CODE AND PRESENCE OF SPIROMETRY)

		Missed COPD diagnosis N=37,763	COPD diagnosis N=40,858	P-Value
Age at Death		80 (73-87)	79 (72-85)	<0.001
Sex	Male	19,424 (51.4%)	21,951 (53.7%)	<0.001
	Female	18,339 (48.6%)	18,907 (46.3%)	
IMD	1 - least deprived	5,544 (14.7%)	5,812 (14.2%)	0.085
	2	6,508 (17.2%)	7,221 (17.7%)	
	3	7,258 (19.2%)	7,965 (19.5%)	
	4	8,205 (21.7%)	9,088 (22.2%)	
	5 - most deprived	9,986 (26.4%)	10,693 (26.2%)	
	Missing	262 (0.7%)	79 (0.2%)	
Region	South of England	20,154 (53.4%)	20,836 (51.0%)	<0.001
	North of England	17,609 (46.6%)	20,022 (49.0%)	
Ethnicity	White	31,593 (83.7%)	37,949 (92.9%)	<0.001
	Asian	236 (0.6%)	223 (0.5%)	
	Black	162 (0.4%)	121 (0.3%)	
	Mixed/Other	253 (0.7%)	200 (0.5%)	
	Missing	5,519 (14.6%)	2,365 (5.8%)	
BMI (kg/m^2)	Underweight (<18.5)	3,004 (8.0%)	6,433 (15.7%)	<0.001
	Healthy Weight (18.5-24.9)	11,697 (31.0%)	17,361 (42.5%)	
	Overweight (25.0-39.9)	5,727 (15.2%)	8,274 (20.3%)	
	Obese (>40)	3,399 (9.0%)	5,619 (13.8%)	
	Missing	13,936 (36.9%)	3,171 (7.8%)	
Comorbid Conditions	Heart Failure	14,716 (39.0%)	17,001 (41.6%)	<0.001
	Asthma [ever]	15,645 (41.4%)	24,846 (60.8%)	<0.001
	Asthma [year prior]	3,177 (8.4%)	4,318 (10.6%)	<0.001
	Bronchiectasis	2,324 (6.2%)	4,872 (11.9%)	<0.001
	Interstitial Lung Disease	1,686 (4.5%)	2,795 (6.8%)	<0.001
Symptom Burden	Cough symptoms	13,453 (35.6%)	27,843 (68.1%)	<0.001
	Sputum production	6,752 (17.9%)	18,886 (46.2%)	<0.001
	Breathlessness	27,351 (72.4%)	38,179 (93.4%)	<0.001
Smoking Status	Current smoker	13,201 (35.0%)	13,072 (32.0%)	<0.001
	Former smoker	9,478 (25.1%)	23,366 (57.2%)	
	Non smoker	5,061 (13.4%)	3,410 (8.3%)	
	Missing smoking status	10,023(26.5%)	1,010 (2.5%)	

IMD: Index of Multiple Deprivation (patient level), BMI: Body Mass Index, Data are presented as n (%) for categorical measures, Median and IQR for numerical variables. Comorbidities assessed as occurring at any point in medical record prior to death.

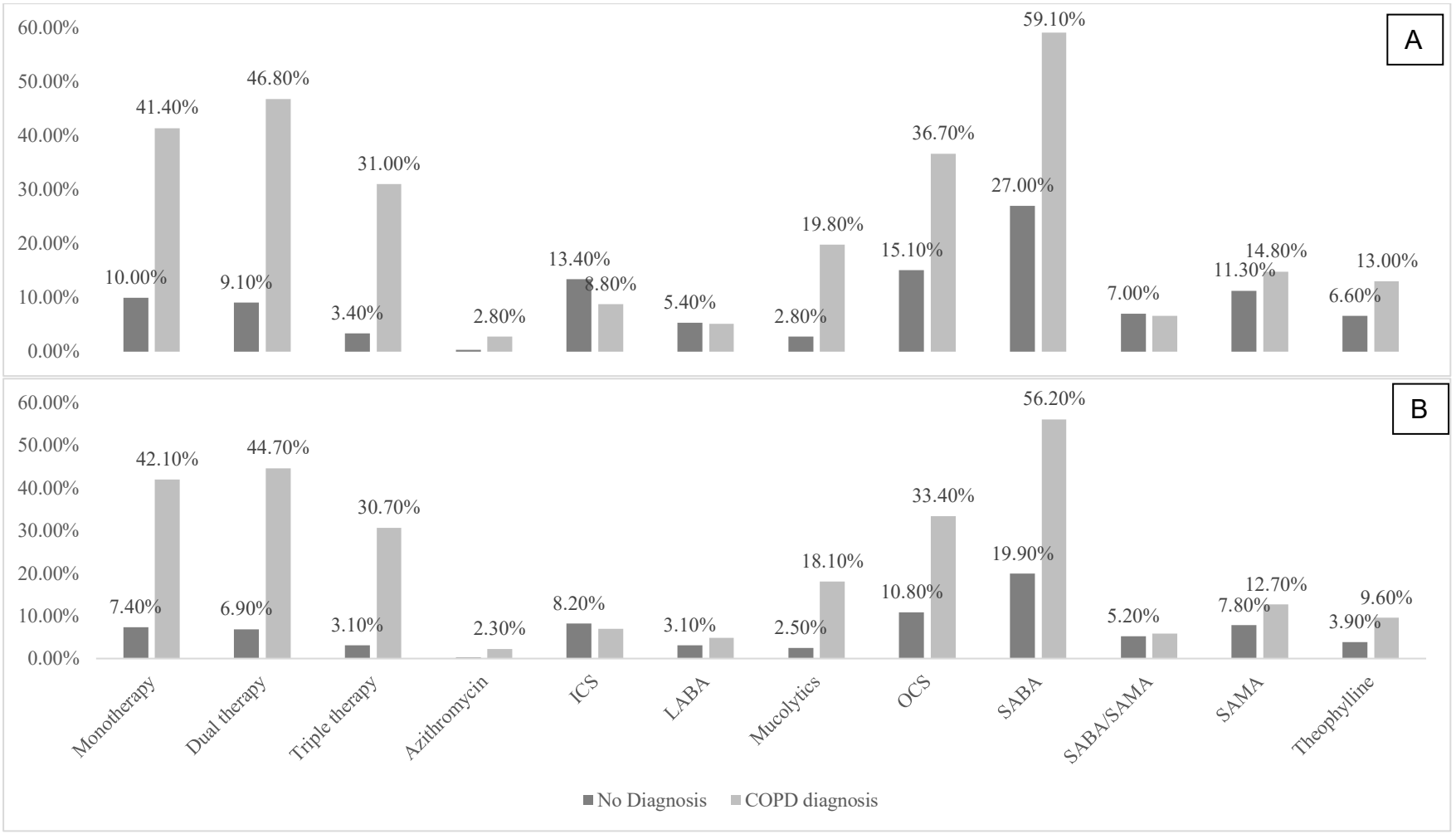


FIGURE 4-5 PRESCRIBED COPD PHARMACOTHERAPIES IN THE 3 MONTHS PRIOR TO DEATH

Panel A displays therapies prescribed among all patients (N = 78,621). Panel B displays therapies prescribed among those without an asthma diagnosis at any point in their medical history (N = 38,130). ICS: Inhaled Corticosteroids, LABA: Long-acting bronchodilator, OCS: Oral corticosteroids, SABA: Short-acting beta agonist, SAMA: Short-acting muscarinic antagonist

In the year prior to death, patients with a COPD diagnosis had more interactions with healthcare professionals. The median number of GP attendances was 15 over a year (IQR 7 – 25) vs 9 among those with a missed diagnosis (IQR 2 – 17). Those with a diagnosis had substantially higher rates of flu vaccination in the year prior to death than those with missed diagnosis (72% vs 53%). For hospitalisations, just over half of patients attended hospital in the month prior to death (57% among those with a diagnosis vs 52% among those without) and just under half of patients had a death in hospital (48% among those with a diagnosis and 45% among those without) (**Table 4.4**).

TABLE 4-4 HEALTHCARE INTERACTIONS PRIOR TO DEATH

	Missed COPD diagnosis N=37,763	COPD diagnosis N=40,858	P-Value
GP attendances [in week prior to death]	1 (0-3)	2 (0-4)	<0.001
GP attendances [in year prior to death]	9 (2-17)	15 (7-25)	<0.001
Hospital attendance [in month prior to death]	19,661 (52.1%)	23,135 (56.6%)	<0.001
Death in hospital	17,053 (45.2%)	19,742 (48.3%)	<0.001
Flu vaccination [in year prior to death]	6,669 (53.3%)	11,127 (72.2%)	<0.001

Data are presented as n (%) for categorical measures, Median and IQR for numerical variables.

The majority of patients with a COPD diagnosis (93%, N = 37,784) had a diagnostic code recorded in both primary and secondary care records, while 125 (0.3%) COPD diagnoses were detected in secondary care only and 2,949 (7.2%) in primary care only (**Table 4.5**). Those identified in secondary care only were less symptomatic and less likely to have key characteristics (e.g. smoking status, BMI) recorded, which may be partially attributed to fewer interactions with primary care.

TABLE 4-5 PATIENT CHARACTERISTICS OF THOSE WITH A COPD DIAGNOSIS BY SOURCE OF DIAGNOSIS CODE

		Primary care N=2,949	Secondary Care N= 125	Primary & Secondary Care N= 37,784
Age at Death		79 (71-86)	80 (72-86)	79 (72-85)
Sex	Male	1,605 (54.4%)	75 (60.0%)	20,271 (53.6%)
	Female	1,344 (45.6%)	50 (40.0%)	17,513 (46.4%)
IMD	1 - least deprived	499 (16.9%)	13 (10.4%)	5,300 (14.0%)
	2	552 (18.7%)	24 (19.2%)	6,645 (17.6%)
	3	593 (20.1%)	22 (17.6%)	7,350 (19.5%)
	4	612 (20.8%)	29 (23.2%)	8,447 (22.4%)
	5 - most deprived	687 (23.3%)	36 (28.8%)	9,970 (26.4%)
	Missing	6 (0.2%)	<5 (0.8%)	72 (0.2%)
Region	South of England	1,609 (54.6%)	60 (48.0%)	19,167 (50.7%)
	North of England	1,340 (45.4%)	65 (52.0%)	18,617 (49.3%)
Ethnicity	White	1,836 (62.3%)	113 (90.4%)	36,000 (95.3%)
	Asian	19 (0.6%)	<5 (1.6%)	202 (0.5%)
	Black	10 (0.3%)	<5 (1.6%)	109 (0.3%)
	Mixed/Other	21 (0.7%)	<5 (0.8%)	178 (0.5%)
	Missing	1,063 (36.0%)	7 (5.6%)	1,295 (3.4%)
BMI (kg/m^2)	Underweight (<18.5)	476 (16.1%)	10 (8.0%)	5,947 (15.7%)
	Healthy Weight (18.5-24.9)	1,262 (42.8%)	44 (35.2%)	16,055 (42.5%)
	Overweight (25.0-39.9)	552 (18.7%)	28 (22.4%)	7,694 (20.4%)
	Obese (>40)	373 (12.6%)	15 (12.0%)	5,231 (13.8%)
	Missing	286 (9.7%)	28 (22.4%)	2,857 (7.6%)
Comorbid Conditions	Heart Failure	503 (17.1%)	60 (48.0%)	16,438 (43.5%)
	Asthma [ever]	1,496 (50.7%)	55 (44.0%)	23,295 (61.7%)
	Asthma [year prior]	371 (12.6%)	15 (12.0%)	3,932 (10.4%)
	Bronchiectasis	164 (5.6%)	8 (6.4%)	4,700 (12.4%)
	Interstitial Lung Disease	99 (3.4%)	8 (6.4%)	2,688 (7.1%)
Symptom Burden	Cough symptoms	1,836 (62.3%)	18 (14.4%)	25,989 (68.8%)
	Sputum production	1,062 (36.0%)	<5 (3.2%)	17,820 (47.2%)
	Breathlessness	2,159 (73.2%)	34 (27.2%)	31,810 (84.2%)
Smoking Status	Current smoker	1,133 (38.4%)	54 (43.2%)	11,885 (31.5%)
	Former smoker	1,330 (45.1%)	41 (32.8%)	21,995 (58.2%)
	Non smoker	361 (12.2%)	18 (14.4%)	3,031 (8.0%)
	Missing smoking status	125 (4.2%)	12 (9.6%)	873 (2.3%)

IMD: Index of Multiple Deprivation (patient level), BMI: Body Mass Index, Data are presented as n (%) for categorical measures, Median and IQR for numerical variables. Comorbidities assessed as occurring at any point in medical record prior to death.

4.4.2 Factors associated with missed diagnosis

A number of factors were identified as independently associated with missed diagnosis in the multiple regression model (**Table 4.6**). Missed COPD diagnosis was more likely in individuals who had no recorded smoking status compared with current smokers. Similarly, being a non-smoker, being overweight or obese and black, Asian and unknown ethnicities were associated with increased odds of missed diagnosis. Conversely, several factors reduced the likelihood of missed diagnosis: calendar time, being a former smoker compared with current smoking, being underweight, residing in the north of England, comorbid asthma, bronchiectasis and ILD.

TABLE 4-6 ADJUSTED ODDS RATIOS FOR MISSED COPD DIAGNOSIS FOR ALL FACTORS TESTED IN THE MULTIPLE REGRESSION MODEL

		Odds Ratio (95%CI)	P-Value
Birth Year		**0.99 (0.99 – 1.00)**	<0.001
Female		**1.16 (1.12 – 1.21)**	<0.001
Year of Death		**0.86 (0.86 – 0.87)**	<0.001
Smoking Status	Former-Smoker vs Current Smoker	**0.42 (0.40 – 0.43)**	<0.001
	No Smoking Record vs Current smoker	**4.52 (4.13 – 4.95)**	<0.001
	Non-smoker vs Current smoker	**1.26 (1.18 – 1.35)**	<0.001
BMI (kg/m^2)	Underweight vs Healthy Weight	**0.63 (0.59 – 0.67)**	<0.001
	Overweight vs Healthy Weight	**1.15 (1.10 – 1.21)**	<0.001
	Obese vs Healthy Weight	**1.11 (1.05 – 1.17)**	<0.001
Region	North of England vs South of England	**0.86 (0.80 – 0.92)**	<0.001
IMD Quintile	2 vs 1 (least deprived)	0.96 (0.90 – 1.03)	0.230
	3 vs 1	0.96 (0.90 – 1.03)	0.255
	4 vs 1	0.95 (0.88 – 1.02)	0.122
	5 vs 1	1.02 (0.95 – 1.10)	0.630
Ethnicity	Black vs White	**1.87 (1.37 – 2.54)**	<0.001
	Mixed/Other vs White	1.08 (0.83 – 1.39)	0.654
	Asian vs White	**1.54 (1.21 – 1.96)**	<0.001
	Unknown vs White	**1.28 (1.20 – 1.38)**	<0.001
Comorbid Conditions	Asthma	**0.39 (0.38 – 0.41)**	<0.001
	Interstitial Lung Disease	**0.92 (0.85 – 1.00)**	0.040
	Bronchiectasis	**0.72 (0.68 – 0.77)**	<0.001

CI: confidence interval. Northern regions include: Northeast, Northwest, Yorkshire and the Humber, East Midlands, West Midlands. Southern Regions: East of England, Southwest, South Central, London, Southeast Coast. IMD: index of multiple deprivation

Sensitivity Analysis

Findings from the sensitivity analysis removing patients with asthma were consistent with those of the main analysis; missed COPD diagnosis remained more likely in individuals with no recorded smoking status compared with current smokers (OR 5.34; 95%CI 4.57 – 6.23), and less likely for former compared to current smoking (OR 0.39; 95%CI 0.37 – 0.41), presence of bronchiectasis (OR 0.68; 95%CI 0.62 – 0.76), and calendar time (year of death, OR 0.90; 95%CI 0.98-0.99) (**Table 4.7**).

TABLE 4-7 ODDS OF MISSED DIAGNOSIS AMONG THOSE WITH A COPD-RELATED DEATH EXCLUDING THOSE WITH CONCOMITANT ASTHMA DIAGNOSIS

		Odds Ratio (95%CI)	P-Value
Birth Year		**0.99 (0.98 – 0.99)**	<0.001
Female		**1.09 (1.03 – 1.15)**	0.004
Year of Death		**0.90 (0.89 – 0.90)**	<0.001
Smoking Status	Former-Smoker vs Current Smoker	**0.39 (0.37 - 0.41)**	<0.001
	No Smoking Record vs Current smoker	**5.34 (4.57 - 6.23)**	<0.001
	Non-smoker vs Current smoker	**1.31 (1.18 - 1.46)**	<0.001
BMI (kg/m^2)	Underweight vs Healthy Weight	**0.61 (0.56 – 0.66)**	<0.001
	Overweight vs Healthy Weight	**1.16 (1.08 – 1.24)**	<0.001
	Obese vs Healthy Weight	1.08 (1.00 – 1.18)	0.064
Region	North of England vs South of England	**0.89 (0.81 – 0.96)**	0.003
IMD Quintile	2 vs 1 (least deprived)	0.98 (0.89 – 1.08)	0.657
	3 vs 1	0.95 (0.86 – 1.04)	0.318
	4 vs 1	0.98 (0.88 – 1.08)	0.622
	5 vs 1	1.01 (0.92 – 1.12)	0.784
Ethnicity	Black vs White	**2.14 (1.27 – 3.62)**	0.004
	Mixed/Other vs White	1.39 (0.95 – 2.02)	0.088
	Asian vs White	1.50 (0.98 – 2.27)	0.060
	Unknown vs White	**1.43 (1.30 – 1.57)**	<0.001
Comorbid Conditions	Interstitial Lung Disease	0.95 (0.85 – 1.06)	0.329
	Bronchiectasis	**0.68 (0.62 – 0.76)**	<0.001

CI: confidence interval. Northern regions include: Northeast, Northwest, Yorkshire and the Humber, East Midlands, West Midlands. Southern Regions: East of England, Southwest, South Central, London, Southeast Coast. IMD: index of multiple deprivation

4.5 Discussion

4.5.1 Summary of main findings

This population-based retrospective cohort study estimated the proportion of people with death attributed to COPD who had evidence of a COPD diagnosis in their medical records. Regardless of the definition used, the proportion of patients with a missed diagnosis during their lifetime decreased between 2000 and 2017, suggesting that there were improvements in COPD detection and/or recording. However, the proportion of people with missed diagnosis varied widely depending on the definition of COPD used; anywhere from 4% to as high as 73% of patients were identified with missed diagnosis of COPD, with those definitions including spirometry recorded having lower proportions. Patients without evidence of a COPD diagnosis were more likely to have no smoking information recorded, little or no respiratory symptoms, and fewer comorbid conditions, suggesting less frequent contact with healthcare and therefore less opportunity for diagnosis.

4.5.2 Comparison with other work

Globally, the estimated proportion of undiagnosed COPD patients varies (Diab et al., 2018). In a Danish prospective cohort study, Çolak et al. concluded that 78% of people at high risk of developing COPD (former and current smokers aged 40 years or older with a cumulated tobacco consumption of ten pack-years or higher, and who did not have asthma) had undiagnosed disease (Çolak et al., 2017). Similarly, among a random sample of adults without a previous history of asthma or COPD in Canada, Preteroti et al. estimated that 12% of adults with respiratory symptoms had spirometry-confirmed COPD (Preteroti et al., 2020). Miravitalles et al. investigated the prevalence of persistent airflow limitation in Spain using a definition of post-bronchodilator $FEV_1/FVC < 0.7$; among 4,274 adults aged 40 to 80 years, the prevalence of persistent airflow obstruction was 10%, with only 27% of those subjects identified having previously received a diagnosis of COPD (Miravitlles et al., 2009). Using data obtained from the NHANES survey in the US, Hangaard et al. estimated that among 1,098 subjects with post-bronchodilator $FEV_1/FVC < 0.7$ or < LLN, 92% had no previous diagnosis of COPD, defined by patient self-report (Hangaard et al., 2019). Their findings starkly contrast the estimated number of missed patients presented in this study when considering definitions including

spirometry (34% and 27%, E and F respectively). The current estimate of the proportion of missed COPD diagnosis differs from previous research due to the definition of the study population: whilst the previous research in this area identifies patients prospectively from mid-age or select a group of high-risk individuals whom guidelines recommend should receive a diagnosis, the present study identified COPD diagnosis retrospectively and considered all available medical records to detect physician-identified disease.

I found that the absence of any recording of smoking status in GP records is frequent and is strongly associated with an increased odds of missed COPD diagnosis. While it is well established that cigarette smoking is the most important and consistent determinant of the development and progression of COPD in the UK (Devereux, 2006), this finding highlights the importance of including smoking habits in clinical records in order to identify patients at risk of chronic lung disease. Furthermore, former smokers were less likely to have a missed diagnosis compared to current smokers; this was an expected finding as former smokers are more likely to exhibit health seeking behaviour as they commit to quitting and therefore have more opportunities to be diagnosed. Smoking status and other factors, including BMI, sex and comorbid conditions, identified as being associated with missed diagnosis are similar to those identified in other studies. The Canadian Obstructive Lung Disease study, a prospective population-based sample of adults ≥40 years, estimated the proportion of adults with undiagnosed COPD (post-bronchodilator $FEV_1/FVC < 0.7$ but not physician diagnosis) to be 14% (Gershon et al., 2018). Similar to the present study, they found that 60% of those without a diagnosis presented with fewer COPD symptoms (cough, sputum, wheeze or breathlessness) and were more likely to have no smoking record. Using data from multiple surveys, Lamprecht et al. demonstrated that the probability of missed COPD (post-bronchodilator $FEV_1/FVC <$ LLN but no diagnosis of COPD by a physician or health-care professional) increased with male sex, younger age, lower education, a “never” smoking status, lack of previous spirometry, and milder severity of airflow limitation (Lamprecht et al., 2015). The current study confirms the characteristics associated with the probability that a COPD patient may be missed, these could be used to identify high-risk individuals using routinely collected information partnered with spirometry and supports the inclusion of these key patient characteristics in targeted screening initiatives.

Differences between those who received a COPD diagnosis and those who were missed may be further explained by factors that we were not able to measure. Whilst the majority of diagnosed patients had COPD recorded in both primary care and secondary care, the communication between these settings is not always complete. Practice related reasons are important for missing COPD diagnoses; having trained staff to carry out spirometry correctly according to validated guidelines is sometimes short in supply and may not be possible through virtual healthcare delivery (Poels et al., 2006). A recent BLF report estimates that 46,000 people had a missed diagnosis during the pandemic, with 34% of those with COPD not receiving spirometry at diagnosis (BLF, 2021). In this study, a small proportion of patients without recorded diagnosis while alive had spirometry performed, and where this was done, the majority did not have lung function measures that met diagnostic criteria for COPD. This suggests that some COPD deaths may have been recorded in error, that some spirometry tests are performed/interpreted incorrectly, or that the selection of patients to test for COPD needs refining. Active case finding can identify around 70% more cases than opportunistic examination (Fromer, 2011), and significant variation in where this takes place across the country has been shown (Haroon et al., 2015). Many of the non-diagnosed patients presented with no or few respiratory symptoms, which may prevent a GP to investigate possible COPD; therefore, a broader targeted screening-based approach that included many of the patient characteristics identified in this study would be needed to estimate the proportion of less symptomatic COPD patients.

I also observed improvements in the proportion of patients with a diagnosis over time. This may be partially attributed to improvements in recording of data. When considering evidence of COPD diagnosis defined by presence of a diagnostic code only [A], the proportion of patients missed reduced to 0% in 2017, demonstrating that diagnostic coding of COPD is becoming more complete among those with a COPD recorded death. The QOF was introduced in 2004 and provided incentives for primary care practices to keep registers of patients with chronic disease (James et al., 2014); practices were rewarded for documenting confirmed diagnosis of COPD with spirometry, recording FEV_1, checking inhaler technique, offering flu vaccination, and recording smoking status of all patients identified on the registers. This may have contributed towards the 50% increase over a 10-year period in the recorded

prevalence of COPD between 2000 and 2009 (Falzon et al., 2013) as well as the decline in the proportion of patients that had a missed diagnosis after 2004 (Figure 3). Improvements in COPD diagnosis may also be attributed to increased case-finding and targeted screening initiatives at the local and regional level (Falzon et al., 2013, Wright et al., 2015). The British Lung Foundation's "missing millions" campaign raised awareness of the possibility that a large proportion of COPD patients were undiagnosed (BLF, 2006).

4.5.3 Strengths and Limitations

A major strength of this study was the breadth of data available, as linked data between primary and secondary care provide near complete records of the patient clinical journey. Results of spirometry performed in hospital and hospital recorded medical information (e.g. comorbid conditions) were not included in this study; however, I expect the impact of this to me minimal as outpatient activity is poorly coded and the majority of diagnostic services sit within primary care. Diagnosis of COPD was based on physician coding which does not include free text notes; however, this previously validated definition using a combination of presence of a COPD diagnostic code with evidence of spirometry in the medical record has been shown to have high specificity and sensitivity (Quint et al., 2014b).

This is the first study to use a COPD recorded death as the reference for confirmed COPD, and this approach assumes that death certificates are a clinical "gold standard". Mortality data for England and Wales are nearly 100% complete, a large proportion of registered deaths are certified by a medical practitioner and accuracy of recording has improved over time (ONS, 2020b). However, a key limitation of this study design is that undiagnosed COPD patients may have died due to other causes, and therefore this study does not reflect a complete assessment of the number of COPD patients who are missed; further research inclusive of broader causes of death is needed for a complete estimate of these patients.

4.6 Conclusion

The majority of COPD patients received a diagnosis prior to a COPD-related death, and this appeared to have improved over time. Those who did not were more likely to be non-smokers, did not present with symptoms to the GP and therefore may not have been flagged to have diagnostic spirometry; this suggests that there is room for improvement in either the performance of and/or recording of spirometry. Obtaining granular information on patient's clinical status in medical records is of high importance as it has implications on the quality of care delivered. Disease management plans are informed by the details included in patient records, regardless of where a patient is managed; therefore, there is a need to ensure that these vital tests are performed, recorded, and shared transparently between primary and secondary care.

5 Chapter 5: Mortality rates in diagnosed COPD

Chapter 5 describes the mortality burden associated with a diagnosis of COPD in the UK and how this has changed over a 10-year period. Leading causes of death among the diagnosed population are explored.

Parts of the research presented in this chapter has been previously published at Gayle, Alicia V., et al. "Changing causes of death for patients with chronic respiratory disease in England, 2005-2015." *Thorax* 74.5 (2019): 483-491. This publication benefitted from the input of several co-authors as well as my thesis supervisors. My role consisted in conducting the statistical analyses and writing the first draft of the manuscript.

5.1 Background

The past 40 years have brought considerable improvements in COPD management. New pharmacologic treatments reduce the risk of exacerbations and manage disease symptoms. To date smoking cessation (Anthonisen et al., 1994), and long term oxygen therapy (where indicated) (NOTTG, 1980) have been shown in clinical trials to reduce mortality. Maintaining and managing a register of COPD patients in primary care has been incentivised through the Quality and Outcomes Framework (NHS Digital, 2017). Community and hospital-based multidisciplinary management teams, including doctors, nurses, physiotherapists, occupational therapists, pharmacists, dieticians, social workers and mental health specialists, have been brought together to improve coordination, communication, and decision making between healthcare professionals and COPD patients (NICE, 2018). Despite these developments, respiratory-related mortality rates seem stable and remains the third highest cause of death in the UK (**Chapter 3**).

COPD itself is a major cause of mortality for COPD patients, along with other respiratory diseases and cancer; it has been reported that one-third of patients with COPD die from CVD (Rabe and Watz, 2017, Hansell et al., 2003b, Mannino and Kiri, 2006). While mortality rates for CVD in the general population have fallen in recent years, mortality due to lung diseases has remained constant (BLF, 2016a). With an ageing population, improvements in treatments, and earlier diagnosis, it is not known whether there have been changes in the underlying causes of death in patients with COPD over time.

Many studies have investigated respiratory deaths reported on death certificates (BLF, 2016a, Soriano et al., 2017); however, relying on death certificates alone means that a large number of diagnosed patients are missed. In an earlier study analysing the epidemiology of deaths in England and Wales, only 60% of deaths where obstructive lung disease (COPD or asthma) was mentioned on the death certificate were attributed to obstructive lung disease as the underlying cause of death (Hansell et al., 2003a). In contrast, for the leading cause of death, 94% of deaths mentioning myocardial infarction (MI) on the death certificate were attributed to MI as the underlying cause of death. Therefore, there is a need to understand the mortality burden attributed to COPD among those with a COPD diagnosis.

5.2 Study aims and objectives

The aim of this study is to describe the mortality burden among the diagnosed COPD population. The specific study objectives include:

- calculate the all-cause and age standardised mortality rates of patients with COPD
- compare mortality among the COPD population to the general population
- determine the leading causes of death in COPD patients
- investigate the temporal pattern of causes of death between 2005 and 2015

5.3 Methods

5.3.1 Study Design

I used a prevalent cohort study design as the basis for this analysis. The study population comprised individuals who, according to their primary care records, had a diagnosis of COPD prior to the end of the study period (31st December 2015) and resided in England. The primary outcome of interest was death due to any cause. The study period was defined as 1st January 2005 – 31st December 2015. Follow up began at the latest of the following dates:

- study start date (1st January 2005)
- the date CPRD deemed the submitting general practice was "up to standard" (i.e. the practice had passed a number of quality checks and was deemed suitable for research use)
- the date a patient joined the practice
- the date of the first diagnosis COPD

Patients were followed until the earliest of:

- study end date (31st December 2015)
- the date the general practice stopped contributing data to the CPRD (last collection date)
- the date the patient transferred out of a GP practice
- the date the patient died

5.3.2 Data Sources

The September 2017 build of the CPRD GOLD dataset was used for this analysis. Linked IMD and ONS mortality data was obtained for patients belonging to practices that were eligible for linkage (linkage set 14). The approval for this research was published at https://cprd.com/protocol/changes-cause-mortality-over-time-people-chronic-respiratory-disease-uk.

5.3.3 Study Population

To be eligible for inclusion in the cohort, patients had to satisfy the following inclusion criteria:

- A GP diagnosis of COPD (at least one recorded COPD diagnosis prior to 31st December 2015)
- Age over 35 at the time of COPD diagnosis
- "acceptable" patient status in CPRD (See **Section 2.3.3**)
- Alive at least one day between 1 January 2005 and 31 December 2015

5.3.4 Exposure

The exposure is COPD diagnosis. A validated COPD code list (Quint et al., 2014a) was the basis for the COPD diagnosis definition (see **Appendix 9.3: Table C** for codes used).

5.3.5 Outcome

The outcome is mortality, using the date of death as reported in ONS and classified using The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes, grouped into chapters. The cause of death was obtained from ONS data, which has been derived using standardized guidelines from information available on death certificates (Devis and Rooney, 1999b). The underlying cause of death derived by ONS was considered as the main cause of death (See **Section 2.2.1**).

Causes of death were grouped according to ICD-10 chapters: respiratory disease (ICD J00 – J99), cardiovascular disease (ICD F01, G45, I00–I99, Q20, Q28, and R96), any malignant neoplasm (ICD C00–C99 and D1–D48), diseases of the digestive system (ICD K00 –K93), mental and behavioural disease (ICD F00- F99), and other causes (see **Appendix 9.3: Table A** for ICD-10 grouping).

5.3.6 Covariates

Covariates were measured at the closest date to the beginning of the follow up (See **Section 5.3.1**), and they included age at study start, age at death, sex, smoking status, BMI, comorbid respiratory disease, and IMD. Age was measured in years. Socioeconomic score was determined using linked CPRD-IMD 2015 data divided into quintiles, where 1- is most deprived and 5- is least deprived (Quint et al., 2014b). Baseline BMI was calculated using height and weight data from CPRD, and was categorised using WHO groupings, where <18.5 kg/m² was 'underweight', 18.5-24.9 kg/m² 'healthy weight', 25.0-29.9 kg/m² 'overweight',>30.0 kg/m² 'obese', and

'missing'. Smoking status was classified, based on recorded status at the start of follow-up, as 'never smoker', 'current smoker', 'former smoker' (Quint et al., 2016).

Comorbid chronic respiratory disease included asthma (Bloom et al., 2017), bronchiectasis (Quint et al., 2016) and interstitial lung disease (ILD) (Dalleywater et al., 2015), diagnosed at any point prior to COPD diagnosis. The code lists used to identify these conditions have been previously published (see **Appendix 9.3: Tables F, R & U** for codes used).

5.3.7 Statistical Analyses

Patient characteristics were described at baseline and separately for COPD patients who had died during the study period. Patient characteristics were described using me and SD (for continuous variables), median and IQR (for non-normal distributed variables), and N and proportions (%) for categorical/binary variables.

Cause of Death

The five most common ICD-10 chapter causes of death were listed, and the most frequently coded individual causes of death within each chapter were highlighted. Changes in disease-specific mortality were described as the proportions of deaths due to specific ICD-10 chapter causes in each calendar year. Changes in the proportion of deaths attributed to each cause over time were evaluated using the Cochrane-Armitage test for trend.

Mortality Rates

Mortality trends were analysed between 2005 and 2015. Mortality rates for the COPD population were calculated and compared with mortality rates in the general population from ONS data. The crude 10-year all-cause mortality rate was obtained by calculating the number of deaths in the COPD population in the CPRD dataset and dividing by the midpoint COPD population for that year, then averaging over the 10-year study period. Additionally, using direct standardisation (adjusting for differences in the age distribution across study populations by referring to the age structure of a common population used as standard) against the 2013 European standard population (Eurostat, 2013), age standardised mortality rates (ASMR) were calculated, and results were compared to the ONS published data on all-cause mortality figures in England for each year (ONS, 2013, ONS, 2016).

Sensitivity Analyses

As a sensitivity analysis, ONS derived causes of death were compared with the cause of death reported in the first position on the death certificate; this enabled better understanding of whether using diseases recorded in the first position altered the results.

In an additional sensitivity analysis, mortality rates and causes of death were computed after excluding patients that had a co-diagnosis of another chronic respiratory disease (asthma, bronchiectasis, or an interstitial lung disease).

All statistical analyses were performed in STATA version 15 (StataCorp LP, College Station, Texas, US).

5.4 Results

5.4.1 Cohort Characteristics

137,709 COPD patients who met the inclusion criteria were identified (**Figure 5.1**), of whom 54,320, died (39%) between 2005 and 2015. Patients were followed for a median of 3.4 years (IQR 1.4 – 6.1), and the average age at study start was 69 (SD 12); the average age at death was 79.1 (SD 9.8), and this was higher among females compared to males (80.0 vs 78.3 respectively). **Table 5.1** details patient characteristics. Only 47% of patients who died (n = 25,760) had a COPD listed in any position on their death certificate.

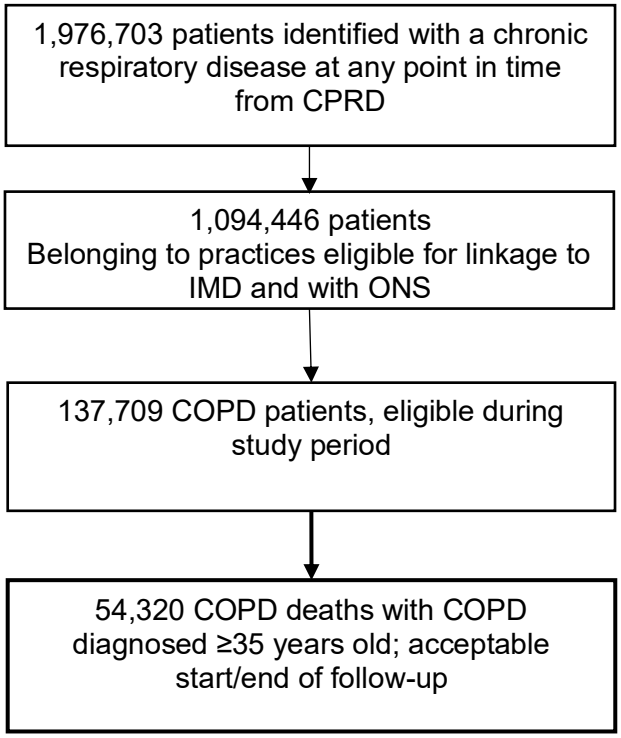


FIGURE 5-1 FLOW CHART OF PATIENT INCLUSION

TABLE 5-1 DESCRIPTIVE CHARACTERISTICS OF COPD PATIENT COHORT

	Baseline Cohort, N (%) N = 137,709	**Deceased Cohort,** N (%) N = 54,320
Female	65,060 (47.2)	24,696 (45.5)
Smoking Status		
Never Smoker/Not Recorded	26,598 (19.3)	10,561 (19.4)
Current Smoker	47,472 (34.5)	16,042 (29.5)
Former Smoker	63,639 (46.2)	27,717 (51.0)
Body Mass Index (kg/m²)		
Underweight (< 18.5)	6,522 (4.7)	3,839 (7.1)
Healthy Weight (18.5-24.9)	42,639 (31.0)	18,334 (33.8)
Overweight (25.0-29.9)	39,474 (28.7)	13,730 (25.3)
Obese (>= 30)	32,458 (23.6)	9,971 (18.4)
Missing	16,616 (12.1)	8,446 (15.5)
Diagnosis of Asthma	46,653 (33.9)	11,870 (21.9)
Diagnosis of Bronchiectasis	6,625 (4.81)	2,664 (4.90)
Diagnosis of ILD	2,635 (1.91)	1,481 (2.73)
Diagnosis IPF	307 (0.2)	206 (0.4)
Diagnosis Pneumoconiosis	670 (0.5)	311 (0.6)
Diagnosis Sarcoidosis	105 (0.1)	34 (0.1)
Index of Multiple Deprivation		
1- Most Deprived	20,358 (14.8)	7,878 (14.5)
2-	25,798 (18.8)	10,352 (19.1)
3-	27,888 (20.3)	11,159 (20.6)
4-	30,623 (22.3)	11,886 (21.9)
5- Least Deprived	32,923 (23.9)	12,998 (24.0)

IPF: idiopathic pulmonary fibrosis

5.4.2 Mortality rates

The crude all-cause 10-year mortality rate for patients with COPD was 1,245 per 100,000 (95%CI: 1,241 – 1,248). The 10-year ASMR was 1,503 per 100,000 (95%CI: 1,492-1,513). After removing those with a comorbid respiratory disease (n = 39,468), this was 3,106 per 100,000 (95%CI: 3,085-3,126). The ASMR among those without comorbid conditions was consistently higher than that among those with comorbid respiratory diseases. Rates among COPD patients were substantially and consistently higher than in the general population (**Figure 5.2**).

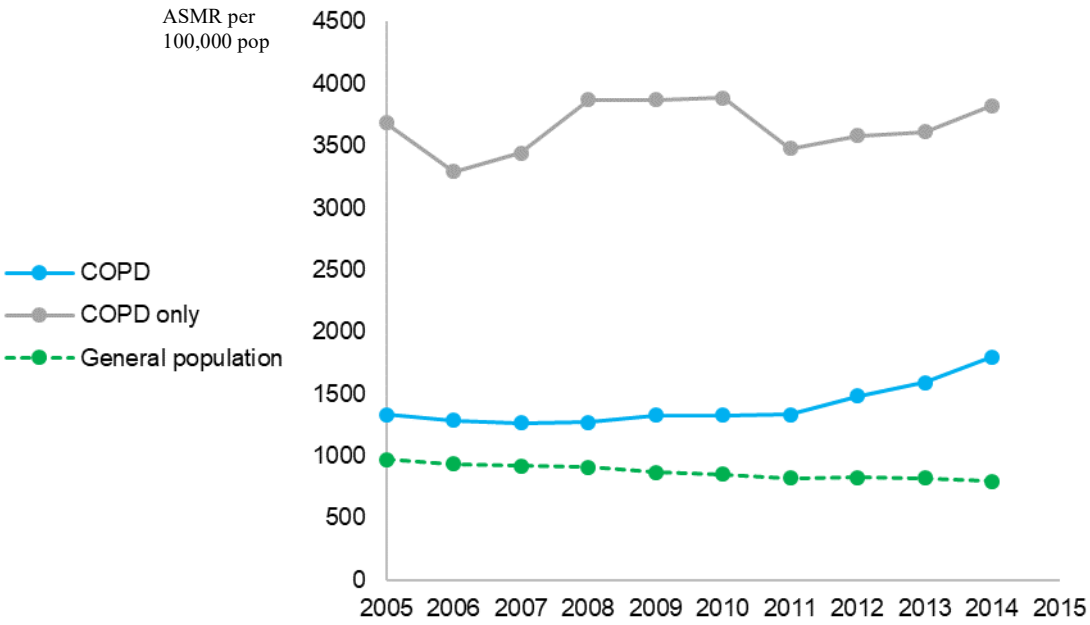


FIGURE 5-2 AGE-STANDARDIZED MORTALITY RATES (ASMR) PER 100,000 POPULATION COMPARED TO THE GENERAL POPULATION, 2005-2015.

Rates compared to the general population. 'COPD only' refer to those patients with that COPD and no other respiratory disease comorbidities. 'COPD' refers to real-world population allowing for additional respiratory disease comorbidities. Pop = population.

5.4.3 Cause of death

The leading causes of death are shown in **Figure 5.3**. The largest proportion of deaths were attributed to respiratory diseases (36%) (**Table 5.2**); among respiratory deaths, deaths due to COPD (77%) and pneumonia (11%) accounted for 88% of all respiratory deaths (**Table 5.4**). The second most common cause of death were diseases of the circulatory system (25%). Neoplasms (23%) were the third leading causes of death with lung cancer accounting for over one-third (45%) of deaths in this chapter. The other main causes were mental and behavioural disorders and diseases of the nervous system (6%). Diseases of the digestive system was assigned as the cause in 4% of all deaths. These five leading causes of death accounted for 94% of all deaths (**Figure 5.3**). When considering the cause of death reported in the first position on the death certificate, the leading causes of death remained the same (**Table 5.3**).

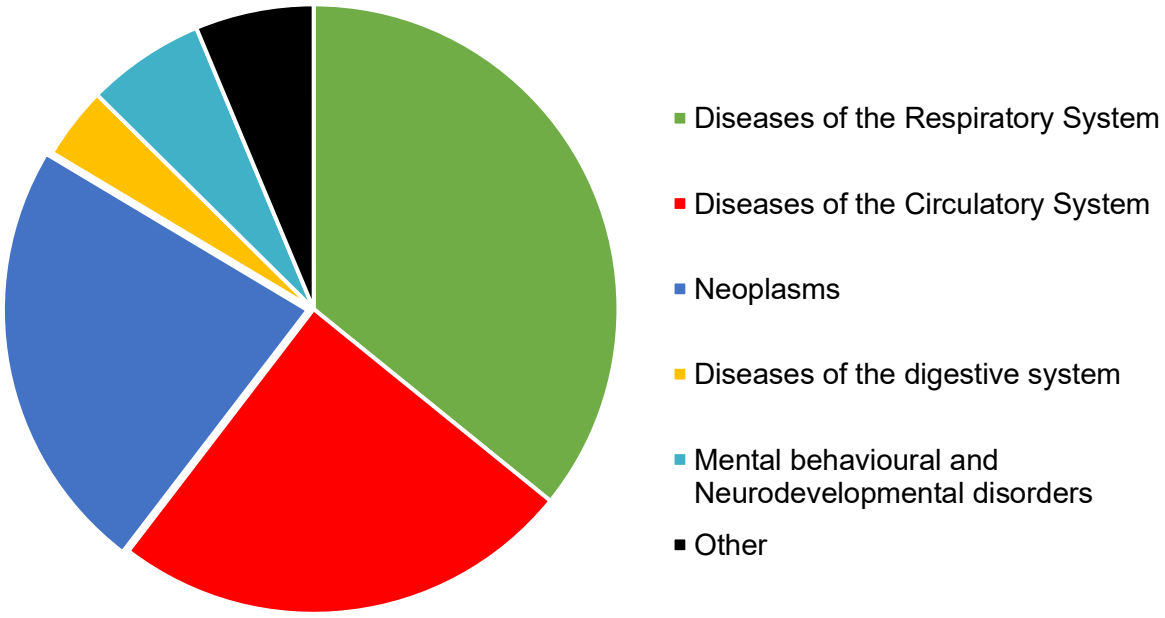


FIGURE 5-3 LEADING CAUSES OF DEATH

ICD-10 chapters F (mental and behavioural disorders) and G (diseases of the nervous system) have been combined. 'Other' refers to causes of death categorized in all ICD-10 chapters outside of C, D00-48, F, G, J, K., and I

TABLE 5-2 CAUSE OF DEATH BY ICD-10 CHAPTER

Chapter (ICD-10)	N	% of all Deaths
Diseases of the respiratory system (J00-J99)	19,638	36%
Diseases of the circulatory system (I00-I99)	13,334	25%
Neoplasms (C00-D48)	12,743	23%
Mental and behavioural disorders (F00-F99)	2,129	4%
Diseases of the digestive system (K00-K93)	2,103	4%
Diseases of the nervous system (G00-G99)	914	2%
External causes of morbidity (V01-Y98)	871	2%
Diseases of the genitourinary system (N00-N99)	823	2%
Certain infectious and parasitic diseases (A00-B99)	586	1%
Endocrine, nutritional and metabolic diseases (E00-E90)	494	1%
Diseases of the musculoskeletal system and connective tissue (M00-M99)	302	1%
Diseases of the skin and subcutaneous tissue (L00-L99)	168	0%
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	89	0%
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	82	0%
Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	35	0%
Provisional assignment of new diseases of uncertain aetiology or emergency use (U00-U49)	6	0%
Diseases of the eye and adnexa, the ear and mastoid process (H00-H95)	< 5	0%
Pregnancy, childbirth and the puerperium (O00-O99)	0	0%
Total	**54,320**	**100%**

TABLE 5-3 CAUSES OF DEATH BY CHAPTER - USING THE ICD-10 CODE IN FIRST POSITION ON DEATH CERTIFICATE.

Chapter (ICD-10)	N	% of all deaths
Diseases of the respiratory system (J00-J99)	23,567	43%
Diseases of the circulatory system (I00-I99)	11,397	21%
Neoplasms (C00-D48)	9,902	19%
Mental and behavioural disorders (F00-F99)	2,273	5%
Certain infectious and parasitic diseases (A00-B99)	2,057	4%
Diseases of the digestive system (K00-K93)	1,586	3%
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	1,160	2%
Diseases of the genitourinary system (N00-N99)	992	2%
External causes of morbidity (V01-Y98)	588	1%
Diseases of the nervous system (G00-G99)	456	1%
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	180	0%
Endocrine, nutritional and metabolic diseases (E00-E90)	101	0%
Diseases of the skin and subcutaneous tissue (L00-L99)	32	0%
Diseases of the musculoskeletal system and connective tissue (M00-M99)	22	0%
Provisional assignment of new diseases of uncertain aetiology or emergency use (U00-U49)	6	0%
Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	<5	0%
Pregnancy, childbirth and the puerperium (O00-O99)	0	0%
Diseases of the eye and adnexa, the ear and mastoid process (H00-H95)	0	0%
Total	**54,320**	**100%**

The most common individual causes of death were COPD, ischaemic heart disease, and lung cancer for each chapter, respectively (**Table 5.4**). For COPD patients without other chronic respiratory diseases (n = 39,468), the leading causes of death were respiratory disease (35%), circulatory (25%), and neoplasms (24%) and similarities were seen among the leading individual causes within each chapter (**Table 5.5**).

TABLE 5-4 LEADING FIVE CAUSES OF DEATH. PRESENTED AS COUNTS, % OF ALL DEATHS, AND % OF DEATHS WITHIN ICD-10 CHAPTER.

Chapter (ICD10)	N	% of all deaths	% of chapter
Diseases of the Respiratory System (J00-J99)	19,638	36%	100%
COPD	15,164	28%	77%
Pneumonia	2145	4%	11%
Idiopathic pulmonary fibrosis	486	1%	2%
Bronchiectasis	461	1%	2%
Asthma	239	0%	1%
Lung disease due to external agents	371	1%	2%
Influenza	7	0%	0%
Other	765	1%	4%
Diseases of the Circulatory System (I00-I99)	13,334	25%	100%
Ischaemic Heart Disease	6,688	12%	50%
Cerebrovascular Disease	2,706	5%	20%
Heart Failure	665	1%	5%
Other	3,275	6%	25%
Neoplasms (C00-D48)	12,743	23%	100%
Lung Cancer	5,713	11%	45%
Prostate Cancer	681	1%	5%
Breast Cancer	391	1%	3%
Pancreatic Cancer	471	1%	4%
Bladder Cancer	418	1%	3%
Pleural Mesothelioma	16	0%	0%
Other	12,743	23%	40%
Mental and behavioural disorders and Diseases of the nervous system (F00-G99)	3,043	6%	100%
Diseases of the digestive system (K00-K93)	2,103	4%	100%
TOTAL	50,861	94%	

TABLE 5-5 TOP 5 CAUSES OF DEATH AMONG PATIENTS WITHOUT COMORBID RESPIRATORY DISEASE

Chapter (ICD10)	N	% of all deaths	% of chapter
Diseases of the Respiratory System (J00-J99)	13,784	35%	70%
COPD	11,102	28%	57%
Pneumonia	1,559	4%	8%
Idiopathic pulmonary fibrosis	136	0%	1%
Bronchiectasis	101	0%	1%
Asthma	112	0%	1%
Lung disease due to external agents	247	1%	1%
Influenza	<5	0%	0%
Other	527	1%	3%
Diseases of the Circulatory System (I00-I99)	9,783	25%	73%
Ischaemic Heart Disease	4,834	12%	36%
Cerebrovascular Disease	2,038	5%	15%
Heart Failure	496	1%	4%
Other	2,415	6%	18%
Neoplasms (C00-D48)	9,393	24%	74%
Lung Cancer	4,346	11%	34%
Prostate Cancer	501	1%	4%
Breast Cancer	268	1%	2%
Pancreatic Cancer	329	1%	3%
Bladder Cancer	312	1%	2%
Pleural Mesothelioma	13	0%	0%
Other	9,393	24%	74%
Mental and behavioural disorders and Diseases of the nervous system (F00-G99)	2,524	6%	100%
Diseases of the digestive system (K00-K93)	1,479	4%	100%
TOTAL	36,963	94%	

Temporal trends in cause of death

The proportion of deaths due to respiratory diseases remained steady overall and by disease between 2005-2015 (p-trend > 0.05) (**Figure 5.4**). An increase in deaths attributed to mental, behavioural and neurodevelopmental disorders was observed over time (p-trend <0.0001). A significant decrease in the proportion of deaths attributed to circulatory disease over the study period was observed (p-trend <0·0001) (**Figure 5.4**).

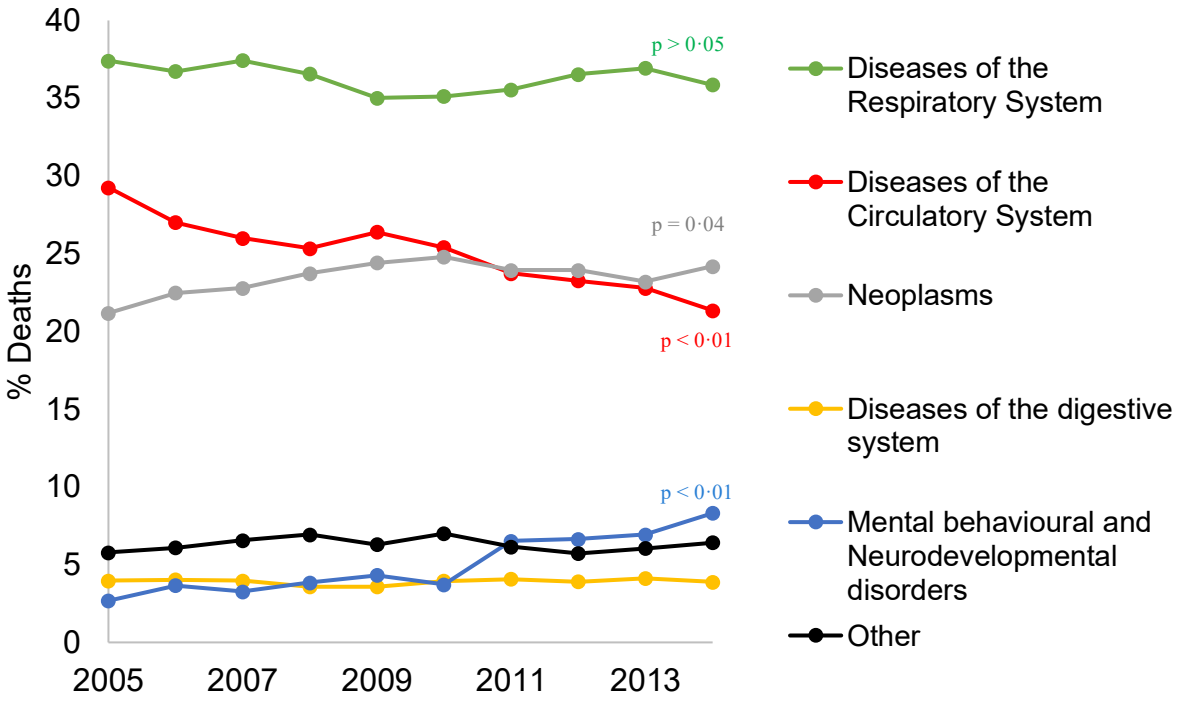


FIGURE 5-4 TRENDS IN LEADING CAUSES OF DEATH, 2005-2015

Presented as percentage of all deaths per year. ICD-10 chapters F (mental and behavioral disorders) and G (diseases of the nervous system) have been combined. 'Other' refers to causes of death categorized in all ICD-10 chapters outside of C, D00-48, F, G, I, J, and K. Significant p-values (α < 0·05) from Cochran-Armitage test for trend are shown.

5.5 Discussion

5.5.1 Summary of findings

The present study confirmed that living with COPD carries a high mortality risk. These results suggested increasing all-cause mortality rates in COPD patients. While a significant decrease in deaths attributed to CVD over time was observed, the same cannot be said for respiratory-attributed deaths. The majority of deaths in COPD patients were attributed to the underlying respiratory disease, and the stability of respiratory-related mortality over time emphasizes the urgent need to continue research in respiratory disease management in order to improve survival.

Patients with COPD were more likely to die from neoplasms or respiratory illness, but less likely to die of CVD, than they were 10 years ago. This decline is not dissimilar to that of the decrease in CVD deaths seen in the general population (See **Figure 3.2** for trends in CVD death in the general population). Over this period, improvements in comorbid disease management, risk stratification, and new medications had driven this reduction in CVD deaths and is reflected in the general population. Furthermore, improvements in cancer screening programmes and diagnostics may explain the consistent trends in cancer deaths despite the expected decline as seen in the general population and globally (Hashim et al., 2016). In addition to the change in cause of death coding in 2010 (Wells, 2014), increased life expectancy may contribute towards rising numbers of deaths due to mental and behavioural disorders and diseases of the nervous system, largely dementia and Alzheimer's disease.

5.5.2 Comparison with other work

This was the first study to report ASMRs for COPD patients in England using EHR data. Rates were higher than previous estimates of 98 per 100,000 (Burney et al., 2015), and over time showed an increasing trend. This may be partly explained by changes in awareness, diagnostic habit, labelling or possibly by the variability in uptake of survival-modifying interventions (Pride and Soriano, 2002, Godtfredsen et al., 2008).

The ASMRs observed in this chapter were also higher than population estimates illustrated in **Section 3.4.1** (70 - 62 per 100,000 people among males, and 43 –45 per 100,000 among females). The differences are attributed to the definition of the

underlying population; in Chapter 3 I use population statistics wherein COPD is only identified in death certificates whereas, in the current chapter I estimate ASMR among a population of COPD patients. Further, as I found that just under half of COPD patients have their disease listed in their death certificate it was expected that the ASMR of COPD-related death in the general population would be lower than that observed among the COPD population.

These results were similar to those of previous studies estimating the leading causes of death in COPD patients. Hansell et al. reported that, between 1993 and 1999, 8% of death certificates mentioned an obstructive lung disease (Hansell et al., 2003b). In a later study, Berry and Wise summarised clinical trial data and found that between 8% and 39% of deaths among COPD patients were attributed to non-malignant respiratory disease; however, trial populations are not always representative of the real world (Berry and Wise, 2010). The proportion of deaths with COPD mentioned observed in this investigation was above those observed in previous research (47%), which highlights a significant improvement in recognising COPD in death certificates.

5.5.3 Strengths and limitations

This study was the first to use linked primary care and mortality data to assess cause of death in patients with COPD. Previous studies investigating cause of death in COPD identified patients as those for whom COPD was recorded on their death certificate or who were hospitalised (Hutchinson et al., 2014, Hansell et al., 2003b, Goldacre et al., 2012). Relying on death certificates alone means that many patients are missed. This study utilised diagnosis of disease in primary care and captured a large representative sample of the COPD population. Furthermore, as ONS data for England is nearly 100% complete, a large proportion of registered deaths are certified by a medical practitioner and accuracy of recording has improved over time (Wells, 2014). Since 1993, automated coding has been in place for cause of death with application of WHO rules allowing international comparisons (ONS, 2017). There have been issues surrounding the accuracy of the underlying cause provided by ONS, which is a derived variable (See **Section 2.2.1**) (Sinha et al., 2008b) however, the sensitivity analysis using the first position for cause of death did not significantly change the proportions of leading causes of death, suggesting that the algorithm used to derived cause of death is a sufficient measure.

This study did not include a comparison of mortality rates using person-time of disease as data for the general population were obtained via publicly available ONS mortality reports. Therefore, results should be interpreted considering that duration of disease was not included in estimating mortality rates. In addition, details on disease severity or use of medications were not included, which may have an impact on overall survival. Future research should investigate disease phenotypes with use of interventions to evaluate whether the excess risk of mortality observed is modifiable.

5.6 Conclusion

This study provided a contemporary description of the underlying causes of death and mortality trends over time in COPD patients in a real-world setting. Patients experienced a high risk of mortality due to their underlying respiratory disease, as evidenced by the stability of respiratory-related mortality over time, while deaths due to CVD significantly decreased. Declining CVD mortality rates might be due to improvements comorbid disease management, risk stratification, and new pharmacological interventions over the last decade. Further interventions are needed to address respiratory-related mortality.

6 Chapter 6: Excess mortality

In the previous chapter, I showed how mortality rates among those with COPD are higher than the general population. In this chapter, I build on the results of the previous chapter by estimating the excess mortality risk among those with a diagnosis of COPD compared to those without.

Parts of the research presented in this chapter has been previously published at Gayle, A.V., Minelli,C., Quint,J.K.,2022. Respiratory-related death in individuals with incident asthma and COPD: a competing risk analysis. *BMC Pulmonary Medicine* 22(28). This publication benefitted from the input of my thesis supervisors. My role consisted in conducting the statistical analyses and writing the first draft of the manuscript.

6.1 Background

The previous chapter has shown that respiratory-related deaths have remained constant over time in the COPD population, while cardiovascular-related deaths declined and deaths attributed to mental and behavioural disorders increased. While these underlying shifts may be attributed to improved management in comorbid conditions, there is a need to estimate the risk of all-cause and cause-specific mortality after taking into account risk of death attributed to other causes; this would help to disentangle the risk of cause-specific mortality from other competing causes of death and allow more accurate estimation of the mortality burden of COPD.

Estimating Competing Risks

Competing risks are said to be present when a patient is at risk of more than one mutually exclusive event, such as death from different causes, and the occurrence of one of these will prevent any other event from ever happening (Abdul Sultan et al., 2015, Baena-Diez et al., 2016). Not taking competing risks into account would lead to an overestimate of the risk attributed to any specific event (Andersen et al., 2012).

One of the classical methods for analysing competing risk data is the proportional hazard (PH) model (Cox, 1972), which examines how specified factors influence the rate of death at a particular point in time. The major limitation of using the PH model in a competing risk scenario is that during estimation of regression parameters under a specific cause it considers the individuals failing from causes other than the cause of interest as censored observations (Porta et al., 2007). Cox regression assumes that censoring is non-informative, i.e. individuals censored at a certain time point are representative of all those still at risk at that same time point, an assumption that does not hold for an individual who has died from a non-respiratory cause and therefore cannot be still at risk of respiratory-related death(Lau et al., 2009).

To overcome this limitation, Fine and Gray (Fine and Gray, 1999) developed a survival regression model based on the cumulative incidence function (CIF) which describes the probability of an event occurring prior to a specific time. Unlike the PH model, using CIF does not ignore the other competing risks when a specific cause of

interest is observed (Porta et al., 2007, Coviello and Boggess, 2004, Austin and Fine, 2017). Competing risk analyses allow for a death due to the primary cause of interest (e.g. respiratory disease) to be precluded by a death due to another cause (e.g., cardiovascular disease); the occurrence of the latter would not prevent the former (Abdul Sultan et al., 2015, Baena-Diez et al., 2016). This approach avoids overestimating of risk of respiratory-related death, which is of particular importance as **Chapter 5** highlighted that patients with COPD have high rates of respiratory-related deaths (Andersen et al., 2012).

Therefore, I chose to conduct a competing risks analysis, in which I considered each cause of death associated with COPD with the contribution of other competing causes of death, by actively maintaining individuals in the cohort when they die of an alternative cause (Andersen et al., 2012). The subdistribution hazard ratios estimated the relative change in the instantaneous *rate* of respiratory-related death in those people who have not died or who have died due to a competing cause (Austin and Fine, 2017), and it is interpreted as *the magnitude of the relative change in rate of cause-specific death associated with the presence of COPD*. This relies on the assumption that time to cause-specific death is independent between people and on the assumption of proportionality between groups, (i.e. the difference in rate of cause-specific death between those with disease and without disease remains constant over time).

ACO

Most clinicians can easily distinguish asthma and COPD. Asthma usually has an early onset with intermittent symptoms, a good response to inhaled therapy, and is often associated with other allergic diseases, whereas COPD is of late onset, slowly progressive symptoms, poor response to inhaled therapy, and is usually associated with long-term smoking. However, patients can sometimes have features of both diseases, and this condition has been termed asthma-COPD overlap syndrome (ACO) (Barnes, 2016). Around 11% of people have ACO, and people with ACO may have worse outcomes than those with COPD alone (Hosseini et al., 2019, Ray and Kelly, 2019, Nissen et al., 2018, Hurst et al., 2019a). However, the evidence around the impact of comorbid asthma on COPD mortality is conflicting.

6.2 Study aims and objectives

The aim of this study is to estimate the risk of respiratory-related death among those with a diagnosis of COPD compared to a population without COPD, using competing risk regression to account for the presence of “competing” causes of deaths. Considering the paucity of epidemiological evidence around co-occurring asthma and COPD (ACO), I also estimate the risk of both overall and respiratory-related mortality of people diagnosed with ACO compared to those with COPD alone.

6.3 Methods

6.3.1 Study Design

This study used an incident matched cohort design. The study population comprised individuals who either, according to their primary care records, had a new diagnosis of COPD prior to the end of the study period (31st December 2015) or did not have evidence of COPD. The study period was defined as 1st January 2005 – 31st December 2015 and included individuals residing in England.

Follow up began at the date of the first diagnosis COPD or index date in the matched group.

Patients were followed until the earliest of:

- study end date (31st December 2015)
- the date the general practice stopped contributing data to the CPRD (last collection date)
- the date the patient transferred out of a GP practice
- the date the patient died

6.3.2 Data source

The same extract of CPRD data that was used for the previous chapter (September 2017 build) was also employed in this analysis (see **Chapter 5.3** for further details).

6.3.3 Study Population

COPD group

The COPD group included:

- patients over the age of 35 with a GP diagnosis of COPD (at least one recorded diagnosis between 1st January 2005 and 31st December 2015)
- "acceptable" patient status in CPRD (See **Section 2.3.3**)
- patients alive at least one day between 1 January 2005 and 31 December 2015

Matched non-disease group

From the general CPRD population, I identified a "non-disease" group from the general population who did not have a diagnosis of COPD for matching. For the present study, non-disease patients were only included if they met the same inclusion criteria as for the COPD group.

Each patient with COPD was matched to 5 people without COPD (on age within 5 years, practice and sex) to increase statistical power. People in the non-disease group had to be registered in a practice at the index date, i.e. the date corresponding to the incident COPD diagnosis date of their match.

ACO group

I also identified a group of patients with comorbid asthma (ACO). This was defined as either (**Figure 6.1**):

- patients with an asthma diagnosis followed by a COPD diagnosis (asthma at least 2 years prior to COPD, to avoid misdiagnosis (Nissen et al., 2018)), or
- patients with a COPD diagnosis followed by an asthma diagnosis (COPD diagnosis at any time before asthma diagnosis)

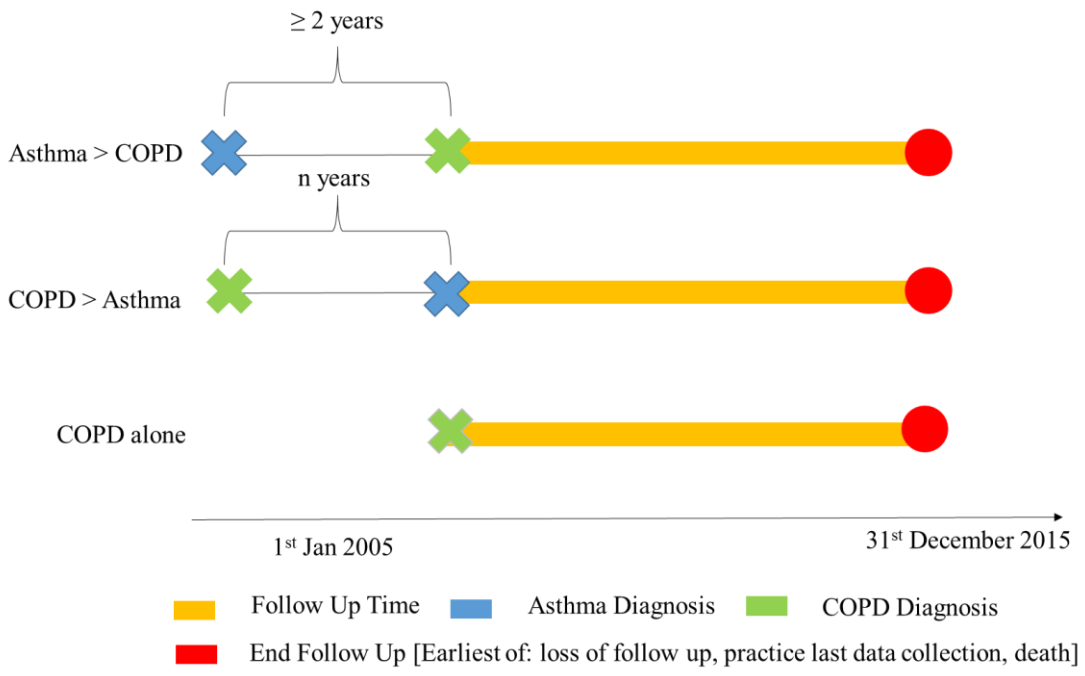


FIGURE 6-1 STUDY DESIGN

6.3.4 Covariates

Covariates were measured at the closest date to the beginning of the follow up and were similar to that of those used in the previous chapter (See **Section 5.3.6**); they included age at study start, age at death, sex, smoking status, BMI, comorbid respiratory disease, and IMD. In addition, the Charlson Comorbidity Index (CCI) was calculated for all patients for conditions diagnosed prior to COPD diagnosis (codes available from (Metcalfe et al., 2019), see **Appendix 9.3: Table AA** for disease scoring), scores were grouped into categories [0,1,2,3,4,≥5].

6.3.5 Mortality

Mortality and the leading causes of death during follow-up were ascertained using the electronic medical record for deaths and by death certificates from the ONS (See **Section 2.2.1**). All deaths were coded according to the ICD-10 chapter. Mortality was classified as being due to respiratory disease (ICD J00 – J99), cardiovascular diseases (ICD F01, G45, I00–I99, Q20, Q28, and R96), all malignant neoplasms (ICD C00–C99 and D1–D48), diseases of the digestive system (K00 –K93), mental and behavioural disease (F00- F99), and other causes (see **Appendix 9.3: Table A** for full list).

6.3.6 Statistical Analysis

Baseline characteristics were considered at the diagnosis/index date. The balance of baseline characteristics between patients with and without disease obtained with the matching was assessed by calculating a standardised difference, which is a difference in means or proportions expressed in units of the pooled standard deviation(Austin, 2009). Standardised differences of <0.1 suggest that covariates were well balanced (Austin, 2009).

Mortality rates

Cause-specific mortality rates were estimated using the number of deaths during the study period and expressed as a rate per 100,000 person-years. The subdistribution hazard ratio (HR) for death and 95% confidence interval (95%CI) associated with COPD was calculated using Fine-Gray regression, implemented with the “stcrreg” command in STATA (Fine and Gray, 1999). The regression models were adjusted for age, sex, smoking status, BMI, CCI, and IMD, and they accounted for deaths

from other causes as competing risks. I assessed the proportional hazard assumption by plotting the Schoenfeld residuals and checking that the pattern against time was constant (Zhang, 2017).

Sensitivity analysis included estimation of respiratory mortality associated with overlapping asthma and COPD by order of diagnosis. Overlapping groups were compared to those who had COPD only.

Cumulative incidence function (CIF) (i.e., the predicted cumulative risk of death) by 10 years from diagnosis for each specific cause of death was derived. The 10-year cut-off point was used, as the majority of deaths had occurred by then. The excess risk of death was calculated for each specific cause as the difference between the cumulative incidence of death for those with disease and the cumulative incidence of death for non-disease patients. The cumulative incidence of death and excess risk for each cause of death was plotted using stacked line graphs. All calculations were made with Stata version 15/MP4 (StataCorp LP, College Station, Texas).

6.4 Results

6.4.1 Cohort characteristics

45,702 patients with an incident diagnosis of COPD were identified. Patients were then matched to patients without disease. The final cohort included, 45,649 COPD patients, in addition 22,145 people with ACO were identified (**Figure 6.1**). Patients were well matched with balanced distributions of matched characteristics (age, sex) between groups. The mean follow-up was 6.24 years (SD = 4.73) and 6.10 (SD = 4.68) years for those with and without COPD, respectively. Individuals with COPD were more likely to smoke, had a similar BMI, and were more likely to live in areas of greater deprivation compared with individuals without COPD (**Table 6.1**).

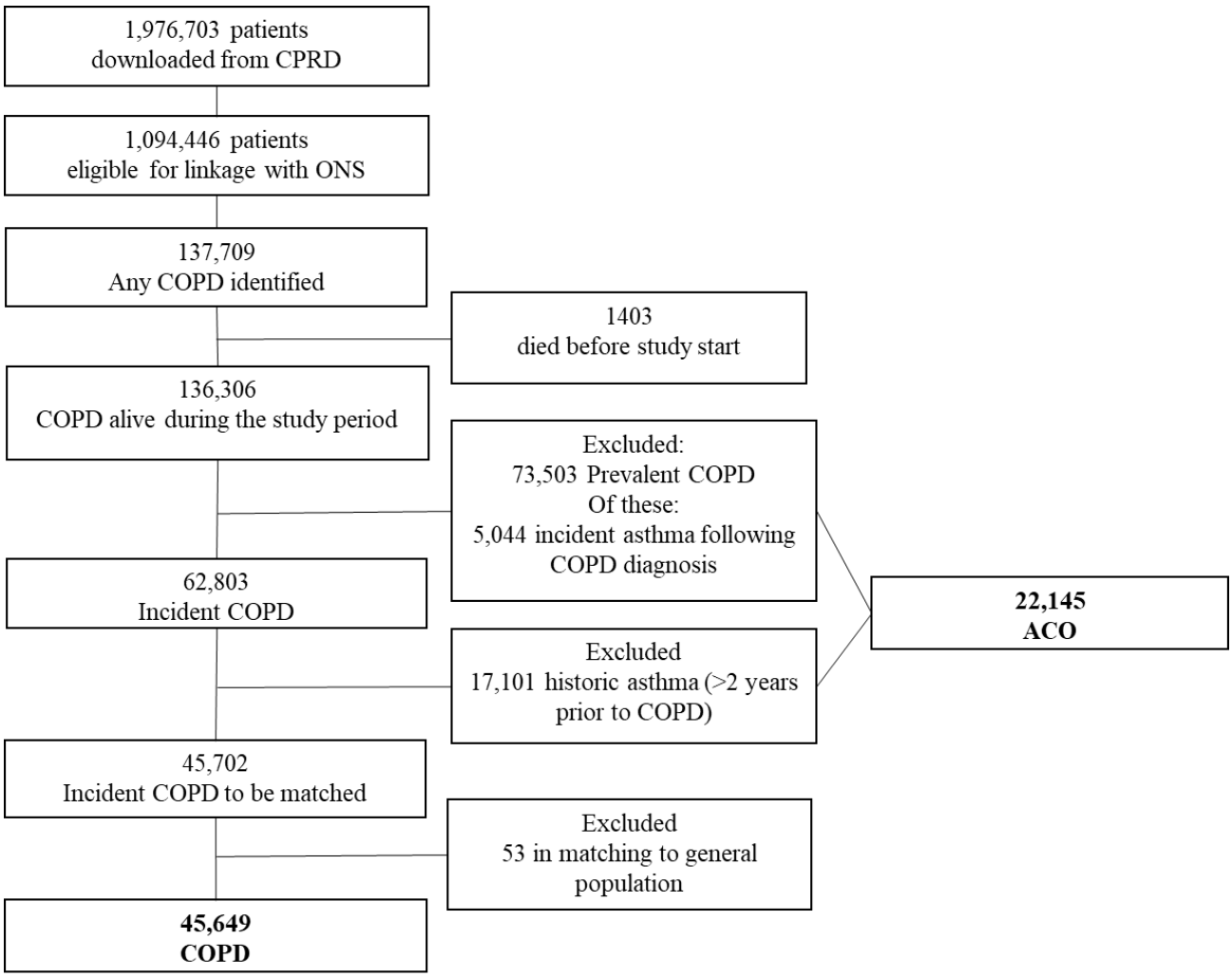


FIGURE 6-2 PATIENT SELECTION

TABLE 6-1 BASELINE CHARACTERISTICS

N		COPD (N=45,649)	Non-COPD (N=228,076)	Std. Diff
Sex (N, %)				
	Male	25,377 (56)	126,775 (56)	0.00
	Female	20,272 (44)	101,301 (44)	
Age at diagnosis (Mean, SD)		67.8 ± 11.5	67.8 ± 11.4	0.00
Age at diagnosis (N, %)				
	18 - 44	1,262 (3)	6,307 (3)	0.00
	45 - 64	16,207 (36)	81,036 (36)	
	65-84	25,185 (55)	125,911 (55)	
	>85	2,995 (7)	14,822 (7)	
Follow-up time, years (Mean, SD)		3.8 (1.8-6.4)	3.9 (1.8-6.5)	
Total person years		193,309	994,000	
Smoking Status (N, %)				
	Never Smoker	3,859 (9)	101,784 (45)	0.99
	Current	18,298 (40)	31,493 (14)	
	Former Smoker	21,560 (47)	90,698 (40)	
	Missing	1,932 (4)	4,101 (2)	
BMI (kg/m^2)				
	Underweight (<18.5)	2,023 (4)	3,084 (1)	0.22
	Normal weight (18.5 - 24.9)	14,393 (32)	65,811 (29)	
	Overweight (25 - 29.9)	14,030 (31)	84,417 (37)	
	Obese (30+)	12,264 (27)	57,943 (25)	
	Missing	2,939 (6)	16,821 (7)	
IMD (N, %)				
	1 (least deprived)	7,125 (16)	48,593 (21)	0.22
	2	8,765 (19)	50,683 (22)	
	3	9,181 (20)	47,146 (21)	
	4	10,006 (22)	42,979 (19)	
	5 (most deprived)	10,524 (23)	38,476 (17)	
	Missing	48 (0)	199 (0)	
CCI (N, %)				
	0	0 (0)	117,111 (51)	1.51
	1	23,765 (52)	41,445 (18)	
	2	7,457 (16)	31,724 (14)	
	3	6,367 (14)	18,351 (8)	
	4	3,688 (8)	8,912 (4)	
	≥5	4,372 (10)	10,533 (5)	

Std. Diff: Standardised Difference, IMD – Index of Multiple Deprivation, CCI - Charlson Comorbidity Index, BMI – Body Mass Index - figures shown are the absolute value of the calculated differences between COPD and Non-COPD. Calculated at the date nearest to index (diagnosis)

6.4.2 Mortality rates

15,800 deaths were observed during the follow up period among individuals with COPD and 46,036 among non-disease patients giving overall mortality rates of 8,173 per 100 000 person-years among patients with COPD vs 4,631 per 100,000 among those without COPD. Mortality rates in those with COPD were approximately 2-fold compared with those without COPD for most causes of death, with the largest difference seen comparing the mortality rate for deaths attributed to the respiratory system (2,409 per 100,000 person-years vs 509 per 100,000 person-years, respectively). The mortality rate for deaths attributed to mental and behavioural disorders was lower among COPD patients compared to the general population (252 per 100,000 person-years vs 458 per 100,000 person-years) (**Table 6.2)**.

After adjusting for competing risks, patients with a diagnosis of COPD were estimated to have over a four-fold (HR = 3.96; 95%CI 3.79 – 4.14) increased risk of respiratory-related mortality compared to individuals without COPD (**Table 6.2**). An elevated risk was also observed for deaths attributed to the circulatory system (HR = 1.21 95%CI 1.16 – 1.26). Elevated risks were seen for all major causes of death, with the exception of mental and behavioural disorders (HR = 0.48; 95%CI 0.43-0.53).

TABLE 6-2 MORTALITY RATES PER 100,000 PERSON-YEARS BY DISEASE AND ICD-10 CAUSE OF DEATH

	COPD n = 45,649		The general population n = 228,076			
Cause of death	**deaths**	**rate**	**deaths**	**rate**	**Hazard Ratio (95%CI)**	**p-value**
All-cause mortality	15,800	8,173	46,036	4,631	~	
Diseases of the respiratory system (J00-J99)	4,656	2,409	5,058	509	3.96 (3.79 - 4.14)	<0.0001
Diseases of the circulatory system (I00-I99)	4,075	2,108	14,398	1,448	1.21 (1.16 - 1.26)	<0.0001
Neoplasms (C00-D48)	4,606	2,383	13,536	1,362	1.35 (1.30 - 1.39)	<0.0001
Diseases of the digestive system (K00-K93)	631	326	2,070	208	1.16 (1.06 - 1.28)	0.002
Mental and behavioural disorders (F00-F99)	487	252	4,551	458	0.48 (0.43 - 0.53)	<0.0001
Other	1,345	696	6,423	646	0.94 (0.89 - 1.00)	0.064

CI: CONFIDENCE INTERVAL. * INCLUDES MISSING CAUSE OF DEATH. SUBDISTRIBUTION HAZARD RATIOS WERE ADJUSTED FOR AGE, GENDER, SMOKING, BMI, IMD, AND OTHER CAUSES OF DEATH AS COMPETING RISKS. STANDARD ERRORS ESTIMATED USING ROBUST METHOD

For patients with comorbid asthma, the mortality rate was 4,485 per 100,000 person-years, with the highest rate observed for deaths attributed to the respiratory system (1,488 per 100,000 person-years) (**Table 6.3**). When considering the order of overlapping diagnosis, having COPD followed by asthma was associated with a lower risk of respiratory-related death when compared to COPD alone (HR = 0.67; 95%CI 0.58 – 0.79) (**Figure 6.3**).

TABLE 6-3 MORTALITY RATES PER 100,000 PERSON-YEARS BY DISEASE AND ICD-10 CAUSE OF DEATH AMONG THOSE WITH OVERLAP OF ASTHMA AND COPD

	ACO (N = 22,145)	
	deaths	**rate**
All-cause mortality	4,307	4,485
Diseases of the respiratory system (J00-J99)	1,429	1,488
Diseases of the circulatory system (I00-I99)	1,081	1,126
Neoplasms (C00-D48)	1,075	1,119
Diseases of the digestive system (K00-K93)	212	221
Mental and behavioural disorders (F00-F99)	142	148
Other	368	383

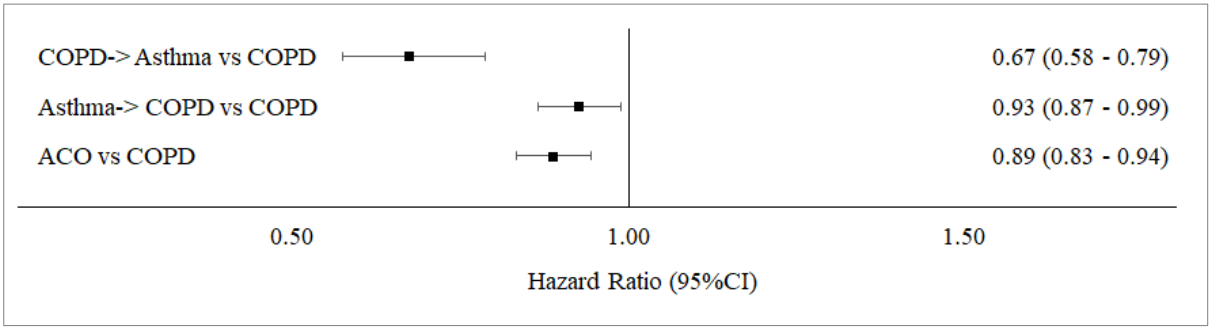


FIGURE 6-3 SUBHAZARD OF RESPIRATORY-RELATED MORTALITY BETWEEN DISEASE GROUPS BY ORDER OF OVERLAPPING DIAGNOSIS

➔ Denotes order of diagnosis (see **Figure 6.1** for definitions), ACO: Asthma COPD overlap, CI: Confidence Interval

Most common causes of respiratory death are presented in **Table 6.4**. COPD is coded most frequently as the underlying cause of death among COPD patients (33.6%) and among those with comorbid asthma (32.9%). For people without COPD this was pneumonia (27.5%) or bronchopneumonia (23.1%).

TABLE 6-4 MOST COMMON 15 RESPIRATORY-RELATED CAUSES OF DEATH BY DISEASE

Cause of Death (ICD-10 J00 – J99)	COPD		ACO
	Yes (N=4,656)	No (N=5,058)	(N=1,429)
Chronic obstructive pulmonary disease, unspecified (J44.9)	33.6%	5.3%	32.9%
Chronic obstructive pulmonary disease with acute lower respiratory infection (J44.0)	29.0%	6.5%	28.1%
Pneumonia, unspecified (J18.9)	5.8%	27.5%	6.3%
Bronchopneumonia, unspecified (J18.0)	5.0%	23.1%	5.4%
Chronic obstructive pulmonary disease with acute exacerbation, unspecified (J44.1)	7.6%	1.3%	8.0%
Other interstitial pulmonary diseases with fibrosis (J84.1)	5.2%	8.6%	2.9%
Bronchiectasis (J47)	2.1%	1.9%	4.2%
Asthma, unspecified (J45.9)	0.4%	1.2%	2.8%
Emphysema, unspecified (J43.9)	3.5%	0.8%	2.1%
Unspecified acute lower respiratory infection (J22)	0.8%	5.5%	1.2%
Pneumonitis due to food and vomit (J69.0)	1.2%	4.5%	0.9%
Other specified respiratory disorders (J98.8)	1.4%	5.6%	1.5%
Lobar pneumonia, unspecified (J18.1)	1.1%	2.7%	0.3%
Interstitial pulmonary disease, unspecified (J84.9)	0.8%	1.6%	0.6%
Other specified chronic obstructive pulmonary disease (J44.8)	0.6%	0.1%	0.5%

6.4.3 Cumulative Incidence

The overall cumulative incidence of respiratory-related death by 10 years was calculated to be 98 in 100,000, an excess of 0.07% (95%CI 0.04 – 0.10) when compared to people without COPD (**Table 6.5**). This estimate was also higher than the predicted incidence of deaths related to the circulatory system and neoplasms (106 and 149 in 100,000 respectively). No significant excess was observed for the other causes of death.

TABLE 6-5 CUMULATIVE INCIDENCE FUNCTION BY 10 YEARS (%) AND EXCESS RISK OF CAUSE-SPECIFIC DEATH ADJUSTED FOR AGE, GENDER, BMI, SMOKING STATUS, IMD AND COMPETING RISKS

Cause of death	Cumulative Incidence at 10 years		Excess (95%CI)
	COPD	Gen. Pop	
Diseases of the respiratory system (J00-J99)	0.098%	0.031%	0.067% (0.038,0.095)
Diseases of the circulatory system (I00-I99)	0.106%	0.088%	0.018% (-0.012,0.047)
Neoplasms (C00-D48)	0.149%	0.113%	0.036% (0.014,0.071)
Diseases of the digestive system (K00-K93)	0.018%	0.016%	0.003% (-0.010,0.015)
Mental and behavioural disorders (F00-F99)	0.008%	0.016%	-0.008% (-0.017,0.000)
Other*	0.039%	0.041%	-0.002% (-0.020,0.016)

CI: confidence interval. COPD: Chronic Obstructive Pulmonary Disease * Includes missing cause of death

6.5 Discussion

6.5.1 Summary of main findings

A diagnosis of COPD was strongly associated with an increased risk of respiratory-related mortality after controlling for competing risks; the most probable cause of death at 10 years after COPD diagnosis was respiratory disease when compared to those without COPD. Coexistence of asthma and COPD was associated with a lower risk of respiratory-related death compared to COPD alone.

6.5.2 Comparison with other work

Among COPD patients, results were consistent with previous literature (Abukhalaf et al., 2018, Celli et al., 2008). Using a similar analytical approach, Abukhalaf et al. found that disease severity and smoking status were linked to risk of respiratory-related mortality when applying a competing risk approach to a cohort of 512 people in the US with COPD (Abukhalaf et al., 2018). People with COPD are usually current or former smokers (Sears, 2015), older, and have comorbid conditions; whereas people with asthma are younger on average, less likely to smoke and so have an attenuated risk (Royal College of Physicians, 2018). Furthermore, there are increased opportunities to misdiagnose COPD for example as heart failure, as both conditions have clinical symptoms and signs that frequently overlap (Pirina et al., 2017, Hawkins et al., 2009), and coexistence of both diseases has been shown to increase mortality risk (Axson et al., 2020). This study provided further evidence that COPD is associated with a high respiratory-related mortality burden and that interventions such as smoking cessation programmes, use of prognostic risk calculators (Kiddle et al., 2020) partnered with targeted therapeutics are warranted in order to mitigate an increased risk of respiratory-driven mortality.

An increased risk of CVD-related deaths was observed in patients with COPD compared to the general population (**Table 6.2**), however no significant excess was observed up to 10 years post diagnosis (**Table 6.5**). This may be partially explained by the changes in CVD management over the last 10 years. In **Chapter 5**, I observed a decline in the proportion of CVD deaths among patients with diagnosed COPD over the last 10 years. Among the UK general

population, Bhatnager et al. report the age-standardised trends in CVD mortality; between 2005 and 2013, death rates declined in all UK regions from 400 per 100,000 population to 280 per 100,000 population (Bhatnagar et al., 2016). The majority of the improvements were attributed to therapeutic and surgical interventions, and while the authors note that mortality has significantly improved, the prevalence of CVD has remained constant at around 3% in England and 4% in Scotland, Wales, and Northern Ireland between 2004/2005 and 2014/2015 (Bhatnagar et al., 2016). COPD patients will remain at significant risk of CVD-related death despite improvements in CVD management.

ACO and its associated burden remains a hotly debated yet critical evidence gap. In the National Health and Nutrition Examination Survey III (NHANES-III) cohort, Diaz-Guzman et al. found that the hazard ratio for mortality in ACO was 1.8, compared with 1.4 in COPD and 1.2 in asthma, with COPD defined by spirometry (Diaz-Guzman et al., 2011). However, in a cohort of spirometry confirmed ACO and COPD patients, Bai et al. concluded that patients with ACO were more likely to have better prognosis and lower mortality than those with COPD alone (Bai et al., 2017). Similarly, Fu et al. observed poorer prognosis for patients with COPD compared to ACO (Fu et al., 2014). The conflicting literature may be partly explained by misclassification, or driven by the proportion of current smokers in each group (Royal College of Physicians, 2018). The observed decreased risk in respiratory-related death in ACO compared to COPD may be explained by the underlying biological mechanisms that are not well characterised in people with co-existing asthma and COPD. It has been hypothesised previously that the presence of airflow reversibility could have a protective effect on disease progression (Fu et al., 2014). Another explanation could be the impact of treatments used, but the current study could not include therapeutic interventions due to the difficulty in classifying durations of treatment exposure and establishing compliance across all cohorts included in the study. Currently, the lack of clinical consensus on ACO remains and the guidance still considers asthma and COPD as different disorders despite common traits and clinical features (e.g., eosinophilia, some degree of reversibility) (GOLD, 2020). These results show that risk of respiratory-related

death is distinct between ACO and COPD and, if confirmed in further studies, suggest that ACO patients should not be excluded from clinical trials.

6.5.3 Strengths and limitations

One of the recommendations in the recent NHS Long Term plan (Sinha et al., 2019) (in which chronic respiratory disease has been identified as a major area of focus for improvement) is the use of linked data sources to measure current standards of care (Hurst et al., 2019b) and aid direction of resources to reduce the COPD burden across the UK. This was the first study to accurately estimate excess risk of respiratory-related death in a representative UK population using a competing risk approach. A major strength of this study was the use of linked primary care and mortality data to estimate mortality rates for people with a chronic disease, whereas other common approaches rely on general population mortality statistics alone, which underestimates chronic disease burden, as only around 40% of patients with chronic respiratory diseases have their disease recorded on their death certificates (**Chapter 5**). This approach could be adapted at local levels to evaluate the impact of interventions targeting reductions in respiratory mortality.

Linked electronic health record and mortality data have the advantage of providing further person-level information to control for confounding factors, such as demographic data, as well as area-level deprivation which has been previously associated with wide variation in respiratory mortality (Gupta et al., 2018). CPRD is recognised as a reliable source for investigating UK general practice and health behaviours and has been used in over 1,500 publications to date. Furthermore, mortality data are complete for all people and therefore there is confidence that mortality rate estimates are accurate. Additional cohorts of overlap of asthma and COPD were included, for which there is limited mortality data (Backman et al., 2018).

However, this study had a number of limitations; it is possible that competing causes of death can be misrepresented since only a single underlying cause of death is identified on death certificates, and the counterfactual situation (i.e. what someone would have died of if that particular cause had not been present) is unknown. Further, other respiratory comorbid diseases (i.e. lung cancer) were

not included. It is generally more difficult to determine the underlying cause of death among people having multiple diseases, especially when a common risk factor, such as tobacco use, is responsible for several of them.

The definition of ACO used in this research required people to have survived one disease in order to be diagnosed with the second, which may have missed deaths that could have occurred between the two diagnoses and potentially introduce bias. While this algorithm (**Figure 6.1**) has been shown to reduce misclassification of overlap disease in electronic health records (Nissen et al., 2018), I could not account for diagnostic uncertainty which may explain the variance in cause-specific mortality observed. I expect the impact of this to have been minimal as the likelihood of observing a death within this period would be low as patients will be more likely to be closely monitored following a new diagnosis of respiratory disease.

6.6 Conclusion

In conclusion, this study demonstrated that COPD was associated with an increased risk of respiratory death; furthermore, COPD is associated with a high 10-year probability of respiratory-related mortality after adjusting for competing risks of death from other causes. Further research including phenotypes of both asthma and COPD is warranted considering the clinical heterogeneity of ACO. These results support the argument that effective interventions are needed for people with a diagnosis of COPD in order to reduce their lifetime excess respiratory mortality risk.

7 Chapter 7: Discussion

The overarching objective of this thesis was to add to the understanding of the mortality burden of COPD by:

- describing mortality trends over the last decade, both among those with and without a clinician-recorded diagnosis
- estimating cause-specific mortality and excess risk of cause-specific death
- investigating the extent to which environmental factors are associated with COPD mortality
- quantifying the proportion of patients who may have had a missed diagnosis prior to death

This chapter provides a brief summary of the findings of each of the main data analyses, discussed in the wider context of current knowledge and the implications for clinical practice.

7.1 Summary of main findings

7.1.1 COPD mortality trends

Re: Chapter 3 (AIM 1.1), Chapter 5 (AIM 3.1), and Chapter 6 (AIM 4)

Describing mortality trends was the focus of chapters 3, 5 and 6, which estimate mortality rates both among the UK general population and among those with a diagnosis of COPD.

AIM 1.1 Describe COPD mortality rates in the UK over the last 10 years among the general population

This analysis aimed to describe the mortality rates in the UK among the general population using population statistics through selected respiratory codes. Globally respiratory disease is predicted to remain one of the leading causes of death into 2040 (Foreman et al., 2018) and, whilst smoking rates in the western countries have declined, this trend is predicted to continue beyond 2040. Understanding the current mortality trends in the UK was needed to understand the extent to which respiratory deaths remain a concern relative to other major causes of death, to compare UK contemporary trends in respiratory mortality with those in other countries, and to provide context for subsequent chapters.

I found that rates of COPD mortality in the UK have remained constant over the last decade. In absolute terms, deaths attributed to respiratory disease have decreased between the early 2000's and 2018; however, this decrease was not as steep compared to deaths attributed to cardiovascular disease. When comparing respiratory mortality rates between men and women, I observed much higher mortality rates in men compared with women. This was unsurprising given the differences in smoking prevalence over the last few decades, and it highlights that significant improvements in COPD prevention are needed as well as the importance of continuing to search for better ways to improve mortality outcomes for people with this common disease.

One of the most heavily funded and researched interventions for managing patients with COPD is pharmacotherapy, and a growing body of evidence indicates that there may be a survival benefit for treatment with ICS or long-acting bronchodilators(Soriano et al., 2003, Soriano et al., 2002). However,

conclusive data are currently lacking, and no comparative studies have been conducted to date. To drive improvements in clinical management, there is a need for large clinical trials in COPD, based on hard clinical outcomes, such as death, respiratory-related death or excess death adjusting for competing risks. The TORCH trial (Celli et al., 2008) was the first and largest trial on COPD survival, and it will be interesting to observe whether its impact on guideline recommendations and hence clinical practice is as dramatic as the corresponding major cardiovascular disease trials.

AIM 3.1 Describe the current mortality trends among those with a diagnosis of COPD

This analysis aimed to estimate mortality rates among the diagnosed COPD population. Using a large population of patients who were identified using general practice records and linked with their corresponding death certificates, I was able to ascertain the leading causes of death to understand whether these differed from those in the general population identified in Chapter 3.

In people diagnosed with COPD, mortality rates were considerably higher compared to the general population and remained consistent over the 10-year study period. Respiratory-related death remained the biggest cause of death among COPD patients. Compared to the general population, similarities were seen in the decreasing rates of cardiovascular disease related deaths. This was expected as increased awareness and implementation of treatment guidelines have contributed to reductions in CVD mortality, with physicians and patients becoming better educated about treatment goals and effective disease management, leading to increased uptake of statins and other cardiovascular medications. In addition, lifestyle modification programmes promoting improved awareness and better control of risk factors for CVD, such as reductions in smoking, blood pressure and cholesterol, have proved effective and help to explain the slowing of CVD mortality observed.

Unlike for CVD mortality, there have been little improvements in COPD mortality, suggesting that current interventions are not enough to significantly reduce and change the trajectory of these national trends. The largest population interventions to date that have addressed COPD more broadly

include: the smoking legislation introduced on 1st July 2007 that banned smoking indoors in public areas; the introduction of the quality and outcomes framework in 2004, which facilitated better documentation of disease registers in general practice; the introduction of a number of clinical guidelines; vaccination programmes for seasonal infections; and general improvements in early detection of disease in general practice. However, this research did not directly evaluate the impact of these initiatives. There is a need to quantify the impact of these interventions using patient-level healthcare data. Future research of population-wide interventions should evaluate the direct impact on population mortality rates, excess mortality, and cause-specific mortality controlling for competing risks.

AIM 4 Ascertain the excess risk of death among patients with COPD while taking into account competing risks

After considering the changes in leading causes of death among COPD patients, it became apparent that diseases associated with older age (i.e. dementia and other neurological diseases) were trending towards a leading position among patients with COPD. This trend occurred in parallel to a decline in CVD deaths and suggests that improvements in more typically acute causes of death may lead to dominance of chronic diseases being responsible for the majority of deaths. Therefore, when understanding respiratory mortality risk it was important to account for theses chronic diseases and other causes of death as competing risks. Therefore, the aim of chapter 6 was to investigate the excess risk of leading causes of death taking into account competing risks from other causes.

Overall, I found that patients with COPD have a marked increased risk in respiratory-related mortality compared to individuals without COPD, after controlling for the risk of death from another cause. Whilst this finding was expected, the minimal excess risk of death observed for the other causes of death was surprising considering the multi-morbidity typically associated with COPD. A possible explanation for this could be the progressive and irreversible nature of COPD, further evidenced by the observed significant excess risk of

death at 10 years post diagnosis for cancers. For major causes of death with effective preventative interventions (like some cardiovascular causes) it's possible that the impact of these could reduce the excess risk observed in the COPD population, this hypothesis merits further investigation.

Co-existing COPD and asthma was associated with a decreased risk of respiratory-related death when compared to COPD alone, suggesting that presentation of similar/or overlapping asthma and COPD symptoms should be considered carefully when assessing patient mortality risk. A possible explanation for this decreased risk could be a protective effect of asthma being present in COPD; the biological mechanisms underpinning ACO remain unclear but warrant additional research. Another explanation could be the unmeasured impact of treatments used; however, this was a key limitation for this research due to the difficulty in classifying durations of treatment exposure and establishing compliance across all cohorts included in the study. Further, there are no specific treatment guidelines for managing ACO, and almost no evidence from clinical trials on which to base such guidelines. This is in part due to the fact that people with ACO have traditionally been excluded from trials involving COPD medications. This implies a clear and critical need for future trials of respiratory treatments to include patients with ACO. Not only is further research needed to understand whether a simple and replicable differential diagnosis of ACO is possible (which will prevent misclassification in clinical practice and further establish guidelines for easier identification of disease), but clinical trials are the most appropriate setting to determine the safety and efficacy of new and current treatments. Any resulting new indications for treatments that address ACO would increase disease awareness for both patients and healthcare professionals and help to reduce the associated morbidity.

7.1.2 Factors related to COPD mortality trends

External factors related to mortality

Re: Chapter 3 (AIM 1.2)

AIM 1.2 Determine the impact of environmental factors such as geographic area, season, pollutants, and temperature on COPD mortality in the UK

The aim of this analysis was to determine the relationship between environmental factors and respiratory-related mortality. Several epidemiological investigations have assessed the association between air pollution and mortality, reporting increased risks for the most prevalent pollutants including $PM_{2.5}$. However, most of these studies relied on analyses using largely aggregated data and/or simplistic study designs, preventing a thorough characterisation of pollution-related mortality risks and related impacts. Using the case time series design (Gasparrini, 2021), this study was one of the first to model mortality risks across 34,752 small census areas of England and Wales.

Firstly, I found a strong association of changes in daily average temperature with COPD mortality. This was expected as cold winters and heatwaves are known to increase hospitalisations for many chronic illnesses. Temperatures up to 3 days prior were associated with daily mortality rates; a non-linear relationship whereby the coldest temperatures and the hottest temperatures increased mortality rates was observed. The provision of high-resolution risk estimates including excess mortality rates for both heat and cold allows a fine geographical comparison and the identification of high-risk areas. These results were similar to those observed in previous research and continue to highlight the importance of seasonal planning in healthcare settings and the potential health impact of any further extreme weather changes due to climate change in the UK. This evidence is critical for designing national and local public health and climate policies.

Secondly, and contrary to the published literature, I found that air pollution was not associated with COPD mortality rates. This was unexpected as previous literature suggests that exposure to high air pollution levels impacts

exacerbation frequency through inflammation of the airway. This could be partially due to the observed improvements in pollution levels in the UK, whilst COPD mortality has remained constant over time. An alternative explanation might be that the study design does not allow for individual exposure-time or to account for individual clinical characteristics which may confound the association. To further understand the mechanisms of this association a more patient-focused analysis would be needed, whereby individual long-term exposure is assessed to understand the impact of patients' immediate environment while controlling for clinical factors and health behaviour. As one way forward, Chatzidiakou et al. proposed that COPD patients could be equipped with real-time apps informing on air quality to help them avoid high-air-pollution routes (Chatzidiakou et al., 2019, Gayle et al., 2020), which in turn would accurately estimate the individual risk that people living with COPD face.

Another issue is that population level research of air pollutants and respiratory outcomes in countries with low levels of pollution can be underpowered to detect associations. One potential solution for future research could be through multi-disciplinary collaborations; having input from environmental and social health experts would provide opportunities to pool expertise and implement common research protocols. This would standardise approaches to estimating environmental exposures and address country differences such as climate variation, pollution and population demographics. Such initiatives are needed to further understand the impact of air pollution on COPD and if an increased risk between pollution and COPD mortality is confirmed could be used as evidence to encourage decision makers locally and globally to implement strategies to combat the causes and effects of high air pollution levels.

Patient risk factors

Re: Chapter 4 (AIM 2)

AIM 2 Estimate the proportion of people with a diagnosis of COPD prior to COPD-recorded death and understand factors associated with missing lifetime COPD diagnosis

This chapter set out to estimate the proportion of patients with a COPD recorded death who had no evidence of a COPD diagnosis prior to death, how this has changed over time, and factors associated with a missed diagnosis. Patients sometimes can be completely asymptomatic, especially at early stages of the disease, making it difficult to be diagnosed. This was quantified in earlier research by the British Lung Foundation who estimated that millions of COPD patients were being missed (BLF, 2007). Little is known about patients without diagnosis in COPD their lifetime. Estimating the number of patients who received a COPD label in their death certificate but may have been missed prior to death explains an important part of the “missing millions” story.

In this chapter, I found that most people with a COPD-recorded death have a diagnosis of COPD prior to death and that this has improved over time, suggesting that death certification is accurate and that fewer patients are being missed. After plotting the proportion of patients missed over time, two time points became apparent, the introduction of the Quality and Outcomes Framework in 2004 and the BLF’s missing millions campaign in 2007. Whilst I was not able to draw direct associations between these events and their impact on COPD diagnosis, there appeared to be a steeper decline in the proportion of patients missed following 2004 and 2007. QOF has been shown in similar research to improve both the estimates of COPD prevalence and the documentation of key COPD management criteria, such as referrals to specialists and medication review (Doran et al., 2011) which may reduce the morbidity and mortality associated with COPD.

Whilst COPD diagnosis is confirmed using spirometry, much of the diagnostic spirometry performed is conducted in secondary care settings and thus not necessarily routinely coded in hospital records. This study therefore could not provide a detailed picture on the proportion of patients with diagnosed COPD

according to airflow obstruction, and therefore results were presented largely through the lens of primary care. It is encouraging, however, to report that the majority of COPD patients who are seen in secondary care settings have their diagnosis recorded in primary care, suggesting that the majority of clinical information is transferred to GPs.

Smoking status was the most significant factor related to the probability that a patient will have evidence of a COPD diagnosis in their medical record. This was unsurprising as smoking remains the biggest risk factor for developing COPD, and as the single biggest contributor to the development of COPD; continued public health efforts to prevent the initiation of tobacco use and smoking cessation among those who continue to smoke are needed to further lower the prevalence of tobacco use. The use of online disease or exacerbation risk calculators as diagnostic, prognostic, and decision aids has increased in clinical practice. There is evidence that such point-of-care resources may improve diagnostic accuracy and adherence to guidelines, therefore the inclusion of smoking status in patient risk scores is imperative and may even be cost-effective in motivating smoking cessation (Adamson et al., 2021).

7.2 Future work

A number of additional analysis are possible to further the understanding of COPD mortality using the data obtained for this research.

A further extension to the analysis in **Chapter 3** would include deprivation information to account for area-level confounding. The IMD (See **Section 2.4.2**) would be modified by excluding two domains (the health and disability domains and the living environment domain) that partially include variables that would be incorporated in the main analytical model (small-area statistics of mortality and ambient concentration of particulate matter and temperature, respectively), keeping the overall weights of the five remaining domains (income; employment; education, skills, and training; barriers to housing and services; crime) proportional to those in the original index, following the approaches used in previous studies (Adams and White, 2006, Goodman et al., 2011).

To further illustrate the impact of temperature and pollution on COPD mortality, additional calculations of the attributable risk would be beneficial. Epidemiological studies usually rely on effect summaries based on ratio measures, such as relative risk, odds ratio or rate ratio, with the choice depending on the specific study design(Rothman et al., 2008). Although these measures are ideal for summarizing the association of interest, they offer limited information on the actual impact of the exposure. This information is critical for the planning and evaluation of public health interventions, and it is better provided by relative excess measures such as the attributable fraction (AF), or absolute excess measures such as the attributable number (AN). Gasparrini et. al propose an approach to estimating the attributable risk from lag distributed models (Gasparrini and Leone, 2014) which would be an appropriate additional analysis for the data used. This analysis would compliment the results obtained to date and provide healthcare practitioners and public health officials translatable findings for consideration in policy discussions.

7.3 Concluding comments

Mortality data can be expressed in many ways, for different purposes. Absolute death counts are useful to clinicians and for local use; crude mortality rates allow comparisons with other conditions, and regional healthcare planning, while standardised mortality rates are valuable for comparison between countries and/or period by adjusting for differences in the demographic composition. For this research, COPD deaths were described utilising both publicly available health data as well as linked electronic health records allowing for an accurate analysis that is both generalisable and replicable.

This research provides a comprehensive picture of the COPD burden by describing both the number of people in the UK who died *from* COPD and those who died *with* COPD. This distinction is crucial as the difference in definition impacts the scale of ASMRs estimated. The most frequently used definition for international comparisons is based on population estimates of people dying *from* COPD and therefore this research highlights that these standard measures not only underestimate the true mortality burden attributed to COPD but that they should be interpreted as an indicator of the broad direction of trends and then followed by more detail analysis for disease-specific evaluation. Among the diagnosed population, COPD mortality rates in the UK over the last decade have been relatively stagnant compared to the improvements seen in CVD mortality. With changing climates and growing fluctuations in weather, these rates are likely to further increase in the extreme coldest and hottest days of the year, creating greater variation in observed mortality rates.

Results of this work suggest that recording of COPD in EHR has improved over time, and that many COPD patients have a diagnosis in their medical records prior to a COPD recorded death. There are several factors that are key to ensuring that patients are not missed, most important being the recording of spirometry. Ensuring that complete medical coding and recording is maintained represents a key step in meeting some of the NHS' long-term goals (NHS, 2018). Having good communication and exchange of information on diagnosis of COPD between primary and secondary care generates opportunities to use population-wide approaches to optimise disease management.

Following diagnosis, COPD patients can expect a significant excess risk of respiratory-related mortality that is independent of other causes of death. This finding, while unsurprising, builds on previous studies and emphasises the need for more to be done to shift more focus onto reducing mortality in addition to current efforts to manage symptoms and reduce exacerbations. A number of pathways aimed at restoring lung function to reduce mortality have previously been explored with biological plausibility proven in animal models; however, “cure” is still considered a far-fetched goal as these have yet to translate into clinical benefit in human studies (Rennard and Vestbo, 2011). Ad-hoc analysis of pharmacotherapeutic trials have failed to show significant survival benefit of the existing therapies (Han et al., 2018, Chen et al., 2020, Beeh et al., 2013), and other than the TORCH trial, there is seldom interest to robustly investigate mortality in COPD trials. Despite these challenges, I recommend that the research community continue in their pursuit to reduce both the morbidity and mortality of patients with COPD by exploring all plausible interventions, as the high mortality burden associated with COPD is likely to remain for the foreseeable future.

8 References

ABDUL SULTAN, A., CROOKS, C. J., CARD, T., TATA, L. J., FLEMING, K. M. & WEST, J. 2015. Causes of death in people with coeliac disease in England compared with the general population: a competing risk analysis. *Gut,* 64**,** 1220-1226.

ABUKHALAF, J., DAVIDSON, R., VILLALOBOS, N., MEEK, P., PETERSEN, H., SOOD, A., TESFAIGZI, Y. & VAZQUEZ GUILLAMET, R. 2018. Chronic obstructive pulmonary disease mortality, a competing risk analysis. *The Clinical Respiratory Journal,* 12**,** 2598-2605.

ADAMS, J. & WHITE, M. J. J. O. P. H. 2006. Removing the health domain from the Index of Multiple Deprivation 2004—effect on measured inequalities in census measure of health. 28**,** 379-383.

ADAMSON, A., PORTAS, L., ACCORDINI, S., MARCON, A., JARVIS, D., BAIO, G. & MINELLI, C. 2021. Communication of personalised disease risk by general practitioners to motivate smoking cessation in England: A cost-effectiveness and research prioritisation study. *Addiction*.

ALMAGRO, P., CALBO, E., OCHOA DE ECHAGUEN, A., BARREIRO, B., QUINTANA, S., HEREDIA, J. L. & GARAU, J. 2002. Mortality after hospitalization for COPD. *Chest,* 121**,** 1441-8.

ALMAGRO, P., SORIANO, J. B., CABRERA, F. J., BOIXEDA, R., ALONSO-ORTIZ, M. B., BARREIRO, B., DIEZ-MANGLANO, J., MURIO, C. & HEREDIA, J. L. 2014. Short-and medium-term prognosis in patients hospitalized for COPD exacerbation: the CODEX index. *Chest,* 145**,** 972-980.

ANDERSEN, P. K., GESKUS, R. B., DE WITTE, T. & PUTTER, H. 2012. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol,* 41**,** 861-70.

ANDERSON, H., SPIX, C., MEDINA, S., SCHOUTEN, J., CASTELLSAGUE, J., ROSSI, G., ZMIROU, D., TOULOUMI, G., WOJTYNIAK, B. & PONKA, A. 1997. Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: results from the APHEA project. *European respiratory journal,* 10**,** 1064-1071.

ANNESI-MAESANO, I. 2017. Chemical air pollution and allergen exposure. *Acute Exacerbations of Pulmonary Diseases (ERS Monograph).* Sheffield: European Respiratory Soceity.

ANTHONISEN, N. R., CONNETT, J. E., KILEY, J. P., ALTOSE, M. D., BAILEY, W. C., BUIST, A. S., CONWAY, W. A., JR., ENRIGHT, P. L., KANNER, R. E., O'HARA, P. & ET AL. 1994. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *Jama,* 272**,** 1497-505.

ANTHONISEN, N. R., SKEANS, M. A., WISE, R. A., MANFREDA, J., KANNER, R. E. & CONNETT, J. E. 2005. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Annals of internal medicine,* 142**,** 233-239.

ANTO, J., VERMEIRE, P., VESTBO, J. & SUNYER, J. 2001. Epidemiology of chronic obstructive pulmonary disease. *European Respiratory Journal,* 17**,** 982-994.

ARMSTRONG, B. 2006. Models for the relationship between ambient temperature and daily mortality. *Epidemiology***,** 624-631.

ARMSTRONG, B. G., GASPARRINI, A. & TOBIAS, A. 2014. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. *BMC Medical Research Methodology,* 14**,** 122.

ATS AND ERS. 2004. *Standards for the diagnosis and management of COPD* [Online]. Available: http://www.thoracic.org/clinical/copd-guidelines/index.php [Accessed August 2011].

AUSTIN, P. C. 2009. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in medicine,* 28**,** 3083-3107.

AUSTIN, P. C. & FINE, J. P. 2017. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Statistics in medicine,* 36**,** 4391-4400.

AXSON, E. L., RAGUTHEESWARAN, K., SUNDARAM, V., BLOOM, C. I., BOTTLE, A., COWIE, M. R. & QUINT, J. K. 2020. Hospitalisation and mortality in patients with comorbid COPD and heart failure: a systematic review and meta-analysis. *Respir Res,* 21**,** 54.

BACKMAN, H., JANSSON, S.-A., STRIDSMAN, C., MUELLEROVA, H., WURST, K., HEDMAN, L., LINDBERG, A. & RÖNMARK, E. 2018. Chronic airway obstruction in a population-based adult asthma cohort: Prevalence, incidence and prognostic factors. *Respiratory Medicine,* 138**,** 115-122.

BAENA-DIEZ, J. M., PENAFIEL, J., SUBIRANA, I., RAMOS, R., ELOSUA, R., MARIN-IBANEZ, A., GUEMBE, M. J., RIGO, F., TORMO-DIAZ, M. J., MORENO-IRIBAS, C., CABRE, J. J., SEGURA, A., GARCIA-LAREO, M., GOMEZ DE LA CAMARA, A., LAPETRA, J., QUESADA, M., MARRUGAT, J., MEDRANO, M. J., BERJON, J., FRONTERA, G., GAVRILA, D., BARRICARTE, A., BASORA, J., GARCIA, J. M., PAVONE, N. C., LORA-PABLOS, D., MAYORAL, E., FRANCH, J., MATA, M., CASTELL, C., FRANCES, A. & GRAU, M. 2016. Risk of Cause-Specific Death in Individuals With Diabetes: A Competing Risks Analysis. *Diabetes Care,* 39**,** 1987-1995.

BAI, J.-W., MAO, B., YANG, W.-L., LIANG, S., LU, H.-W. & XU, J.-F. 2017. Asthma–COPD overlap syndrome showed more exacerbations however lower mortality than COPD. *QJM: An International Journal of Medicine,* 110**,** 431-436.

BARNES, P. J. 2008. Emerging Pharmacotherapies for COPD. *CHEST,* 134**,** 1278-1286.

BARNES, P. J. 2016. Asthma-COPD Overlap. *Chest,* 149**,** 7-8.

BEEH, K. M., GLAAB, T., STOWASSER, S., SCHMIDT, H., FABBRI, L. M., RABE, K. F. & VOGELMEIER, C. F. 2013. Characterisation of exacerbation risk and exacerbator phenotypes in the POET-COPD trial. *Respiratory Research,* 14**,** 116.

BENNETT, J. E., BLANGIARDO, M., FECHT, D., ELLIOTT, P. & EZZATI, M. 2014. Vulnerability to the mortality effects of warm temperature in the districts of England and Wales. *Nature Climate Change,* 4**,** 269-273.

BERRY, C. E. & WISE, R. A. 2010. Mortality in COPD: Causes, Risk Factors, and Prevention. *COPD: Journal of Chronic Obstructive Pulmonary Disease,* 7**,** 375-382.

BHATNAGAR, P., WICKRAMASINGHE, K., WILKINS, E. & TOWNSEND, N. J. H. 2016. Trends in the epidemiology of cardiovascular disease in the UK. 102**,** 1945-1952.

BIXBY, H., HODGSON, S., FORTUNATO, L., HANSELL, A. & FECHT, D. 2015. Associations between green space and health in English cities: an ecological, cross-sectional study. *PloS one,* 10**,** e0119495.

BLAK, B., THOMPSON, M., DATTANI, H. & BOURKE, A. 2011. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Journal of Innovation in Health Informatics,* 19**,** 251-255.

BLF. 2006. *MISSING MILLIONS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE CAMPAIGN* [Online]. London: UK Parliament. Available: https://edm.parliament.uk/early-day-motion/31797/missing-millions-with-chronic-obstructive-pulmonary-disease-campaign [Accessed 16 April 2021 2021].

BLF 2007. British Lung Foundation. Invisible Lives: Chronic Obstructive Pulmonary Disease (COPD) - finding the missing millions. *Invisible Lives: Chronic Obstructive Pulmonary Disease (COPD) - finding the missing millions.*

BLF 2016a. The Battle for Breath- The Impact of Lung Disease in the UK. British Lung Foundation.

BLF 2016b. The battle for breath: the impact of lung disease in the UK. The British Lung Foundation.

BLF 2021. Failing on the fundamentals: Insights from those living with chronic obstructive pulmonary disease (COPD). London: British Lung Foundation.

BLOOM, C. I., NISSEN, F., DOUGLAS, I. J., SMEETH, L., CULLINAN, P. & QUINT, J. K. 2017. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax*.

BOZZO, A., REMY, S., BENEDETTI, A., FLEMMING, J., BECHTOLD, P., RODWELL, M. & MORCRETTE, J.-J. 2017. *Implementation of a CAMS-based aerosol climatology in the IFS*, European Centre for Medium-Range Weather Forecasts.

BRAGA, A. L., ZANOBETTI, A. & SCHWARTZ, J. 2002. The effect of weather on respiratory and cardiovascular deaths in 12 US cities. *Environmental health perspectives,* 110**,** 859-863.

BROCK, A., GRIFFITHS, C. & ROONEY, C. 2006. The impact of introducing ICD-10 on analysis of respiratory mortality trends in England and Wales.

BURGE, P. S., CALVERLEY, P. M., JONES, P. W., SPENCER, S., ANDERSON, J. A. & MASLEN, T. K. 2000. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *Bmj,* 320**,** 1297-303.

BURGE, S. & WEDZICHA, J. A. 2003. COPD exacerbations: definitions and classifications. *Eur Respir J Suppl,* 41**,** 46s-53s.

BURNEY, P. G., PATEL, J., NEWSON, R., MINELLI, C. & NAGHAVI, M. 2015. Global and regional trends in COPD mortality, 1990-2010. *European Respiratory Journal,* 45**,** 1239-47.

BUTLER, A. M., NICKEL, K. B., OVERMAN, R. A. & BROOKHART, M. A. 2021. IBM MarketScan Research Databases. *Databases for Pharmacoepidemiological Research.* Springer.

CALVERLEY, P. M. A., ANDERSON, J. A. & CELLI, B. R. 2007. Salmeterol and fluticasone propionate and survival in COPD. *New England Journal of Medicine,* 356.

CARSLAW, D. & ROPKINS, K. 2015. openair: Open-Source tools for the analysis of air pollution data. R package version 1.6. Obtenido de http://CRAN. R-project. org/package= openair.

CARSLAW, D. C. & ROPKINS, K. 2012. Openair—an R package for air quality data analysis. *Environmental Modelling & Software,* 27**,** 52-61.

CAVAILLÈS, A., BRINCHAULT-RABIN, G., DIXMIER, A., GOUPIL, F., GUT-GOBERT, C., MARCHAND-ADAM, S., MEURICE, J.-C., MOREL, H., PERSON-TACNET, C., LEROYER, C. & DIOT, P. 2013. Comorbidities of COPD. *European Respiratory Review,* 22**,** 454-475.

CELLI, B., DECRAMER, M., KESTEN, S., LIU, D., MEHRA, S. & TASHKIN, D. P. 2009. Mortality in the 4-Year Trial of Tiotropium (UPLIFT) in Patients with Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine,* 180**,** 948-955.

CELLI, B. R., COTE, C. G., MARIN, J. M., CASANOVA, C., MONTES DE OCA, M., MENDEZ, R. A., PINTO PLATA, V. & CABRAL, H. J. 2004. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *New England Journal of Medicine,* 350**,** 1005-1012.

CELLI, B. R., THOMAS, N. E., ANDERSON, J. A., FERGUSON, G. T., JENKINS, C. R., JONES, P. W., VESTBO, J., KNOBIL, K., YATES, J. C. & CALVERLEY, P. M. A. 2008. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease - Results from the TORCH study. *American Journal of Respiratory and Critical Care Medicine,* 178**,** 332-338.

CHAPMAN, K., MANNINO, D., SORIANO, J., VERMEIRE, P., BUIST, A. S., THUN, M., CONNELL, C., JEMAL, A., LEE, T. & MIRAVITLLES, M. 2006. Epidemiology and costs of chronic obstructive pulmonary disease. *European Respiratory Journal,* 27**,** 188-207.

CHATZIDIAKOU, L., KRAUSE, A., POPOOLA, O. A. M., DI ANTONIO, A., KELLAWAY, M., HAN, Y., SQUIRES, F. A., WANG, T., ZHANG, H., WANG, Q., FAN, Y., CHEN, S., HU, M., QUINT, J. K., BARRATT, B., KELLY, F. J., ZHU, T. & JONES, R. L. 2019. Characterising low-cost sensors in highly portable platforms to quantify personal exposure in diverse environments. *Atmospheric measurement techniques,* 12**,** 4643-4657.

CHEN, Y., LIU, Y., ZHANG, J., YAO, W., YANG, J., LI, F., LU, L., ZHENG, J., HAN, X. & XU, J.-F. 2020. Comparison of the Clinical Outcomes Between Nebulized and Systemic Corticosteroids in the Treatment of Acute Exacerbation of COPD in China (CONTAIN Study): A Post Hoc Analysis. *International journal of chronic obstructive pulmonary disease,* 15**,** 2343-2353.

ÇOLAK, Y., AFZAL, S., NORDESTGAARD, B. G., VESTBO, J. & LANGE, P. 2017. Prognosis of asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark: a prospective cohort study. *The Lancet Respiratory Medicine,* 5**,** 426-434.

COLEMAN, M. & AYLIN, P. 2000. Death certification and mortality statistics: an international perspective. *STUDIES ON MEDICAL AND POPULATION SUBJECTS-OFFICE OF POPULATION CENSUSES AND SURVEYS*.

COMEAP 2009. *Long-Term Exposure to Air Pollution: Effect on Mortality,* London, Public Health England.

CONNORS JR, A. F., DAWSON, N. V., THOMAS, C., HARRELL JR, F. E., DESBIENS, N., FULKERSON, W. J., KUSSIN, P., BELLAMY, P., GOLDMAN, L. & KNAUS, W. A. 1996. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *American journal of respiratory and critical care medicine,* 154**,** 959-967.

CORNISH, D., BROOKMAN, A., HORTON, M. & SCANLON, S. 2019. Adult smoking habits in the UK: 2018. *Office For National Statistics: Office For National Statistics*.

COVIELLO, V. & BOGGESS, M. 2004. Cumulative incidence estimation in the presence of competing risks. *The Stata Journal,* 4**,** 103-112.

COX, D. R. 1972. Regression models and life-tables. *Journal of the Royal Statistical Society: Series B (Methodological),* 34**,** 187-202.

CPRD. 2021. *Clinical Practice Research Datalink (CPRD). Observational research* [Online]. Available: https://www.cprd.com/Observational-research [Accessed 06/08/2021 2021].

DALLEYWATER, W., POWELL, H. A., HUBBARD, R. B. & NAVARATNAM, V. 2015. Risk factors for cardiovascular disease in people with idiopathic pulmonary fibrosis: a population-based study. *Chest,* 147**,** 150-156.

DECRAMER, M., MIRAVITLLES, M., PRICE, D., ROMAN-RODRIGUEZ, M., LLOR, C., WELTE, T., BUHL, R., DUSSER, D., SAMARA, K. & SIAFAKAS, N. 2011. New horizons in early stage COPD--improving knowledge, detection and treatment. *Respir Med,* 105**,** 1576-87.

DELMESTRI, A. & PRIETO-ALHAMBRA, D. 2020. CPRD GOLD and linked ONS mortality records: Reconciling guidelines. *International Journal of Medical Informatics,* 136**,** 104038.

DEVEREUX, G. 2006. Definition, epidemiology, and risk factors. *Bmj,* 332**,** 1142-1144.

DEVIS, T. & ROONEY, C. 1999a. Death certification and the epidemiologist. *Health Statistics Quarterly*, 21-34.

DEVIS, T. & ROONEY, C. 1999b. Death certification and the epidemiologist. *Health Statistics Quarterly,* 1.

DEVRIES, R., KRIEBEL, D. & SAMA, S. 2017. Outdoor Air Pollution and COPD-Related Emergency Department Visits, Hospital Admissions, and Mortality: A Meta-Analysis. *COPD: Journal of Chronic Obstructive Pulmonary Disease,* 14, 113-121.

DIAB, N., GERSHON, A. S., SIN, D. D., TAN, W. C., BOURBEAU, J., BOULET, L.-P. & AARON, S. D. 2018. Underdiagnosis and Overdiagnosis of Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine,* 198, 1130-1139.

DIAZ-GUZMAN, E., KHOSRAVI, M. & MANNINO, D. M. 2011. Asthma, chronic obstructive pulmonary disease, and mortality in the US population. *COPD: Journal of Chronic Obstructive Pulmonary Disease,* 8, 400-407.

DIVO, M., COTE, C., DE TORRES, J. P., CASANOVA, C., MARIN, J. M., PINTO-PLATA, V., ZULUETA, J., CABRERA, C., ZAGACETA, J., HUNNINGHAKE, G. & CELLI, B. 2012. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med,* 186.

DONALDSON, G., PFEFFER, P., MACKAY, A. & WEDZICHA, J. 2018. Ambient particulate matter and oxides of nitrogen are associated with an increased incidence of COPD exacerbations with symptoms of infective etiology. *B50. COPD.* American Thoracic Society.

DONALDSON, G. C. & WEDZICHA, J. A. 2006. COPD exacerbations .1: Epidemiology. *Thorax,* 61, 164-8.

DORAN, T., KONTOPANTELIS, E., VALDERAS, J. M., CAMPBELL, S., ROLAND, M., SALISBURY, C. & REEVES, D. 2011. Effect of financial incentives on incentivised and non-incentivised clinical activities: longitudinal analysis of data from the UK Quality and Outcomes Framework. *Bmj,* 342, d3590.

DRUMMOND, M. B., WISE, R. A., JOHN, M., ZVARICH, M. T. & MCGARVEY, L. P. 2010. Accuracy of death certificates in COPD: analysis from the TORCH trial. *COPD,* 7, 179-85.

EUROSTAT 2013. Revision of the European Standard Population—report of Eurostat's task force. Luxembourg: Eurostat.

EVANS, J. D., KAPTOGE, S., CALEYACHETTY, R., DI ANGELANTONIO, E., LEWIS, C., PARAMESHWAR, K. J. & PETTIT, S. J. 2016. Socioeconomic Deprivation and Survival After Heart Transplantation in England: An Analysis of the United Kingdom Transplant Registry. *Circ Cardiovasc Qual Outcomes,* 9**,** 695-703.

FALZON, C., SOLJAK, M., ELKIN, S. L., BLAKE, I. D. & HOPKINSON, N. S. 2013. Finding the missing millions – the impact of a locally enhanced service for COPD on current and projected rates of diagnosis: a population-based prevalence study using interrupted time series analysis. *Primary Care Respiratory Journal,* 22**,** 59-63.

FAN, V. S., BRYSON, C. L., CURTIS, J. R., FIHN, S. D., BRIDEVAUX, P. O., MCDONELL, M. B. & AU, D. H. 2003. Inhaled corticosteroids in chronic obstructive pulmonary disease and risk of death and hospitalization: time-dependent analysis. *Am J Respir Crit Care Med,* 168**,** 1488-94.

FINE, J. P. & GRAY, R. J. 1999. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American statistical association,* 94**,** 496-509.

FLYNN, R. W. V., MACDONALD, T. M., CHALMERS, J. D. & SCHEMBRI, S. 2018. The effect of changes to GOLD severity stage on long term morbidity and mortality in COPD. *Respir Res,* 19**,** 249.

FOREMAN, K. J., MARQUEZ, N., DOLGERT, A., FUKUTAKI, K., FULLMAN, N., MCGAUGHEY, M., PLETCHER, M. A., SMITH, A. E., TANG, K., YUAN, C.-W., BROWN, J. C., FRIEDMAN, J., HE, J., HEUTON, K. R., HOLMBERG, M., PATEL, D. J., REIDY, P., CARTER, A., CERCY, K., CHAPIN, A., DOUWES-SCHULTZ, D., FRANK, T., GOETTSCH, F., LIU, P. Y., NANDAKUMAR, V., REITSMA, M. B., REUTER, V., SADAT, N., SORENSEN, R. J. D., SRINIVASAN, V., UPDIKE, R. L., YORK, H., LOPEZ, A. D., LOZANO, R., LIM, S. S., MOKDAD, A. H., VOLLSET, S. E. & MURRAY, C. J. L. 2018. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. *The Lancet,* 392**,** 2052-2090.

FROMER, L. 2011. Diagnosing and treating COPD: understanding the challenges and finding solutions. *International journal of general medicine,* 4**,** 729.

FU, J.-J., GIBSON, P. G., SIMPSON, J. L. & MCDONALD, V. M. 2014. Longitudinal changes in clinical outcomes in older patients with asthma, COPD and asthma-COPD overlap syndrome. *Respiration,* 87**,** 63-74.

GALLAGHER, A. M., DEDMAN, D., PADMANABHAN, S., LEUFKENS, H. G. M. & DE VRIES, F. 2019. The accuracy of date of death recording in the Clinical Practice Research Datalink GOLD database in England compared with the Office for National Statistics death registrations. *Pharmacoepidemiol Drug Saf,* 28**,** 563-569.

GASPARRINI, A. 2021. The case time series design. *Epidemiology*.

GASPARRINI, A., GUO, Y., HASHIZUME, M., LAVIGNE, E., ZANOBETTI, A., SCHWARTZ, J., TOBIAS, A., TONG, S., ROCKLÖV, J., FORSBERG, B., LEONE, M., DE SARIO, M., BELL, M. L., GUO, Y. L., WU, C. F., KAN, H., YI, S. M., DE SOUSA ZANOTTI STAGLIORIO COELHO, M., SALDIVA, P. H., HONDA, Y., KIM, H. & ARMSTRONG, B. 2015. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *The Lancet,* 386**,** 369-375.

GASPARRINI, A. & LEONE, M. 2014. Attributable risk from distributed lag models. *BMC Medical Research Methodology,* 14**,** 55.

GASPARRINI, A., MASSELOT, P., SCORTICHINI, M., SCHNEIDER, R., MISTRY, M. N., SERA, F., MACYNTIRE, H. L., PHALKEY, R. & VICEDO-CABRERA, A. M. 2021. Small-area assessment of temperature-related mortality risks: a case time series analysis in England and Wales. *Submitted for Publication*.

GAYLE, A., DICKINSON, S., POOLE, C., PANG, M., FAUCONNOT, O. & QUINT, J. K. 2019a. Incidence of type II diabetes in chronic obstructive pulmonary disease: a nested case–control study. *NPJ primary care respiratory medicine,* 29**,** 1-6.

GAYLE, A. V., AXSON, E. L., BLOOM, C. I., NAVARATNAM, V. & QUINT, J. K. 2019b. Changing causes of death for patients with chronic respiratory disease in England, 2005-2015. *Thorax,* 74**,** 483-491.

GAYLE, A. V., QUINT, J. K. & FUERTES, E. I. 2020. Understanding the relationships between environmental factors and exacerbations of COPD. *Expert Review of Respiratory Medicine*, null-null.

GERSHON, A. S., CAMPITELLI, M. A., CROXFORD, R. & ET AL. 2014. Combination long-acting β-agonists and inhaled corticosteroids compared with long-acting β-agonists alone in older adults with chronic obstructive pulmonary disease. *JAMA,* 312, 1114-1121.

GERSHON, A. S., THIRUCHELVAM, D., CHAPMAN, K. R., AARON, S. D., STANBROOK, M. B., BOURBEAU, J., TAN, W. & TO, T. 2018. Health Services Burden of Undiagnosed and Overdiagnosed COPD. *Chest,* 153, 1336-1346.

GODTFREDSEN, N. S., LAM, T. H., HANSEL, T. T., LEON, M., GRAY, N., DRESLER, C., BURNS, D., PRESCOTT, E. & VESTBO, J. 2008. COPD-related morbidity and mortality after smoking cessation: status of the evidence. *European Respiratory Journal,* 32, 844-853.

GOLD 2006. Global Strategy For The Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.

GOLD 2015. Global Strategy For The Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.

GOLD 2020. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD).

GOLDACRE, M. J., DUNCAN, M., COOK-MOZAFFARI, P. & GRIFFITH, M. 2004. Mortality rates for common respiratory diseases in an English population 1979–1998: artefact and substantive trends. *Journal of Public Health,* 26, 8-12.

GOLDACRE, M. J., DUNCAN, M. E. & GRIFFITH, M. 2012. Death rates for asthma in English populations 1979-2007: comparison of underlying cause and all certified causes. *Public Health,* 126, 386-93.

GOODMAN, A., WILKINSON, P., STAFFORD, M., TONNE, C. J. H. & PLACE 2011. Characterising socio-economic inequalities in exposure to air pollution: a comparison of socio-economic markers and scales of measurement. 17, 767-774.

GOODMAN, N., LANE, R. E. & RAMPLING, S. B. 1953. Chronic bronchitis: an introductory examination of existing data. *Br Med J,* 2, 237-43.

GUERRA, B., HAILE, S. R., LAMPRECHT, B., RAMÍREZ, A. S., MARTINEZ-CAMBLOR, P., KAISER, B., ALFAGEME, I., ALMAGRO, P., CASANOVA, C., ESTEBAN-GONZÁLEZ, C., SOLER-CATALUÑA, J. J., DE-TORRES, J. P., MIRAVITLLES, M., CELLI, B. R., MARIN, J. M., TER RIET, G., SOBRADILLO, P., LANGE, P., GARCIA-AYMERICH, J., ANTÓ, J. M., TURNER, A. M., HAN, M. K., LANGHAMMER, A., LEIVSETH, L., BAKKE, P., JOHANNESSEN, A., OGA, T., COSIO, B., ANCOCHEA-BERMÚDEZ, J., ECHAZARRETA, A., ROCHE, N., BURGEL, P.-R., SIN, D. D., SORIANO, J. B., PUHAN, M. A. & FOR THE, C. I. A. C. 2018. Large-scale external validation and comparison of prognostic models: an application to chronic obstructive pulmonary disease. *BMC Medicine,* 16**,** 33.

GUO, Y., ZHANG, T., WANG, Z., YU, F., XU, Q., GUO, W., WU, C. & HE, J. 2016. Body mass index and mortality in chronic obstructive pulmonary disease: A dose–response meta-analysis. *Medicine,* 95.

GUPTA, R. P., MUKHERJEE, M., SHEIKH, A. & STRACHAN, D. P. 2018. Persistent variations in national asthma mortality, hospital admissions and prevalence by socioeconomic status and region in England. *Thorax,* 73**,** 706-712.

HALES, S., ATKINSON, J., METCALFE, J., KUSCHEL, G. & WOODWARD, A. 2021. Long term exposure to air pollution, mortality and morbidity in New Zealand: Cohort study. *Science of The Total Environment,* 801**,** 149660.

HAN, M. K., TAYOB, N., MURRAY, S., WOODRUFF, P. G., CURTIS, J. L., KIM, V., CRINER, G., GALBAN, C. J., ROSS, B. D., HOFFMAN, E. A., LYNCH, D. A., KAZEROONI, E. & MARTINEZ, F. J. 2018. Association between Emphysema and Chronic Obstructive Pulmonary Disease Outcomes in the COPDGene and SPIROMICS Cohorts: A Post Hoc Analysis of Two Clinical Trials. *American Journal of Respiratory and Critical Care Medicine,* 198**,** 265-267.

HANGAARD, S., KRONBORG, T. & HEJLESEN, O. K. 2019. Characteristics of Subjects With Undiagnosed COPD Based on Post-Bronchodilator Spirometry Data. *Respiratory Care,* 64**,** 63-70.

HANSEL, N. N., MCCORMACK, M. C. & KIM, V. 2016. The Effects of Air Pollution and Temperature on COPD. *COPD: Journal of Chronic Obstructive Pulmonary Disease,* 13**,** 372-379.

HANSELL, A., WALK, J. & SORIANO, J. 2003a. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *European Respiratory Journal,* 22**,** 809-814.

HANSELL, A. L., WALK, J. A. & SORIANO, J. B. 2003b. What do chronic obstructive pulmonary disease patients die from? Amultiple cause coding analysis. *European Respiratory Journal,* 22**,** 809-814.

HAROON, S. M., JORDAN, R. E., O'BEIRNE-ELLIMAN, J. & ADAB, P. 2015. Effectiveness of case finding strategies for COPD in primary care: a systematic review and meta-analysis. *NPJ primary care respiratory medicine,* 25**,** 15056.

HASHIM, D., BOFFETTA, P., LA VECCHIA, C., ROTA, M., BERTUCCIO, P., MALVEZZI, M. & NEGRI, E. 2016. The global decrease in cancer mortality: trends and disparities. *Annals of Oncology,* 27**,** 926-933.

HAWKINS, N. M., PETRIE, M. C., JHUND, P. S., CHALMERS, G. W., DUNN, F. G. & MCMURRAY, J. J. 2009. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail,* 11**,** 130-9.

HERRETT, E., GALLAGHER, A. M., BHASKARAN, K., FORBES, H., MATHUR, R., VAN STAA, T. & SMEETH, L. 2015a. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol,* 44**,** 827-36.

HERRETT, E., GALLAGHER, A. M., BHASKARAN, K., FORBES, H., MATHUR, R., VAN STAA, T. & SMEETH, L. 2015b. Data resource profile: clinical practice research datalink (CPRD). *International journal of epidemiology,* 44**,** 827-836.

HIGGINS, M. W. & KELLER, J. B. 1989. Trends in COPD Morbidity and Mortality in Tecumseh, Michigan. *Am Rev Respir Dis,* 140**,** S42-S48.

HOLGATE, S., GRIGG, J., AGIUS, R., ASHTON, J. R., CULLINAN, P., EXLEY, K., FISHWICK, D., FULLER, G., GOKANI, N. & GRIFFITHS, C. Every breath we take: The lifelong impact of air pollution, Report of a working party. 2016. Royal College of Physicians.

HOLGUIN, F. F., E; REDD, S; MANNINO, D 2005. Comorbidity and Mortality in COPD-Related Hospitalizations in the United States, 1979 to 2001. *Chest,* 128**,** 2005-2011.

HOSSEINI, M., ALMASI-HASHIANI, A., SEPIDARKISH, M. & MAROUFIZADEH, S. 2019. Global prevalence of asthma-COPD overlap (ACO) in the general population: a systematic review and meta-analysis. *Respiratory Research,* 20**,** 229.

HURST, J. R., MCMILLAN, V. & ROBERTS, C. M. 2019a. The National COPD Audit–what you need to know. *Clinical Medicine***,** clinmed. 2019-0202.

HURST, J. R., MCMILLAN, V. & ROBERTS, C. M. 2019b. The National COPD Audit–what you need to know. *Clinical Medicine,* 19**,** 499.

HUTCHINSON, J. P., MCKEEVER, T. M., FOGARTY, A. W., NAVARATNAM, V. & HUBBARD, R. B. 2014. Increasing global mortality from idiopathic pulmonary fibrosis in the twenty-first century. *Ann Am Thorac Soc,* 11**,** 1176-85.

IQAIR 2020. 2019 World Air Quality Report. *Region & City PM2. 5 Ranking.* Switzerland.

ITO, K. & BARNES, P. J. 2009. COPD as a Disease of Accelerated Lung Aging. *CHEST,* 135**,** 173-180.

JAMES, G. D., DONALDSON, G. C., WEDZICHA, J. A. & NAZARETH, I. 2014. Trends in management and outcomes of COPD patients in primary care, 2000-2009: a retrospective cohort study. *NPJ Prim Care Respir Med,* 24**,** 14015.

JI, M., COHAN, D. S. & BELL, M. L. 2011. Meta-analysis of the association between short-term exposure to ambient ozone and respiratory hospital admissions. *Environmental Research Letters,* 6**,** 024006.

JONES, R. C., PRICE, D., RYAN, D., SIMS, E. J., VON ZIEGENWEIDT, J., MASCARENHAS, L., BURDEN, A., HALPIN, D. M., WINTER, R. & HILL, S. 2014. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. *The Lancet Respiratory Medicine,* 2**,** 267-276.

JORDAN JR, J. G. & MANN, J. R. 2010. Obesity and mortality in persons with obstructive lung disease using data from the NHANES III. *Southern medical journal,* 103**,** 323-330.

KATANODA, K., SOBUE, T., SATOH, H., TAJIMA, K., SUZUKI, T., NAKATSUKA, H., TAKEZAKI, T., NAKAYAMA, T., NITTA, H. & TANABE, K. 2011. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. *Journal of epidemiology*, 1102090211-1102090211.

KIDDLE, S. J., WHITTAKER, H. R., SEAMAN, S. R. & QUINT, J. K. 2020. Prediction of five-year mortality after COPD diagnosis using primary care records. *PLOS ONE,* 15, e0236011.

KIRI, V. A., PRIDE, N. B., SORIANO, J. B. & VESTBO, J. 2005. Inhaled corticosteroids in chronic obstructive pulmonary disease: results from two observational designs free of immortal time bias. *Am J Respir Crit Care Med,* 172, 460-4.

KONIETZKO, N. F. J., CARTON, R. W. & LEROY, E. P. 1969. Causes of death in patients with bronchiectasis. *American Review of Respiratory Disease,* 100, 852-858.

LAMPRECHT, B., SORIANO, J., STUDNICKA, M., KAISER, B., VANFLETEREN, L. & GNATIUC, L. 2015. BOLD Collaborative Research Group, the EPI-SCAN Team, the PLATINO Team, and the PREPOCOL Study Group. Determinants of underdiagnosis of COPD in national and international surveys. *Chest,* 148, 971-985.

LANDIS, S. H., MUELLEROVA, H., MANNINO, D. M., MENEZES, A. M., HAN, M. K., VAN DER MOLEN, T., ICHINOSE, M., AISANOV, Z., OH, Y.-M. & DAVIS, K. J. 2014. Continuing to Confront COPD International Patient Survey: methods, COPD prevalence, and disease burden in 2012–2013. *International Journal of Chronic Obstructive Pulmonary Disease,* 9, 597-611.

LANGE, P., MAROTT, J. L., VESTBO, J., OLSEN, K. R., INGEBRIGTSEN, T. S., DAHL, M. & NORDESTGAARD, B. G. 2012. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. *Am J Respir Crit Care Med,* 186, 975-81.

LAU, B., COLE, S. R. & GANGE, S. J. 2009. Competing risk regression models for epidemiologic data. *Am J Epidemiol,* 170, 244-56.

LIPSETT, M. J., OSTRO, B. D., REYNOLDS, P., GOLDBERG, D., HERTZ, A., JERRETT, M., SMITH, D. F., GARCIA, C., CHANG, E. T. & BERNSTEIN, L. 2011. Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. *American journal of respiratory and critical care medicine,* 184**,** 828-835.

LOPEZ-CAMPOS, J. L., MARQUEZ-MARTIN, E. & SORIANO, J. B. 2016. The role of air pollution in COPD and implications for therapy. *Expert Review of Respiratory Medicine,* 10**,** 849-859.

LOZANO, R., NAGHAVI, M., FOREMAN, K., LIM, S., SHIBUYA, K., ABOYANS, V., ABRAHAM, J., ADAIR, T., AGGARWAL, R., AHN, S. Y., ALVARADO, M., ANDERSON, H. R., ANDERSON, L. M., ANDREWS, K. G., ATKINSON, C., BADDOUR, L. M., BARKER-COLLO, S., BARTELS, D. H., BELL, M. L., BENJAMIN, E. J., BENNETT, D., BHALLA, K., BIKBOV, B., BIN ABDULHAK, A., BIRBECK, G., BLYTH, F., BOLLIGER, I., BOUFOUS, S., BUCELLO, C., BURCH, M., BURNEY, P., CARAPETIS, J., CHEN, H., CHOU, D., CHUGH, S. S., COFFENG, L. E., COLAN, S. D., COLQUHOUN, S., COLSON, K. E., CONDON, J., CONNOR, M. D., COOPER, L. T., CORRIERE, M., CORTINOVIS, M., DE VACCARO, K. C., COUSER, W., COWIE, B. C., CRIQUI, M. H., CROSS, M., DABHADKAR, K. C., DAHODWALA, N., DE LEO, D., DEGENHARDT, L., DELOSSANTOS, A., DENENBERG, J., DES JARLAIS, D. C., DHARMARATNE, S. D., DORSEY, E. R., DRISCOLL, T., DUBER, H., EBEL, B., ERWIN, P. J., ESPINDOLA, P., EZZATI, M., FEIGIN, V., FLAXMAN, A. D., FOROUZANFAR, M. H., FOWKES, F. G., FRANKLIN, R., FRANSEN, M., FREEMAN, M. K., GABRIEL, S. E., GAKIDOU, E., GASPARI, F., GILLUM, R. F., GONZALEZ-MEDINA, D., HALASA, Y. A., HARING, D., HARRISON, J. E., HAVMOELLER, R., HAY, R. J., HOEN, B., HOTEZ, P. J., HOY, D., JACOBSEN, K. H., JAMES, S. L., JASRASARIA, R., JAYARAMAN, S., JOHNS, N., KARTHIKEYAN, G., KASSEBAUM, N., KEREN, A., KHOO, J. P., KNOWLTON, L. M., KOBUSINGYE, O., KORANTENG, A., KRISHNAMURTHI, R., LIPNICK, M., LIPSHULTZ, S. E., OHNO, S. L., et al. 2012. 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. *The Lancet,* 380**,** 2095-128.

MAHLER, D. A., WIRE, P., HORSTMAN, D., CHANG, C. N., YATES, J., FISCHER, T. & SHAH, T. 2002. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med,* 166**,** 1084-91.

MANNINO, D. M., BROWN, C. & GIOVINO, G. A. 1997. 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,* 156**,** 814-8.

MANNINO, D. M. & KIRI, V. A. 2006. Changing the burden of COPD mortality. *International Journal of COPD,* 1**,** 219-233.

MANNINO, D. M., THORN, D., SWENSEN, A. & HOLGUIN, F. 2008. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *European Respiratory Journal,* 32**,** 962-969.

MARKS, G. & BURNEY, P. 1997. Diseases of the respiratory system. *In:* CHARLTON J & M, M. (eds.) *The Health of Adult Britain:1841-1994.* London: Stationary Office: Palgrave Macmillan UK.

MARSHALL, L., FINCH, D., CAIRNCROSS, L. & BIBBY, J. 2019. Mortality and life expectancy trends in the UK: stalling progress. *Health Foundation*.

MATHERS, C. D. & LONCAR, D. 2006. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS medicine,* 3**,** e442.

MCCORMACK, M. C., PAULIN, L. M., GUMMERSON, C. E., PENG, R. D., DIETTE, G. B. & HANSEL, N. N. 2017. Colder temperature is associated with increased COPD morbidity. *European Respiratory Journal,* 49**,** 1601501.

MCGARVEY, L. P., JOHN, M., ANDERSON, J. A., ZVARICH, M. & WISE, R. A. 2007. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax,* 62**,** 411-415.

MENACHEMI, N. & COLLUM, T. H. 2011. Benefits and drawbacks of electronic health record systems. *Risk management and healthcare policy,* 4**,** 47-55.

MENEZES, A. M., WEHRMEISTER, F. C., PEREZ-PADILLA, R., VIANA, K. P., SOARES, C., MÜLLEROVA, H., VALDIVIA, G., JARDIM, J. R. & MONTES DE OCA, M. 2017. The PLATINO study: description of the distribution, stability, and mortality according to the Global Initiative for Chronic Obstructive Lung Disease classification from 2007 to 2017. *International journal of chronic obstructive pulmonary disease,* 12**,** 1491-1501.

METCALFE, D., MASTERS, J., DELMESTRI, A., JUDGE, A., PERRY, D., ZOGG, C., GABBE, B. & COSTA, M. 2019. Coding algorithms for defining Charlson and Elixhauser co-morbidities in Read-coded databases. *BMC Medical Research Methodology,* 19**,** 115.

MILOJEVIC, A., WILKINSON, P., ARMSTRONG, B., BHASKARAN, K., SMEETH, L. & HAJAT, S. 2014. Short-term effects of air pollution on a range of cardiovascular events in England and Wales: case-crossover analysis of the MINAP database, hospital admissions and mortality. *Heart,* 100**,** 1093-1098.

MIRAVITLLES, M., SORIANO, J. B., GARCIA-RIO, F., MUÑOZ, L., DURAN-TAULERIA, E., SANCHEZ, G., SOBRADILLO, V. & ANCOCHEA, J. 2009. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. *Thorax,* 64**,** 863-868.

MORALES, D. R., FLYNN, R., ZHANG, J., TRUCCO, E., QUINT, J. K. & ZUTIS, K. 2018. External validation of ADO, DOSE, COTE and CODEX at predicting death in primary care patients with COPD using standard and machine learning approaches. *Respiratory Medicine,* 138**,** 150-155.

MURRAY, C. J., VOS, T., LOZANO, R., NAGHAVI, M., FLAXMAN, A. D., MICHAUD, C., EZZATI, M., SHIBUYA, K., SALOMON, J. A., ABDALLA, S., ABOYANS, V., ABRAHAM, J., ACKERMAN, I., AGGARWAL, R., AHN, S. Y., ALI, M. K., ALVARADO, M., ANDERSON, H. R., ANDERSON, L. M., ANDREWS, K. G., ATKINSON, C., BADDOUR, L. M., BAHALIM, A. N., BARKER-COLLO, S., BARRERO, L. H., BARTELS, D. H., BASANEZ, M. G., BAXTER, A., BELL, M. L., BENJAMIN, E. J., BENNETT, D., BERNABE, E., BHALLA, K., BHANDARI, B., BIKBOV, B., BIN ABDULHAK, A., BIRBECK, G., BLACK, J. A., BLENCOWE, H., BLORE, J. D., BLYTH, F., BOLLIGER, I., BONAVENTURE, A.,

BOUFOUS, S., BOURNE, R., BOUSSINESQ, M., BRAITHWAITE, T., BRAYNE, C., BRIDGETT, L., BROOKER, S., BROOKS, P., BRUGHA, T. S., BRYAN-HANCOCK, C., BUCELLO, C., BUCHBINDER, R., BUCKLE, G., BUDKE, C. M., BURCH, M., BURNEY, P., BURSTEIN, R., CALABRIA, B., CAMPBELL, B., CANTER, C. E., CARABIN, H., CARAPETIS, J., CARMONA, L., CELLA, C., CHARLSON, F., CHEN, H., CHENG, A. T., CHOU, D., CHUGH, S. S., COFFENG, L. E., COLAN, S. D., COLQUHOUN, S., COLSON, K. E., CONDON, J., CONNOR, M. D., COOPER, L. T., CORRIERE, M., CORTINOVIS, M., DE VACCARO, K. C., COUSER, W., COWIE, B. C., CRIQUI, M. H., CROSS, M., DABHADKAR, K. C., DAHIYA, M., DAHODWALA, N., DAMSERE-DERRY, J., DANAEI, G., DAVIS, A., DE LEO, D., DEGENHARDT, L., DELLAVALLE, R., DELOSSANTOS, A., DENENBERG, J., DERRETT, S., DES JARLAIS, D. C., DHARMARATNE, S. D., et al. 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet,* 380**,** 2197-223.

NACUL, L., SOLJAK, M., SAMARASUNDERA, E., HOPKINSON, N. S., LACERDA, E., INDULKAR, T., FLOWERS, J., WALFORD, H. & MAJEED, A. 2011. COPD in England: a comparison of expected, model-based prevalence and observed prevalence from general practice data. *J Public Health (Oxf),* 33**,** 108-16.

NHS. 2018. *NHS Long Term Plan* [Online]. NHS. Available: https://www.longtermplan.nhs.uk/online-version/chapter-3-further-progress-on-care-quality-and-outcomes/better-care-for-major-health-conditions/respiratory-disease/ [Accessed 13/01/2022 2022].

NHS DIGITAL. 2017. *Quality and Outcomes Framework* [Online]. Available: http://content.digital.nhs.uk/qof [Accessed].

NICE. 2018. *Chronic obstructive pulmonary disease in over 16s: diagnosis and management (NICE guideline 115)* [Online]. Available: https://www.nice.org.uk/guidance/NG115 [Accessed].

NISSEN, F., MORALES, D. R., MULLEROVA, H., SMEETH, L., DOUGLAS, I. J. & QUINT, J. K. 2018. Concomitant diagnosis of asthma and COPD: a

quantitative study in UK primary care. *British Journal of General Practice,* 68**,** e775-e782.

NISSEN, F., QUINT, J. K., MORALES, D. R. & DOUGLAS, I. J. 2019. How to validate a diagnosis recorded in electronic health records. *Breathe,* 15**,** 64-68.

NOTTG 1980. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med,* 93**,** 391-8.

ONS. 2013. *Revised Annual Mid-year Population Estimates: 2001 to 2010* [Online]. Office of National Statistics. Available: www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77315018 [Accessed Oct 2017].

ONS. 2016. *Vital Statistics: Population and Health Reference Tables* [Online]. Office of National Statistics. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/vitalstatisticspopulationandhealthreferencetables [Accessed Oct 2017].

ONS. 2017. *Mortality Statistics in England and Wales: Quality and Methodology Information* [Online]. Office of National Statistics. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/qmis/mortalitystatisticsinenglandandwalesqmi [Accessed Oct 2017].

ONS. 2020a. *Population Estimates for UK, England and Wales, Scotland and Northern Ireland: Mid-2020* [Online]. Office for National Statistics. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland [Accessed 04/08/2021 2021].

ONS. 2020b. *User guide to mortality statistics* [Online]. Office For National Statistics. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/userguidetomortalitystatisticsjuly2017 [Accessed 15/01/2021 2021].

OSTRO, B., LIPSETT, M., REYNOLDS, P., GOLDBERG, D., HERTZ, A., GARCIA, C., HENDERSON, K. D. & BERNSTEIN, L. 2010. Long-term exposure to constituents of fine particulate air pollution and mortality: results from the California Teachers Study. *Environmental health perspectives,* 118**,** 363-369.

PADMANABHAN, S., CARTY, L., CAMERON, E., GHOSH, R. E., WILLIAMS, R. & STRONGMAN, H. 2019. Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. *European Journal of Epidemiology,* 34**,** 91-99.

PAUWELS, R. A., LOFDAHL, C. G., LAITINEN, L. A., SCHOUTEN, J. P., POSTMA, D. S., PRIDE, N. B. & OHLSSON, S. V. 1999. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. *N Engl J Med,* 340**,** 1948-53.

PELKONEN, M., TUKIAINEN, H., TERVAHAUTA, M., NOTKOLA, I. L., KIVELA, S. L., SALORINNE, Y. & NISSINEN, A. 2000. Pulmonary function, smoking cessation and 30 year mortality in middle aged Finnish men. *Thorax,* 55**,** 746-50.

PELTOLA, L., PÄTSI, H. & HARJU, T. 2020. COPD Comorbidities Predict High Mortality – Asthma-COPD-Overlap Has Better Prognosis. *COPD: Journal of Chronic Obstructive Pulmonary Disease***,** 1-7.

PETO, R., LOPEZ, A. D., BOREHAM, J., THUN, M. & HEATH, C. 1994. Mortality from smoking in developed countries 1950-2000. Indirect estimates from national statistics. Oxford, New York, Tokyo: Oxford University Press.

PINAULT, L., TJEPKEMA, M., CROUSE, D. L., WEICHENTHAL, S., VAN DONKELAAR, A., MARTIN, R. V., BRAUER, M., CHEN, H. & BURNETT, R. T. 2016. Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian community health survey cohort. *Environmental health,* 15**,** 1-15.

PIRINA, P., MARTINETTI, M., SPADA, C., ZINELLU, E., PES, R., CHESSA, E., FOIS, A. G., MIRAVITLLES, M., PAIS, A., COSSEDDU, S., DESSÌ, M.

A., ACCARDO, G., FRAU, D., PERUZZU, I., UDA, F., IDDA, G., SINI, C., PIRO, S., MUSCAS, A., ARNO, P., MANCA, A., SERRA, F., DEIANA, G., PINTORI, G., CANU, M. G., FANARI, G., SETZU, S., VACCARGIU, A. M., VINCIS, B., SCHIRRU, M. T., MAUREDDU, P. P., DALL'ACQUA, P., CONTINI, R., MELONI, M., MARTINETTI, M., GRANARA, A. R., MASSA, S., CADEDDU, M. G., MARIANI, B., URRU, C., AMBU, R., MELONI, M. C., PUDDU, S., SPANO, F., MUSA, S. & CORONA, M. 2017. Prevalence and management of COPD and heart failure comorbidity in the general practitioner setting. *Respiratory Medicine,* 131**,** 1-5.

POELS, P. J., SCHERMER, T. R., VAN WEEL, C. & CALVERLEY, P. M. 2006. Spirometry in chronic obstructive pulmonary disease: Is available, yet underused in general practice. *BMJ: British Medical Journal,* 333**,** 870.

PORTA, N., GOMEZ, G. & MALATS, N. 2007. Competing risks methods. Technical report, December.

PRETEROTI, M., WHITMORE, G. A., VANDEMHEEN, K. L., FITZGERALD, J. M., LEMIÈRE, C., BOULET, L.-P., PENZ, E., FIELD, S. K., GUPTA, S., MCIVOR, R. A., MAYERS, I., HERNANDEZ, P., LOUGHEED, D., AINSLIE, M., LICSKAI, C., AZHER, T., FRASER, I., MAHDAVIAN, M. & AARON, S. D. 2020. Population-based case-finding to identify subjects with undiagnosed asthma or COPD. *European Respiratory Journal,* 55**,** 2000024.

PRICE, D. B., YAWN, B. P. & JONES, R. C. 2010. Improving the differential diagnosis of chronic obstructive pulmonary disease in primary care. *Mayo Clinic proceedings. Mayo Clinic,* 85**,** 1122-9.

PRIDE, N. B. & SORIANO, J. B. 2002. Chronic obstructive pulmonary disease in the United Kingdom: trends in mortality, morbidity, and smoking. *Curr Opin Pulm Med,* 8**,** 95-101.

PUHAN, M., HANSEL, N., SOBRADILLO, P., ENRIGHT, P., LANGE, P., HICKSON, D., MENEZES, A., RIET GT, H. U., DOMINGO-SALVANY, A. & MOSENIFAR, Z. 2012. International COPD Cohorts Collaboration Working Group: Large-scale international validation of the ADO index in subjects with COPD: an individual subject data analysis of 10 cohorts. *BMJ Open,* 2.

PUN, V. C., KAZEMIPARKOUHI, F., MANJOURIDES, J. & SUH, H. H. 2017. Long-Term PM2.5 Exposure and Respiratory, Cancer, and Cardiovascular Mortality in Older US Adults. *American Journal of Epidemiology,* 186**,** 961-969.

PUTCHA, N., ANZUETO, A. R., CALVERLEY, P. M. A., CELLI, B. R., TASHKIN, D. P., METZDORF, N., MUELLER, A. & WISE, R. A. 2021. Mortality and Exacerbation Risk by Body Mass Index in Patients with COPD in TIOSPIR® and UPLIFT®. *Annals of the American Thoracic Society*.

QUANJER, P. H., TAMMELING, G., COTES, J., PEDERSEN, O., PESLIN, R. & YERNAULT, J. 1993. Lung volumes and forced ventilatory flows. *European Respiratory Journal,* 6**,** 5-40.

QUINT, J. 2017. The Air We Breathe: Effect of Environmental Exposures on COPD. *Tanaffos,* 16**,** S14-S15.

QUINT, J. K., MILLETT, E. R. C., JOSHI, M., NAVARATNAM, V., THOMAS, S. L., HURST, J. R., SMEETH, L. & BROWN, J. S. 2016. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *Eur Respir J,* 47**,** 10-13.

QUINT, J. K., MULLEROVA, H., DISANTOSTEFANO, R. L., FORBES, H., EATON, S., HURST, J. R., DAVIS, K. & SMEETH, L. 2014a. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). *BMJ Open,* 4**,** e005540.

QUINT, J. K., MÜLLEROVA, H., DISANTOSTEFANO, R. L., FORBES, H., EATON, S., HURST, J. R., DAVIS, K. & SMEETH, L. 2014b. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). *BMJ open,* 4**,** e005540.

RABE, K. F. & WATZ, H. 2017. Chronic obstructive pulmonary disease. *The Lancet,* 389**,** 1931-1940.

RAO KONDAPALLY SESHASAI S, K. S., THOMPSON A, DI ANGELANTONIO E, GAO P, SARWAR N, WHINCUP PH, MUKAMAL KJ, GILLUM RF, HOLME I, NJØLSTAD I 2011. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *New England Journal of Medicine,* 364**,** 829-841.

RAY, E. & KELLY, C. 2019. The overlap between asthma and COPD: a case study. *Independent Nurse,* 2019**,** 24-30.

RCP. 2021. *RCP responds to Prevention of Future Deaths report following inquest into death of Ella Adoo-Kissi-Debrah* [Online]. London: Royal College of Physicians. Available: https://www.rcplondon.ac.uk/news/rcp-responds-prevention-future-deaths-report-following-inquest-death-ella-adoo-kissi-debrah [Accessed 23/08/2021 2021].

REID, D. D. & FLETCHER, C. M. 1971. International studies in chronic respiratory disease. *Br Med Bull,* 27**,** 59-64.

RENNARD, S. I. & VESTBO, J. 2011. Hypothesis: in COPD, a pound of cure may be better than an ounce of prevention. *Thorax,* 66**,** 643-645.

ROBERTS, J. & GADUZO, S. 2013. Finding the 'missing millions': do we need incentives to optimise COPD outcomes? *Primary Care Respiratory Journal,* 22**,** 12.

ROTHMAN, K. J., GREENLAND, S. & LASH, T. L. 2008. *Modern epidemiology*, Wolters Kluwer Health/Lippincott Williams & Wilkins Philadelphia.

ROTHNIE, K. J., CHANDAN, J. S., GOSS, H. G., MÜLLEROVÁ, H. & QUINT, J. K. 2017. Validity and interpretation of spirometric recordings to diagnose COPD in UK primary care. *International journal of chronic obstructive pulmonary disease,* 12**,** 1663-1668.

ROYAL COLLEGE OF PHYSICIANS 1971. Smoking and Health Now. Pitman Medical London.

ROYAL COLLEGE OF PHYSICIANS. Hiding in plain sight: treating tobacco dependency in the NHS. 2018. RCP London.

RYTI, N. R., GUO, Y. & JAAKKOLA, J. J. 2016. Global association of cold spells and adverse health effects: a systematic review and meta-analysis. *Environmental health perspectives,* 124**,** 12-22.

SALCICCIOLI, J. D., MARSHALL, D. C., SHALHOUB, J., MARUTHAPPU, M., DE CARLO, G. & CHUNG, K. F. 2018. Respiratory disease mortality in the United Kingdom compared with EU15+ countries in 1985-2015: observational study. *BMJ,* 363.

SCHNEIDER, R., VICEDO-CABRERA, A. M., SERA, F., MASSELOT, P., STAFOGGIA, M., DE HOOGH, K., KLOOG, I., REIS, S., VIENO, M. & GASPARRINI, A. 2020. A Satellite-Based Spatio-Temporal Machine Learning Model to Reconstruct Daily PM2.5 Concentrations across Great Britain. *Remote Sensing,* 12**,** 3803.

SCHWEIKARDT, C., VERHEIJ, R. A., DONKER, G. A. & COPPIETERS, Y. 2016. The historical development of the Dutch Sentinel General Practice Network from a paper-based into a digital primary care monitoring system. *Journal of Public Health,* 24**,** 545-562.

SEARS, M. R. 2015. Smoking, asthma, chronic airflow obstruction and COPD. Eur Respiratory Soc.

SHAVELLE, R. M., PACULDO, D. R., KUSH, S. J., MANNINO, D. M. & STRAUSS, D. J. 2009. Life expectancy and years of life lost in chronic obstructive pulmonary disease: findings from the NHANES III Follow-up Study. *Int J Chron Obstruct Pulmon Dis,* 4**,** 137-48.

SIN, D. D. & MAN, S. F. 2003. Inhaled corticosteroids and survival in chronic obstructive pulmonary disease: does the dose matter? *Eur Respir J,* 21**,** 260-6.

SIN, D. D. & MAN, S. F. 2005. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc,* 2.

SIN, D. D., MCALISTER, F. A., MAN, S. F. & ANTHONISEN, N. R. 2003. Contemporary management of chronic obstructive pulmonary disease: scientific review. *Jama,* 290**,** 2301-12.

SIN, D. D. & TU, J. V. 2001. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med,* 164**,** 580-4.

SINHA, I. P., CALVERT, J., HICKMAN, K. C., HURST, J. R., MCMILLAN, V., QUINT, J. K., SINGH, S. J. & ROBERTS, C. M. 2019. National Asthma and COPD Audit Programme and the NHS Long Term Plan. *The Lancet Respiratory Medicine,* 7**,** 841.

SINHA, S., MYINT, P. K., LUBEN, R. N. & KHAW, K.-T. 2008a. Accuracy of death certification and hospital record linkage for identification of incident stroke. *BMC Medical Research Methodology,* 8**,** 74.

SINHA, S., MYINT, P. K., LUBEN, R. N. & KHAW, K. T. 2008b. Accuracy of death certification and hospital record linkage for identification of incident stroke. *BMC Med Res Methodol,* 8**,** 74.

SNELL, N., STRACHAN, D., HUBBARD, R., GIBSON, J., GRUFFYDD-JONES, K. & JARROLD, I. 2016. 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,* 71**,** A20-A20.

SOLER-CATALUNA, J. J., MARTINEZ-GARCIA, M. A., ROMAN SANCHEZ, P., SALCEDO, E., NAVARRO, M. & OCHANDO, R. 2005. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax,* 60**,** 925-31.

SORIANO, J. B., ABAJOBIR, A. A., ABATE, K. H., ABERA, S. F., AGRAWAL, A., AHMED, M. B., AICHOUR, A. N., AICHOUR, I., AICHOUR, M. T. E., ALAM, K., ALAM, N., ALKAABI, J. M., AL-MASKARI, F., ALVIS-GUZMAN, N., AMBERBIR, A., AMOAKO, Y. A., ANSHA, M. G., ANTÓ, J. M., ASAYESH, H., ATEY, T. M., AVOKPAHO, E. F. G. A., BARAC, A., BASU, S., BEDI, N., BENSENOR, I. M., BERHANE, A., BEYENE, A. S., BHUTTA, Z. A., BIRYUKOV, S., BONEYA, D. J., BRAUER, M., CARPENTER, D. O., CASEY, D., CHRISTOPHER, D. J., DANDONA, L., DANDONA, R., DHARMARATNE, S. D., DO, H. P., FISCHER, F., GEBREHIWOT, T. T., GELETO, A., GHOSHAL, A. G., GILLUM, R. F., GINAWI, I. A. M., GUPTA, V., HAY, S. I., HEDAYATI, M. T., HORITA, N., HOSGOOD, H. D., JAKOVLJEVIC, M. B., JAMES, S. L., JONAS, J. B., KASAEIAN, A., KHADER, Y. S., KHALIL, I. A., KHAN, E. A., KHANG, Y.-H., KHUBCHANDANI, J., KNIBBS, L. D., KOSEN, S., KOUL, P. A., KUMAR, G. A., LESHARGIE, C. T., LIANG, X., EL RAZEK, H. M. A., MAJEED, A., MALTA, D. C., MANHERTZ, T., MARQUEZ, N., MEHARI, A., MENSAH, G. A., MILLER, T. R., MOHAMMAD, K. A., MOHAMMED, K. E., MOHAMMED, S., MOKDAD, A. H., NAGHAVI, M., NGUYEN, C. T., NGUYEN, G., LE NGUYEN, Q., NGUYEN, T. H., NINGRUM, D. N. A., NONG, V. M., OBI, J. I., ODEYEMI, Y. E., OGBO, F. A., OREN, E., PA, M., PARK, E.-K., PATTON, G. C., PAULSON, K., QORBANI, M., QUANSAH, R., RAFAY, A., RAHMAN, M. H. U., RAI, R. K., RAWAF, S., REINIG, N., SAFIRI, S., SARMIENTO-SUAREZ, R., et al. 2017. 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. *The Lancet Respiratory Medicine,* 5**,** 691-706.

SORIANO, J. B., KIRI, V. A., PRIDE, N. B. & VESTBO, J. 2003. Inhaled corticosteroids with/without long-acting beta-agonists reduce the risk of rehospitalization and death in COPD patients. *Am J Respir Med,* 2**,** 67-74.

SORIANO, J. B., MAIER, W. C., EGGER, P., VISICK, G., THAKRAR, B., SYKES, J. & PRIDE, N. B. 2000. Recent trends in physician diagnosed COPD in women and men in the UK. *Thorax,* 55**,** 789-94.

SORIANO, J. B., VESTBO, J., PRIDE, N. B., KIRI, V., MADEN, C. & MAIER, W. C. 2002. Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. *Eur Respir J,* 20**,** 819-25.

SPELTA, F., FRATTA PASINI, A. M., CAZZOLETTI, L. & FERRARI, M. 2018. Body weight and mortality in COPD: focus on the obesity paradox. *Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity,* 23**,** 15-22.

STEER, J., GIBSON, G. & BOURKE, S. 2010. Predicting outcomes following hospitalization for acute exacerbations of COPD. *QJM: An International Journal of Medicine,* 103**,** 817-829.

SUISSA, S. 2003. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. *Am J Respir Crit Care Med,* 168**,** 49-53.

SUISSA, S. 2004. Inhaled steroids and mortality in COPD: bias from unaccounted immortal time. *Eur Respir J,* 23**,** 391-5.

SZAFRANSKI, W., CUKIER, A., RAMIREZ, A., MENGA, G., SANSORES, R., NAHABEDIAN, S., PETERSON, S. & OLSSON, H. 2003. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J,* 21**,** 74-81.

TATE, A. R., BELOFF, N., AL-RADWAN, B., WICKSON, J., PURI, S., WILLIAMS, T., VAN STAA, T. & BLEACH, A. 2014. Exploiting the potential of large databases of electronic health records for research using rapid search algorithms and an intuitive query interface. *J Am Med Inform Assoc,* 21**,** 292-8.

THURSTON, G. D., AHN, J., CROMAR, K. R., SHAO, Y., REYNOLDS, H. R., JERRETT, M., LIM, C. C., SHANLEY, R., PARK, Y. & HAYES, R. B. 2016. Ambient particulate matter air pollution exposure and mortality in

the NIH-AARP diet and health cohort. *Environmental health perspectives,* 124**,** 484-490.

TOBÍAS, A., HASHIZUME, M., HONDA, Y., SERA, F., NG, C. F. S., KIM, Y., ROYE, D., CHUNG, Y., DANG, T. N., KIM, H., LEE, W., ÍÑIGUEZ, C., VICEDO-CABRERA, A., ABRUTZKY, R., GUO, Y., TONG, S., COELHO, M. D. S. Z. S., SALDIVA, P. H. N., LAVIGNE, E., CORREA, P. M., ORTEGA, N. V., KAN, H., OSORIO, S., KYSELÝ, J., URBAN, A., ORRU, H., INDERMITTE, E., JAAKKOLA, J. J. K., RYTI, N. R. I., PASCAL, M., HUBER, V., SCHNEIDER, A., KATSOUYANNI, K., ANALITIS, A., ENTEZARI, A., MAYVANEH, F., GOODMAN, P., ZEKA, A., MICHELOZZI, P., DE'DONATO, F., ALAHMAD, B., DIAZ, M. H., DE LA CRUZ VALENCIA, C., OVERCENCO, A., HOUTHUIJS, D., AMELING, C., RAO, S., DI RUSCIO, F., CARRASCO, G., SEPOSO, X., NUNES, B., MADUREIRA, J., HOLOBACA, I.-H., SCOVRONICK, N., ACQUAOTTA, F., FORSBERG, B., ÅSTRÖM, C., RAGETTLI, M. S., GUO, Y.-L. L., CHEN, B.-Y., LI, S., COLISTRO, V., ZANOBETTI, A., SCHWARTZ, J., DUNG, D. V., ARMSTRONG, B. & GASPARRINI, A. 2021. Geographical Variations of the Minimum Mortality Temperature at a Global Scale: A Multicountry Study. *Environmental Epidemiology,* 5**,** e169.

VAN DER VALK, P., MONNINKHOF, E., VAN DER PALEN, J., ZIELHUIS, G. & VAN HERWAARDEN, C. 2002. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. *Am J Respir Crit Care Med,* 166**,** 1358-63.

VERHEIJ, R. A., CURCIN, V., DELANEY, B. C. & MCGILCHRIST, M. M. 2018. Possible Sources of Bias in Primary Care Electronic Health Record Data Use and Reuse. *J Med Internet Res,* 20**,** e185.

VESTBO J, HURD SS, AGUSTÍ AG, JONES PW, VOGELMEIER C, ANZUETO A, BARNES PJ, FABBRI LM, MARTINEZ FJ, NISHIMURA M, STOCKLEY RA, SIN DD & R, R.-R. 2017. Global Initiative for Chronic Obstructive Pulmonary Disease.

VESTBO, J., ANDERSON, J., BROOK, R. D., CALVERLEY, P. M. A., CELLI, B. R., CRIM, C., HAUMANN, B., MARTINEZ, F. J., YATES, J. & NEWBY, D. E. 2013. The Study to Understand Mortality and Morbidity in COPD (SUMMIT) study protocol. *European Respiratory Journal,* 41**,** 1017-1022.

VESTBO, J., SORENSEN, T., LANGE, P., BRIX, A., TORRE, P. & VISKUM, K. 1999. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet,* 353**,** 1819-23.

VIEGI, G., PISTELLI, F., SHERRILL, D. L., MAIO, S., BALDACCI, S. & CARROZZI, L. 2007. Definition, epidemiology and natural history of COPD. *Eur Respir J,* 30**,** 993-1013.

VOS, T., BARBER, R.M., BELL, B., BERTOZZI-VILLA, A., BIRYUKOV, S., BOLLIGER, I., CHARLSON, F., DAVIS, A., DEGENHARDT, L., DICKER, D. AND DUAN, L., 2015. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet,* 386**,** 743-800.

WANG, B., EUM, K.-D., KAZEMIPARKOUHI, F., LI, C., MANJOURIDES, J., PAVLU, V. & SUH, H. 2020. The impact of long-term PM2.5 exposure on specific causes of death: exposure-response curves and effect modification among 53 million U.S. Medicare beneficiaries. *Environmental Health,* 19**,** 20.

WANG, M., AARON, C. P., MADRIGANO, J., HOFFMAN, E. A., ANGELINI, E., YANG, J., LAINE, A., VETTERLI, T. M., KINNEY, P. L. & SAMPSON, P. D. 2019. Association between long-term exposure to ambient air pollution and change in quantitatively assessed emphysema and lung function. *Jama,* 322**,** 546-556.

WANG, T., CHIANG, E. T., MORENO-VINASCO, L., LANG, G. D., PENDYALA, S., SAMET, J. M., GEYH, A. S., BREYSSE, P. N., CHILLRUD, S. N. & NATARAJAN, V. 2010. Particulate matter disrupts human lung endothelial barrier integrity via ROS-and p38 MAPK–dependent pathways. *American journal of respiratory cell and molecular biology,* 42**,** 442-449.

WELLS, C. 2014. Office for National Statistics - Impact of the Implementation of IRIS Software for ICD-10 Cause of Death Coding on Mortality Statistics, England and Wales.

WISE, R., CONNETT, J., WEINMANN, G., SCANLON, P. & SKEANS, M. 2000. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med,* 343**,** 1902-9.

WOLF, A., DEDMAN, D., CAMPBELL, J., BOOTH, H., LUNN, D., CHAPMAN, J. & MYLES, P. 2019. Data resource profile: clinical practice research Datalink (CPRD) aurum. *International journal of epidemiology,* 48**,** 1740-1740g.

WRIGHT, D., TWIGG, M. & THORNLEY, T. 2015. Chronic obstructive pulmonary disease case finding by community pharmacists: a potential cost-effective public health intervention. *International Journal of Pharmacy Practice,* 23**,** 83-85.

YANG, X., ZHANG, T., ZHANG, Y., CHEN, H. & SANG, S. 2021. Global burden of COPD attributable to ambient PM2.5 in 204 countries and territories, 1990 to 2019: A systematic analysis for the Global Burden of Disease Study 2019. *Science of The Total Environment,* 796**,** 148819.

ZHAN, Z., ZHAO, Y., PANG, S., ZHONG, X., WU, C. & DING, Z. 2017. Temperature change between neighboring days and mortality in United States: A nationwide study. *Science of The Total Environment,* 584-585**,** 1152-1161.

ZHANG, Z. 2017. Survival analysis in the presence of competing risks. *Annals of translational medicine,* 5**,** 47-47.

ZHU, R.-X., NIE, X.-H., CHEN, Y.-H., CHEN, J., WU, S.-W. & ZHAO, L.-H. 2020. Relationship Between Particulate Matter (PM2.5) and Hospitalizations and Mortality of Chronic Obstructive Pulmonary Disease Patients: A Meta-Analysis. *The American Journal of the Medical Sciences,* 359**,** 354-364.

9 Appendices

Contents

9.1 Supplementary material for Chapter 1

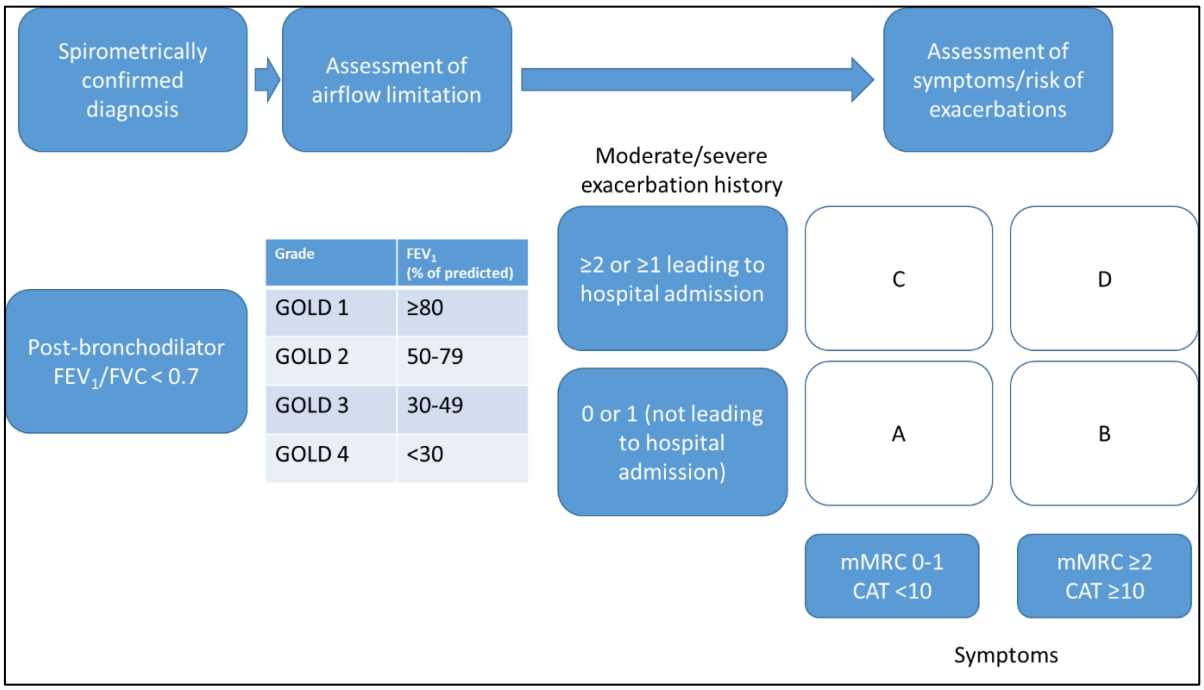
GOLD Classification of Airflow Limitation Severity in COPD

(based on post-bronchodilator FEV_1)

Stage		
GOLD 0	At-risk	presence of risk factors (smoking) and symptoms (chronic cough and sputum production) in the absence of spirometric abnormalities that cross the diagnostic threshold for COPD
In patients with $FEV_1/FVC<0.70$		
GOLD I	Mild	$FEV_1 \geq 80\%$ predicted
GOLD II	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD III	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD IV	Very Severe	$FEV_1 < 30\%$ predicted

Adapted from the GOLD 2006 report (GOLD, 2006)

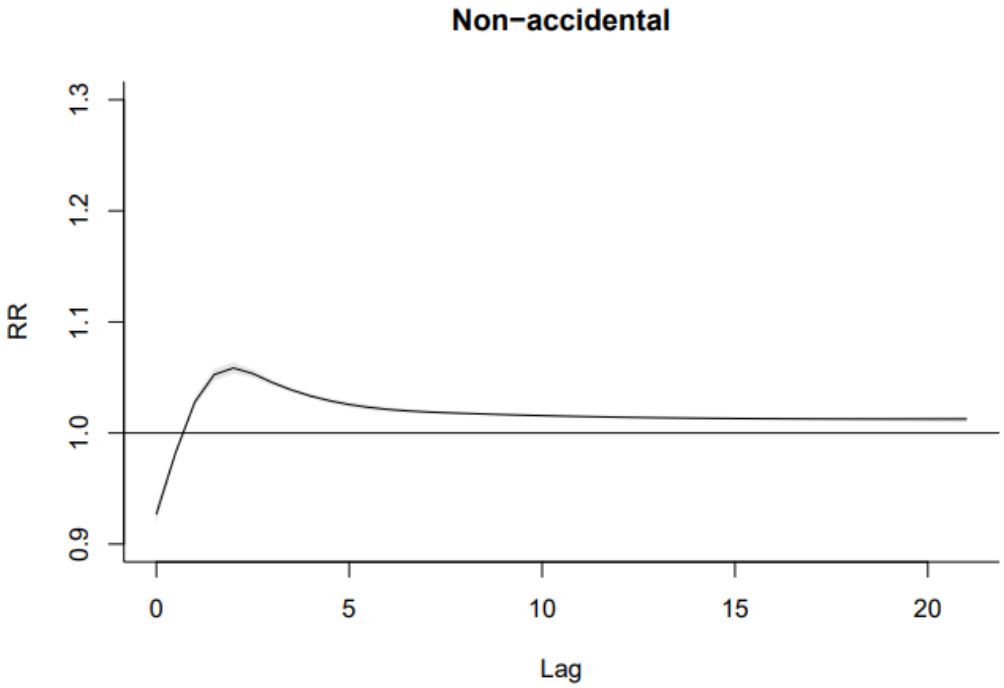
The refined ABCD GOLD Assessment Tool



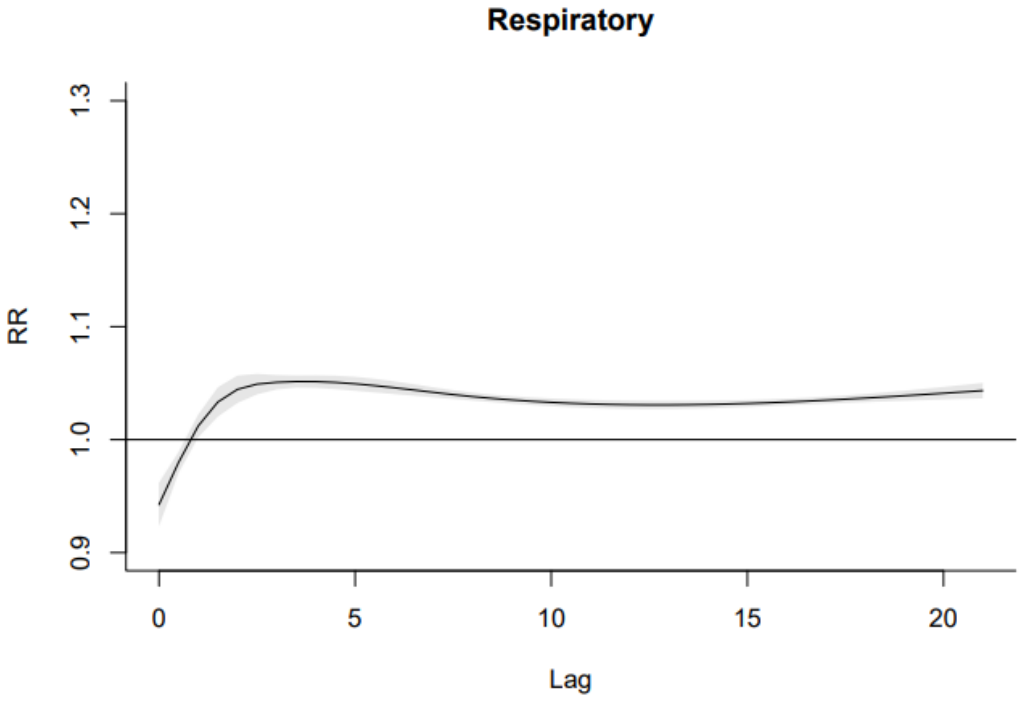
Adapted from the GOLD 2020 report (GOLD, 2020)

9.2 Supplementary material for Chapter 3

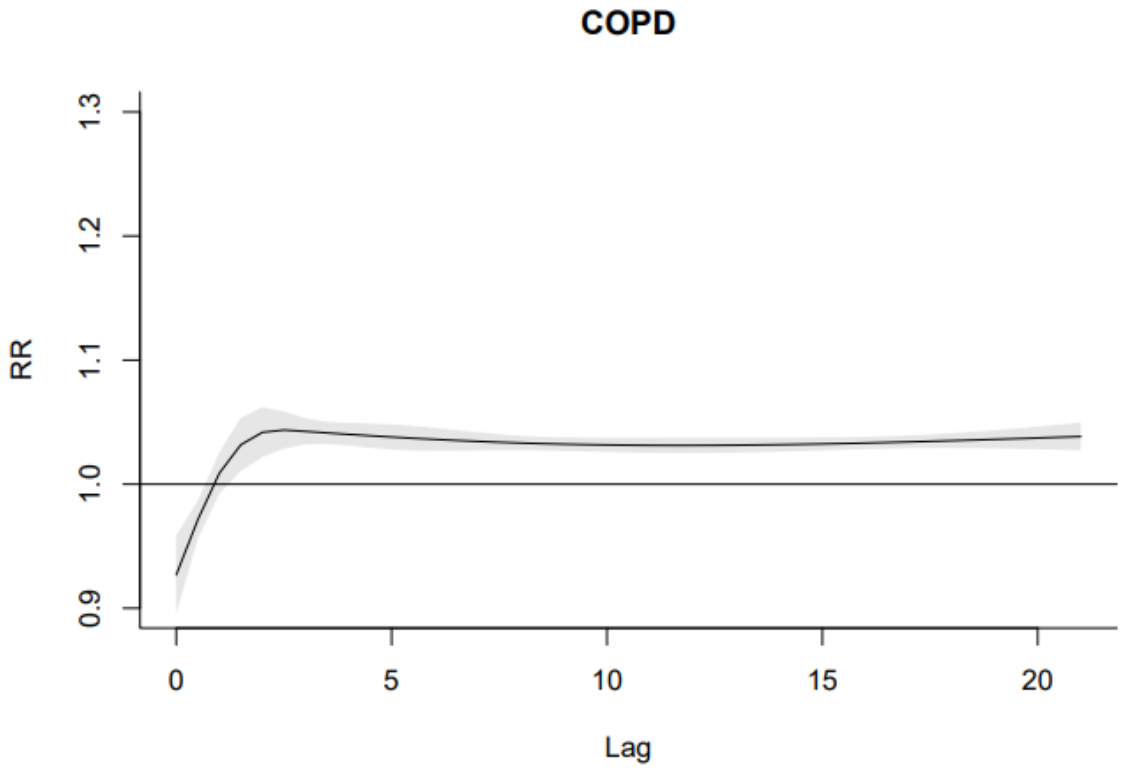
Effect of cold temperature by lag day of exposure on RR of all-cause (non-accidental) mortality



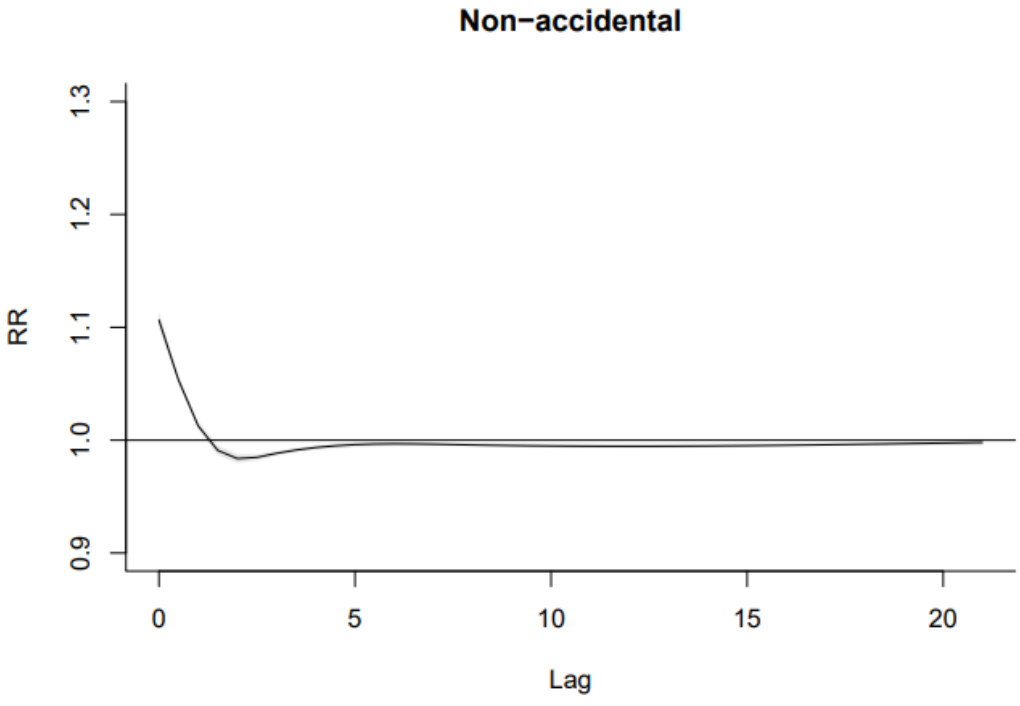
Effect of cold temperature by lag day of exposure on RR of respiratory mortality



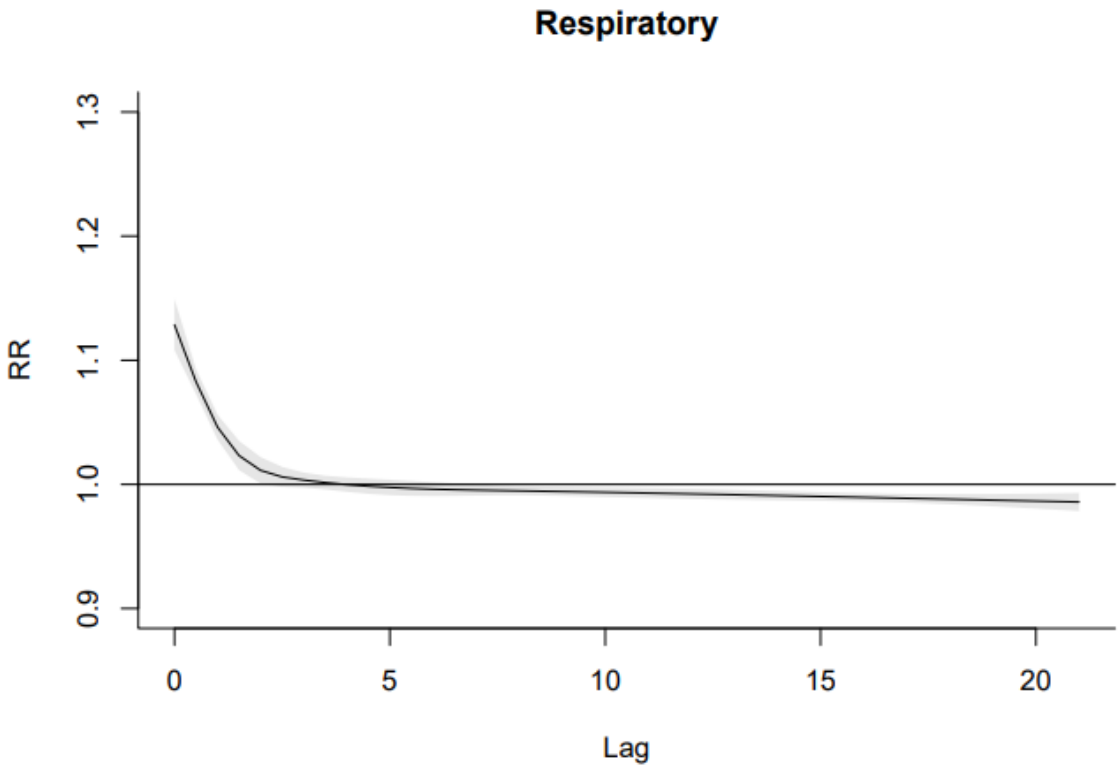
Effect of cold temperature by lag day of exposure on RR of COPD mortality



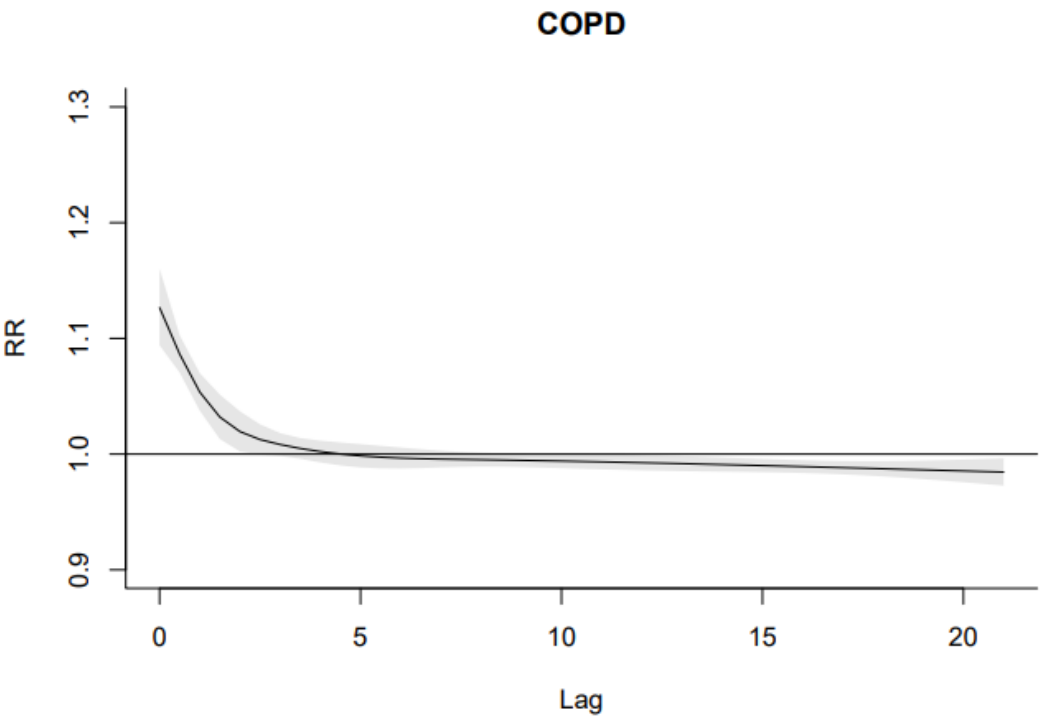
Effect of warm temperature by lag day of exposure on RR of all-cause (non-accidental) mortality



Effect of warm temperature by lag day of exposure on RR of respiratory mortality



Effect of warm temperature by lag day of exposure on RR of COPD mortality



9.3 Code lists

A. Causes of death (ICD-10)

ICD-10 Codes	Term
A00-B99	Certain infectious and parasitic diseases
C00-D49	Neoplasms
D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
E00-E90	Endocrine, nutritional and metabolic diseases
F00-F99, R54	Mental and behavioural disorders
G00-G99	Diseases of the nervous system
H00-H95	Diseases of the eye and adnexa, the ear and mastoid process
I00-I99	Diseases of the circulatory system
J00-J99, R09.2	Diseases of the respiratory system
K00-K93	Diseases of the digestive system
L00-L99	Diseases of the skin and subcutaneous tissue
M00-M99	Diseases of the musculoskeletal system and connective tissue
N00-N99	Diseases of the genitourinary system
O00-O99	Pregnancy, childbirth and the puerperium
Q00-Q99	Congenital malformations, deformations and chromosomal abnormalities
R00-R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
S00- T98, V01-Y98	External causes of morbidity
U00-U49	Provisional assignment of new diseases of uncertain aetiology or emergency use

B. Respiratory-related causes of death (ONS)

ICD-10 Code	Term
J00	Acute nasopharyngitis [common cold]
J01	Acute sinusitis
J01.0	Acute maxillary sinusitis
J01.1	Acute frontal sinusitis
J01.2	Acute ethmoidal sinusitis
J01.3	Acute sphenoidal sinusitis
J01.4	Acute pansinusitis
J01.8	Other acute sinusitis
J01.9	Acute sinusitis, unspecified
J02	Acute pharyngitis
J02.0	Streptococcal pharyngitis
J02.8	Acute pharyngitis due to other specified organisms
J02.9	Acute pharyngitis, unspecified
J03	Acute tonsillitis
J03.0	Streptococcal tonsillitis
J03.8	Acute tonsillitis due to other specified organisms
J03.9	Acute tonsillitis, unspecified
J04	Acute laryngitis and tracheitis
J04.0	Acute laryngitis
J04.1	Acute tracheitis
J04.2	Acute laryngotracheitis
J05	Acute obstructive laryngitis [croup] and epiglottitis
J05.0	Acute obstructive laryngitis [croup]
J05.1	Acute epiglottitis
J06	Acute upper respiratory infections of multiple and unspecified sites
J06.0	Acute laryngopharyngitis
J06.8	Other acute upper respiratory infections of multiple sites
J06.9	Acute upper respiratory infection, unspecified
J09	Influenza due to identified zoonotic or pandemic influenza virus
J10	influenza due to identified seasonal influenza virus
J10.0	Influenza with pneumonia, seasonal influenza virus identified
J10.1	Influenza with other respiratory manifestations, seasonal influenza virus identified
J10.8	Influenza with other manifestations, seasonal influenza virus identified
J11	Influenza, virus not identified
J11.0	Influenza with pneumonia, virus not identified
J11.1	Influenza with other respiratory manifestations, virus not identified
J11.8	Influenza with other manifestations, virus not identified
J12	Viral pneumonia, not elsewhere classified
J12.0	Adenoviral pneumonia

ICD-10 Code	Term
J12.1	Respiratory syncytial virus pneumonia
J12.2	Parainfluenza virus pneumonia
J12.3	Human metapneumovirus pneumonia
J12.8	Other viral pneumonia
J12.9	Viral pneumonia, unspecified
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J15.0	Pneumonia due to Klebsiella pneumoniae
J15.1	Pneumonia due to Pseudomonas
J15.2	Pneumonia due to staphylococcus
J15.3	Pneumonia due to streptococcus, group B
J15.4	Pneumonia due to other streptococci
J15.5	Pneumonia due to Escherichia coli
J15.6	Pneumonia due to other Gram-negative bacteria
J15.7	Pneumonia due to Mycoplasma pneumoniae
J15.8	Other bacterial pneumonia
J15.9	Bacterial pneumonia, unspecified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J16.0	Chlamydial pneumonia
J16.8	Pneumonia due to other specified infectious organisms
J17	Pneumonia in diseases classified elsewhere
J17.0	Pneumonia in bacterial diseases classified elsewhere
J17.0	Pneumonia in bacterial diseases classified elsewhere
J17.1	Pneumonia in viral diseases classified elsewhere
J17.1	Pneumonia in viral diseases classified elsewhere
J17.8	Pneumonia in other diseases classified elsewhere
J17.8	Pneumonia in other diseases classified elsewhere
J18	Pneumonia, organism unspecified
J18.0	Bronchopneumonia, unspecified
J18.1	Lobar pneumonia, unspecified
J18.8	Other pneumonia, organism unspecified
J18.9	Pneumonia, unspecified
J20	Acute bronchitis
J20	Acute bronchitis
J20.0	Acute bronchitis due to Mycoplasma pneumoniae
J20.1	Acute bronchitis due to Haemophilus influenzae
J20.2	Acute bronchitis due to streptococcus
J20.3	Acute bronchitis due to coxsackievirus
J20.4	Acute bronchitis due to parainfluenza virus
J20.5	Acute bronchitis due to respiratory syncytial virus
J20.6	Acute bronchitis due to rhinovirus
J20.7	Acute bronchitis due to echovirus

ICD-10 Code	Term
J20.8	Acute bronchitis due to other specified organisms
J20.9	Acute bronchitis, unspecified
J21	Acute bronchiolitis
J21.0	Acute bronchiolitis due to respiratory syncytial virus
J21.1	Acute bronchiolitis due to human metapneumovirus
J21.8	Acute bronchiolitis due to other specified organisms
J21.9	Acute bronchiolitis, unspecified
J22	Unspecified acute lower respiratory infection
J30	Vasomotor and allergic rhinitis
J30.0	Vasomotor rhinitis
J30.1	Allergic rhinitis due to pollen
J30.2	Other seasonal allergic rhinitis
J30.3	Other allergic rhinitis
J30.4	Allergic rhinitis, unspecified
J31	Chronic rhinitis, nasopharyngitis and pharyngitis
J31.0	Chronic rhinitis
J31.1	Chronic nasopharyngitis
J31.2	Chronic pharyngitis
J32	Chronic sinusitis
J32.0	Chronic maxillary sinusitis
J32.1	Chronic frontal sinusitis
J32.2	Chronic ethmoidal sinusitis
J32.3	Chronic sphenoidal sinusitis
J32.4	Chronic pansinusitis
J32.8	Other chronic sinusitis
J32.9	Chronic sinusitis, unspecified
J33	Nasal polyp
J33.0	Polyp of nasal cavity
J33.1	Polypoid sinus degeneration
J33.8	Other polyp of sinus
J33.9	Nasal polyp, unspecified
J34	Other disorders of nose and nasal sinuses
J34.0	Abscess, furuncle and carbuncle of nose
J34.1	Cyst and mucocele of nose and nasal sinus
J34.2	Deviated nasal septum
J34.3	Hypertrophy of nasal turbinates
J34.8	Other specified disorders of nose and nasal sinuses
J35	Chronic diseases of tonsils and adenoids
J35.0	Chronic tonsillitis
J35.1	Hypertrophy of tonsils
J35.2	Hypertrophy of adenoids
J35.3	Hypertrophy of tonsils with hypertrophy of adenoids
J35.8	Other chronic diseases of tonsils and adenoids

ICD-10 Code	Term
J35.9	Chronic disease of tonsils and adenoids, unspecified
J36	Peritonsillar abscess
J37	Chronic laryngitis and laryngotracheitis
J37.0	Chronic laryngitis
J37.1	Chronic laryngotracheitis
J38	Diseases of vocal cords and larynx, not elsewhere classified
J38.0	Paralysis of vocal cords and larynx
J38.1	Polyp of vocal cord and larynx
J38.2	Nodules of vocal cords
J38.3	Other diseases of vocal cords
J38.4	Oedema of larynx
J38.5	Laryngeal spasm
J38.6	Stenosis of larynx
J38.7	Other diseases of larynx
J39	Other diseases of upper respiratory tract
J39.0	Retropharyngeal and parapharyngeal abscess
J39.1	Other abscess of pharynx
J39.2	Other diseases of pharynx
J39.3	Upper respiratory tract hypersensitivity reaction, site unspecified
J39.8	Other specified diseases of upper respiratory tract
J39.9	Disease of upper respiratory tract, unspecified
J40	Bronchitis, not specified as acute or chronic
J41	Simple and mucopurulent chronic bronchitis
J41.0	Simple chronic bronchitis
J41.1	Mucopurulent chronic bronchitis
J41.8	Mixed simple and mucopurulent chronic bronchitis
J42	Unspecified chronic bronchitis
J43	Emphysema
J43.0	MacLeod syndrome
J43.1	Panlobular emphysema
J43.2	Centrilobular emphysema
J43.8	Other emphysema
J43.9	Emphysema, unspecified
J44	Other chronic obstructive pulmonary disease
J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection
J44.1	Chronic obstructive pulmonary disease with acute exacerbation, unspecified
J44.8	Other specified chronic obstructive pulmonary disease
J44.9	Chronic obstructive pulmonary disease, unspecified
J45	Asthma
J45.0	Predominantly allergic asthma
J45.1	Nonallergic asthma
J45.8	Mixed asthma

ICD-10 Code	Term
J45.9	Asthma, unspecified
J46	Status asthmaticus
J47	Bronchiectasis
J60	Coalworker pneumoconiosis
J61	Pneumoconiosis due to asbestos and other mineral fibres
J62	Pneumoconiosis due to dust containing silica
J62.0	Pneumoconiosis due to talc dust
J62.8	Pneumoconiosis due to other dust containing silica
J63	Pneumoconiosis due to other inorganic dusts
J63.0	Aluminosis (of lung)
J63.1	Bauxite fibrosis (of lung)
J63.2	Berylliosis
J63.3	Graphite fibrosis (of lung)
J63.4	Siderosis
J63.5	Stannosis
J63.8	Pneumoconiosis due to other specified inorganic dusts
J64	Unspecified pneumoconiosis
J65	Pneumoconiosis associated with tuberculosis
J66	Airway disease due to specific organic dust
J66.0	Byssinosis
J66.1	Flax-dresser disease
J66.2	Cannabinosis
J66.8	Airway disease due to other specific organic dusts
J67	Hypersensitivity pneumonitis due to organic dust
J67.0	Farmer lung
J67.1	Bagassosis
J67.2	Bird fancier lung
J67.3	Suberosis
J67.4	Maltworker lung
J67.5	Mushroom-worker lung
J67.6	Maple-bark-stripper lung
J67.7	Air-conditioner and humidifier lung
J67.8	Hypersensitivity pneumonitis due to other organic dusts
J67.9	Hypersensitivity pneumonitis due to unspecified organic dust
J68	Respiratory conditions due to inhalation of chemicals, gases, fumes and vapours
J68.0	Bronchitis and pneumonitis due to chemicals, gases, fumes and vapours
J68.1	Pulmonary oedema due to chemicals, gases, fumes and vapours
J68.2	Upper respiratory inflammation due to chemicals, gases, fumes and vapours, not elsewhere classified
J68.3	Other acute and subacute respiratory conditions due to chemicals, gases, fumes and vapours

ICD-10 Code	Term
J68.4	Chronic respiratory conditions due to chemicals, gases, fumes and vapours
J68.8	Other respiratory conditions due to chemicals, gases, fumes and vapours
J68.9	Unspecified respiratory condition due to chemicals, gases, fumes and vapours
J69	Pneumonitis due to solids and liquids
J69.0	Pneumonitis due to food and vomit
J69.1	Pneumonitis due to oils and essences
J69.8	Pneumonitis due to other solids and liquids
J70	Respiratory conditions due to other external agents
J70.0	Acute pulmonary manifestations due to radiation
J70.1	Chronic and other pulmonary manifestations due to radiation
J70.2	Acute drug-induced interstitial lung disorders
J70.3	Chronic drug-induced interstitial lung disorders
J70.4	Drug-induced interstitial lung disorders, unspecified
J70.8	Respiratory conditions due to other specified external agents
J70.9	Respiratory conditions due to unspecified external agent
J80	Adult respiratory distress syndrome
J81	Pulmonary oedema
J82	Pulmonary eosinophilia, not elsewhere classified
J84	Other interstitial pulmonary diseases
J84.0	Alveolar and parietoalveolar conditions
J84.1	Other interstitial pulmonary diseases with fibrosis
J84.8	Other specified interstitial pulmonary diseases
J84.9	Interstitial pulmonary disease, unspecified
J85	Abscess of lung and mediastinum
J85.0	Gangrene and necrosis of lung
J85.1	Abscess of lung with pneumonia
J85.2	Abscess of lung without pneumonia
J85.3	Abscess of mediastinum
J86	Pyothorax
J86.0	Pyothorax with fistula
J86.9	Pyothorax without fistula
J90	Pleural effusion, not elsewhere classified
J91	Pleural effusion in conditions classified elsewhere
J92	Pleural plaque
J92.0	Pleural plaque with presence of asbestos
J92.9	Pleural plaque without asbestos
J93	Pneumothorax
J93.0	Spontaneous tension pneumothorax
J93.1	Other spontaneous pneumothorax
J93.8	Other pneumothorax
J93.9	Pneumothorax, unspecified

ICD-10 Code	Term
J94	Other pleural conditions
J94.0	Chylous effusion
J94.1	Fibrothorax
J94.2	Haemothorax
J94.8	Other specified pleural conditions
J94.9	Pleural condition, unspecified
J95	Postprocedural respiratory disorders, not elsewhere classified
J95.0	Tracheostomy malfunction
J95.1	Acute pulmonary insufficiency following thoracic surgery
J95.2	Acute pulmonary insufficiency following nonthoracic surgery
J95.3	Chronic pulmonary insufficiency following surgery
J95.4	Mendelson syndrome
J95.5	Postprocedural subglottic stenosis
J95.8	Other postprocedural respiratory disorders
J95.9	Postprocedural respiratory disorder, unspecified
J96	Respiratory failure, not elsewhere classified
J96.0	Acute respiratory failure
J96.1	Chronic respiratory failure
J96.9	Respiratory failure, unspecified
J98	Other respiratory disorders
J98.0	Diseases of bronchus, not elsewhere classified
J98.1	Pulmonary collapse
J98.2	Interstitial emphysema
J98.3	Compensatory emphysema
J98.4	Other disorders of lung
J98.5	Diseases of mediastinum, not elsewhere classified
J98.6	Disorders of diaphragm
J98.8	Other specified respiratory disorders
J98.9	Respiratory disorder, unspecified
J99	Respiratory disorders in diseases classified elsewhere
J99.0	Rheumatoid lung disease
J99.1	Respiratory disorders in other diffuse connective tissue disorders
J99.8	Respiratory disorders in other diseases classified elsewhere

C. COPD Codes (CPRD GOLD)

medical code	read term
794	Emphysema
998	Chronic obstructive airways disease
1001	Chronic obstructive pulmonary disease
3243	Chronic bronchitis
5710	Chronic obstructive airways disease NOS
9876	Severe chronic obstructive pulmonary disease
10802	Moderate chronic obstructive pulmonary disease
10863	Mild chronic obstructive pulmonary disease
11287	Chronic obstructive pulmonary disease annual review
12166	Other specified chronic obstructive airways disease
14798	Emphysematous bronchitis
15157	Chronic bronchitis NOS
15782	Chronic pulmonary heart disease NOS
16410	Other emphysema NOS
21061	Chronic obstruct pulmonary dis with acute lower resp infection
23492	Chronic bullous emphysema NOS
25603	Simple chronic bronchitis
26082	Chronic pulmonary oedema
26306	Chronic bullous emphysema
27819	Obstructive chronic bronchitis
33450	Emphysema NOS
37247	Chronic obstructive pulmonary disease NOS
40788	Other emphysema
44525	Obstructive chronic bronchitis NOS
45770	Chronic obstructive pulmonary disease disturbs sleep
45771	Chronic obstructive pulmonary disease does not disturb sleep
46578	Panlobular emphysema
54893	Compensatory emphysema
56860	Segmental bullous emphysema
60188	Giant bullous emphysema
61118	Simple chronic bronchitis NOS
64721	Chronic emphysema due to chemical fumes
65733	[X]Other specified chronic obstructive pulmonary disease
66043	Other chronic bronchitis
66058	[X]Other emphysema
67040	Other specified chronic obstructive pulmonary disease
68066	Other chronic bronchitis NOS

medical code	read term
68662	Zonal bullous emphysema
70787	Atrophic (senile) emphysema
93568	Very severe chronic obstructive pulmonary disease
99536	Bullous emphysema with collapse

D. COPD Codes (CPRD Aurum)

MedCodeId	Term
1823851000006119	Chronic obstructive pulmonary disease confirmed
301477019	Emphysema NOS
64049100000611	Emphysema
113497011	Centrilobular emphysema
1222334016	Other specified chronic obstructive pulmonary disease
1813871000006117	On chronic obstructive pulmonary disease supprtive care pathway
1813881000006119	On COPD (chr obstruc pulmonary disease) supportive care pathway
216596014	End stage chronic obstructive airways disease
2219551000000113	Seen in chronic obstructive pulmonary disease clinic
27096010	Giant bullous emphysema
285100019	Emphysematous bronchitis
301455018	Obstructive chronic bronchitis NOS
301460019	Chronic bullous emphysema
301468014	Chronic bullous emphysema NOS
301539010	Other specified chronic obstructive airways disease
301836011	[X]Other specified chronic obstructive pulmonary disease
396110016	Other emphysema NOS
405121000000111	Health education - chronic obstructive pulmonary disease
457168017	Mild chronic obstructive pulmonary disease
457169013	Moderate chronic obstructive pulmonary disease
457171013	Severe chronic obstructive pulmonary disease
516801000000112	Very severe chronic obstructive pulmonary disease
845451000006118	COPD follow-up
9337016	Panlobular emphysema
475431013	Chronic obstructive pulmonary disease
1484924013	Chronic obstructive pulmonary disease monitoring
1484971019	Chronic obstructive pulmonary disease monitoring due
1488423019	Chronic obstructive pulmonary disease follow-up
1488424013	Chronic obstructive pulmonary disease annual review
1780380013	Chronic obstructive pulmonary disease monitoring by nurse
1780381012	Chronic obstructive pulmonary disease monitoring by doctor

MedCodeId	Term
299001000000116	Chronic obstructive pulmonary disease disturbs sleep
299031000000110	Chronic obstructive pulmonary disease does not disturb sleep
1222335015	Chronic obstructive pulmonary disease NOS
189761000000117	Chronic obstructive pulmonary disease monitoring 1st letter
198471000000111	Chronic obstructive pulmonary disease monitoring 2nd letter
199481000000116	Chronic obstructive pulmonary disease monitoring 3rd letter
967531000006119	Chronic obstructive pulmonary disease monitoring admin
967571000006116	Chronic obstructive pulmonary disease monitoring verb invite
967581000006118	Chronic obstructive pulmonary disease monitor phone invite
966841000006111	Chronic obstructive pulmonary disease clini management plan
2199261000000110	Chronic obstructive pulmonary disease care pathway
264537018	Airways obstructn irreversible
301545019	Chronic obstructive airways disease
555471000006114	Chronic obstructive airways disease NOS

E. COPD Codes (HES/ONS)

ICD-10 Code	Term
J43	Emphysema
J43.0	MacLeod syndrome
J43.1	Panlobular emphysema
J43.2	Centrilobular emphysema
J43.9	Emphysema, unspecified
J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection
J44.1	Chronic obstructive pulmonary disease with acute exacerbation, unspecified
J44.8	Other specified chronic obstructive pulmonary disease
J44.9	Chronic obstructive pulmonary disease, unspecified

F. Asthma Codes (CPRD GOLD)

medcode	Term
78	asthma
81	asthma monitoring
185	acute exacerbation of asthma
232	asthma attack
233	severe asthma attack
1555	bronchial asthma
2290	allergic asthma
3018	mild asthma
3366	severe asthma
3458	occasional asthma
3665	late onset asthma
4442	asthma unspecified
4606	exercise induced asthma
4892	status asthmaticus nos
5267	intrinsic asthma
5627	hay fever with asthma
5798	chronic asthmatic bronchitis
5867	exercise induced asthma
6707	extrinsic asthma with asthma attack
7058	emergency admission, asthma
7146	extrinsic (atopic) asthma
7191	asthma limiting activities
7378	asthma management plan given
7416	asthma disturbing sleep
7731	pollen asthma
8335	asthma attack nos
8355	asthma monitored
9018	number of asthma exacerbations in past year
9552	change in asthma management plan
9663	step up change in asthma management plan
10043	asthma annual review
10274	asthma medication review
10487	asthma - currently active
11370	asthma confirmed
12987	late-onset asthma
13064	asthma severity
13065	moderate asthma
13175	asthma disturbs sleep frequently
13176	asthma follow-up
14777	extrinsic asthma without status asthmaticus
15248	hay fever with asthma
16070	asthma nos
16667	asthma control step 2
16785	asthma control step 1
18223	step down change in asthma management plan

medcode	Term
18224	asthma control step 3
18323	intrinsic asthma with asthma attack
19167	asthma monitoring by nurse
19519	asthma treatment compliance unsatisfactory
19520	asthma treatment compliance satisfactory
19539	asthma monitoring check done
20860	asthma control step 5
20886	asthma control step 4
21232	allergic asthma nec
22752	occupational asthma
24479	emergency asthma admission since last appointment
24506	further asthma - drug prevent.
24884	asthma causes daytime symptoms 1 to 2 times per week
25181	asthma restricts exercise
25791	asthma clinical management plan
26501	asthma never causes daytime symptoms
26503	asthma causes daytime symptoms most days
26504	asthma never restricts exercise
26506	asthma severely restricts exercise
26861	asthma sometimes restricts exercise
27926	extrinsic asthma with status asthmaticus
29325	intrinsic asthma without status asthmaticus
30458	asthma monitoring by doctor
30815	asthma causing night waking
31167	asthma night-time symptoms
31225	asthma causes daytime symptoms 1 to 2 times per month
38143	asthma never disturbs sleep
38144	asthma limits walking up hills or stairs
38145	asthma limits walking on the flat
38146	asthma disturbs sleep weekly
39478	wood asthma
39570	asthma causes night symptoms 1 to 2 times per month
40823	brittle asthma
41017	aspirin induced asthma
41020	absent from work or school due to asthma
42824	asthma daytime symptoms
45073	intrinsic asthma nos
45782	extrinsic asthma nos
46529	attends asthma monitoring
47337	asthma accident and emergency attendance since last visit
47684	detergent asthma
58196	intrinsic asthma with status asthmaticus
73522	work aggravated asthma
93353	sequoiosis (red-cedar asthma)
93736	royal college of physicians asthma assessment
98185	asthma control test
99793	patient has a written asthma personal action plan

medcode	Term
100107	health education - asthma self management
100397	asthma control questionnaire
100509	under care of asthma specialist nurse
100740	health education - structured asthma discussion
102170	asthma review using roy colleg of physicians three questions
102209	mini asthma quality of life questionnaire
102301	asthma trigger - seasonal
102341	asthma trigger - pollen
102395	asthma causes symptoms most nights
102400	asthma causes night time symptoms 1 to 2 times per week
102449	asthma trigger - respiratory infection
102713	asthma limits activities 1 to 2 times per month
102871	asthma trigger - exercise
102888	asthma limits activities 1 to 2 times per week
102952	asthma trigger - warm air
103318	health education - structured patient focused asthma discuss
103321	asthma trigger - animals
103612	asthma never causes night symptoms
103631	royal college physician asthma assessment 3 question score
103813	asthma trigger - cold air
103944	asthma trigger - airborne dust
103945	asthma trigger - damp
103952	asthma trigger - emotion
103955	asthma trigger - tobacco smoke
103998	asthma limits activities most days
105420	asthma self-management plan review
105674	asthma self-management plan agreed
106805	chronic asthma with fixed airflow obstruction
107167	number days absent from school due to asthma in past 6 month

G. Asthma Codes (CPRD Aurum)

medcodeid	Term
655601000006113	Exercise induced asthma
95786019	Occupational asthma
983771000006118	Work aggravated asthma
929091000006111	Aspirin induced asthma
1739151000000116	Asthma trigger - pollen
1739161000000118	Asthma trigger - tobacco smoke
1739171000000113	Asthma trigger - warm air
636271000000117	Asthma trigger - emotion
636251000000114	Asthma trigger - damp
305611000000115	Asthma trigger - animals
636311000000117	Asthma trigger - seasonal
636231000000119	Asthma trigger - cold air
636291000000118	Asthma trigger - respiratory infection

medcodeid	Term
1739131000000111	Asthma trigger - airborne dust
1739141000000119	Asthma trigger - exercise
1780388018	Asthma confirmed
536221000000110	Royal College of Physicians asthma assessment
1766051000006114	Royal College Physician asthma assessment 3 question score
1118291000000110	Asthma control test
1139011000000112	Asthma control questionnaire
1139051000000111	Mini asthma quality of life questionnaire
2117771000000117	Asthma self-management plan agreed
2115631000000117	Asthma self-management plan review
411877015	Asthma monitoring
264540018	Asthma disturbing sleep
264541019	Asthma causing night waking
264542014	Asthma disturbs sleep weekly
264543016	Asthma disturbs sleep frequently
264545011	Asthma never disturbs sleep
264546012	Asthma limiting activities
1722581000000112	Asthma limits activities 1 to 2 times per month
1722651000000119	Asthma limits activities 1 to 2 times per week
1722731000000116	Asthma limits activities most days
264550017	Asthma management plan given
264551018	Asthma severity
1208971012	Occasional asthma
1208969012	Mild asthma
1208970013	Moderate asthma
1208972017	Severe asthma
264565016	Emergency asthma admission since last appointment
264566015	Asthma restricts exercise
264567012	Asthma sometimes restricts exercise
264568019	Asthma severely restricts exercise
264569010	Asthma never restricts exercise
456163018	Asthma - currently active
216186011	Asthma accident and emergency attendance since last visit
1208977011	Asthma treatment compliance satisfactory
1208976019	Asthma treatment compliance unsatisfactory
1212342016	Asthma daytime symptoms
1208957016	Asthma causes night symptoms 1 to 2 times per month
1208960011	Asthma never causes daytime symptoms
1208954011	Asthma causes daytime symptoms 1 to 2 times per month
1208955012	Asthma causes daytime symptoms 1 to 2 times per week
1208956013	Asthma causes daytime symptoms most days
1208959018	Asthma limits walking up hills or stairs
1208958014	Asthma limits walking on the flat
1208962015	Number of asthma exacerbations in past year

medcodeid	Term
1484905010	Change in asthma management plan
1484910014	Step up change in asthma management plan
1484911013	Step down change in asthma management plan
1484953014	Absent from work or school due to asthma
1488421017	Asthma annual review
1488422012	Asthma follow-up
1488722011	Asthma night-time symptoms
1780378019	Asthma monitoring by nurse
1780379010	Asthma monitoring by doctor
1753401000006117	Asthma review using Roy Colleg of Physicians three questions
1722421000000110	Asthma causes night time symptoms 1 to 2 times per week
1722501000000119	Asthma causes symptoms most nights
1768981000000110	Asthma never causes night symptoms
1811901000006116	Number days absent from school due to asthma in past 6 month
1176501000000114	Health education - asthma self management
1176541000000112	Health education - structured asthma discussion
1739871000006114	Health education - structured patient focused asthma discuss
797211000006117	Further asthma - drug prevent.
282489019	Asthma control step 1
282490011	Asthma control step 2
282491010	Asthma control step 3
282492015	Asthma control step 4
282493013	Asthma control step 5
1488436019	Asthma medication review
1176461000000114	Patient has a written asthma personal action plan
2474332015	Asthma clinical management plan
283550015	Emergency admission, asthma
1139131000000117	Under care of asthma specialist nurse
285727014	Attends asthma monitoring
405055018	Asthma monitoring check done
405054019	Asthma monitored
301450011	Chronic asthmatic bronchitis
301485011	Asthma
301480018	Bronchial asthma
660351000006118	Extrinsic (atopic) asthma
1483199016	Allergic asthma
817361000006114	Hay fever with asthma
350154010	Pollen asthma
104872017	Extrinsic asthma without status asthmaticus
350153016	Hay fever with asthma
151338014	Extrinsic asthma with status asthmaticus
350151019	Extrinsic asthma with asthma attack
301499010	Extrinsic asthma NOS

medcodeid	Term
396114013	Intrinsic asthma
350148014	Late onset asthma
21390015	Intrinsic asthma without status asthmaticus
98546013	Intrinsic asthma with status asthmaticus
350156012	Intrinsic asthma with asthma attack
301508013	Intrinsic asthma NOS
419211018	Acute exacerbation of asthma
338238011	Brittle asthma
2240591000000119	Chronic asthma with fixed airflow obstruction
301511014	Asthma unspecified
396118011	Status asthmaticus NOS
145961000006117	Severe asthma attack
396119015	Asthma attack
409865018	Asthma attack NOS
350149018	Late-onset asthma
396120014	Asthma NOS
655611000006111	Exercise induced asthma
350152014	Allergic asthma NEC
149741000006116	Sequoiosis (red-cedar asthma)
94731013	Wood asthma
69311016	Detergent asthma

H. Asthma Codes (HES/ONS)

ICD-10 Code	Term
J45	Asthma
J45.0	Predominantly allergic asthma
J45.1	Nonallergic asthma
J45.8	Mixed asthma
J45.9	Asthma, unspecified
J46	Status asthmaticus

I. Smoking status codes (CPRD GOLD)

Status	medcode	Term
current smoker	203208	Current smoker
current smoker	285187	Cigarette smoker
current smoker	266944	Rolls own cigarettes
current smoker	309558	Smoking reduced
current smoker	257726	Smoker
current smoker	248526	Pipe smoker
current smoker	257725	Keeps trying to stop smoking
current smoker	203207	Smoking restarted
current smoker	276051	Smoking started
current smoker	276050	Cigar smoker
current smoker	294327	Trying to give up smoking
current smoker	12942	Smoker - amount smoked
current smoker	54	Tobacco consumption
current smoker	12958	Trivial smoker - < 1 cig/day
current smoker	12941	Occasional smoker
current smoker	12944	Light smoker - 1-9 cigs/day
current smoker	1878	Moderate smoker - 10-19 cigs/d
current smoker	3568	Heavy smoker - 20-39 cigs/day
current smoker	1822	Very heavy smoker - 40+cigs/d
current smoker	12964	Keeps trying to stop smoking
current smoker	12240	Trying to give up smoking
current smoker	12947	Pipe smoker
current smoker	12943	Cigar smoker
current smoker	12945	Rolls own cigarettes
current smoker	93	Cigarette smoker
current smoker	1823	Smoker
current smoker	12952	Smoking started
current smoker	12951	Smoking restarted
current smoker	10558	Current smoker
current smoker	12966	Smoking reduced
current smoker	12965	Cigarette consumption
current smoker	12963	Cigar consumption
current smoker	12960	Tobacco consumption NOS
current smoker	12967	Pipe tobacco consumption
current smoker	31114	Ready to stop smoking
current smoker	30423	Thinking about stopping smoking
current smoker	30762	Not interested in stopping smoking
current smoker	41979	Smoking restarted
current smoker	46321	Reason for restarting smoking
current smoker	46300	Cigarette pack-years
current smoker	62686	Minutes from waking to first tobacco consumption

Status	medcode	Term
current smoker	101338	Failed attempt to stop smoking
current smoker	105501	Waterpipe tobacco consumption
current smoker	26096	Smokes drugs
current smoker	34126	Negotiated date for cessation of smoking
current smoker	38112	Smoking cessation programme start date
current smoker	11713	Pack years
current smoker	2111	Health ed. - smoking
current smoker	10184	Pregnancy smoking advice
current smoker	18926	Lifestyle advice regarding smoking
current smoker	98137	Brief intervention for smoking cessation
current smoker	74907	Smoking cessation therapy
current smoker	94958	Smoking cessation drug therapy
current smoker	91708	Other specified smoking cessation therapy
current smoker	90522	Smoking cessation therapy NOS
current smoker	110692	Varenicline smoking cessation therapy offered
current smoker	7622	Smoking cessation advice
current smoker	41042	Smoking cessation advice provided by community pharmacist
current smoker	103507	Stop smoking service opportunity signposted
current smoker	18573	Referral to smoking cessation advisor
current smoker	10742	Referral to stop-smoking clinic
current smoker	98154	Referral to NHS stop smoking service
current smoker	100099	Smoking cessation advice declined
current smoker	106391	Referral to smoking cessation service declined
current smoker	106359	Referral to smoking cessation service
current smoker	11356	Seen by smoking cessation advisor
current smoker	102361	Referral for smoking cessation service offered
current smoker	40418	Refuses stop smoking monitor
current smoker	53101	Stop smoking monitor verb.inv.
current smoker	103400	Referred for COPD structured smoking assessment
current smoker	104310	Current smoker annual review
current smoker	98347	Current smoker annual review - enhanced services admin
current smoker	32687	Tobacco dependence
current smoker	95610	Tobacco dependence, unspecified
current smoker	70746	Tobacco dependence, continuous
current smoker	108835	Tobacco dependence, episodic
current smoker	68658	Tobacco dependence NOS
current smoker	61905	[X]Mental and behavioural disorder due to use of tobacco
current smoker	56144	[X]Mental and behav dis due to use of tobacco: harmful use
current smoker	107792	[X]Mental and behav dis due to use tobacco: dependence syndr

Status	medcode	Term
current smoker	101519	[X]Mental and behav dis due to use tobacco: withdrawal state
current smoker	16717	Smokers' cough
current smoker	9045	Advice on smoking
current smoker	42288	Pack years
current smoker	12954	[V]Tobacco use
current smoker	35055	[V]Tobacco abuse counselling
exsmoker	276052	Date ceased smoking
exsmoker	221248	Ex-very heavy smoker (40+/day)
exsmoker	266945	Ex pipe smoker
exsmoker	248528	Stopped smoking
exsmoker	239315	Ex-heavy smoker (20-39/day)
exsmoker	294328	Ex cigar smoker
exsmoker	230314	Ex-smoker - amount unknown
exsmoker	12961	Ex-trivial smoker (<1/day)
exsmoker	12957	Ex-light smoker (1-9/day)
exsmoker	12955	Ex-moderate smoker (10-19/day)
exsmoker	12956	Ex-heavy smoker (20-39/day)
exsmoker	12959	Ex-very heavy smoker (40+/day)
exsmoker	12946	Ex-smoker - amount unknown
exsmoker	776	Stopped smoking
exsmoker	99838	Recently stopped smoking
exsmoker	60	Current non-smoker
exsmoker	26470	Ex pipe smoker
exsmoker	19488	Ex cigar smoker
exsmoker	90	Ex smoker
exsmoker	12878	Date ceased smoking
exsmoker	97210	Ex-cigarette smoker
exsmoker	100495	Ex roll-up cigarette smoker
exsmoker	105711	Total time smoked
exsmoker	10898	Smoking free weeks
exsmoker	7130	Stop smoking monitoring admin.
exsmoker	100963	Ex-smoker annual review
exsmoker	98447	Ex-smoker annual review - enhanced services administration
exsmoker	72706	Tobacco dependence in remission
exsmoker	72700	[V]Personal history of tobacco abuse
Non smoker	11788	Non-smoker
Non smoker	101878	Non-smoker annual review
Non smoker	33	Never smoked tobacco

J. Smoking status (CPRD Aurum)

Status	MedCodeId	Term
current smoker	904121000006117	Carbon monoxide validation confirms smoker
current smoker	99639019	Cigar smoker
current smoker	108938018	Cigarette smoker
current smoker	854021000006115	Cigarette smoker
current smoker	503483019	Current smoker
current smoker	854071000006119	Current smoker
current smoker	1152111000000118	Current smoker annual review
current smoker	1714541000006110	Current smoker annual review - enhanced services admin
current smoker	854961000006110	Grade B light smoker (1-10/day)
current smoker	854981000006117	Grade C moderate smoker (11-20/day)
current smoker	855001000006114	Grade D heavy smoker (>20 Day)
current smoker	819331000006110	Heavy smoker - 20-39 cigs/day
current smoker	743331000006116	Light smoker - 1-9 cigs/day
current smoker	2474719011	Minutes from waking to first tobacco consumption
current smoker	700121000006118	Moderate smoker - 10-19 cigs/d
current smoker	397733018	Occasional smoker
current smoker	72373013	Passive smoker
current smoker	136515019	Pipe smoker
current smoker	344795016	Pipe tobacco consumption
current smoker	250375014	Rolls own cigarettes
current smoker	852981000006111	Rolls own cigarettes
current smoker	137721000006115	Smoker - amount smoked
current smoker	961581000006114	Smokes/uses tobacco products
current smoker	88471000006112	Trivial smoker - < 1 cig/day
current smoker	67621000006112	Very heavy smoker - 40+cigs/d
current smoker	904041000006113	Waking time to first cigarette
current smoker	1809121000006113	Waterpipe tobacco consumption
current smoker	2170961000000116	Waterpipe tobacco consumption
ex smoker	649821000006115	Ex cigar smoker
ex smoker	649831000006117	Ex pipe smoker
ex smoker	1059701000000119	Ex roll-up cigarette smoker
ex smoker	649841000006110	Ex smoker
ex smoker	852991000006114	Ex-cigar smoker
ex smoker	418914010	Ex-cigarette smoker
ex smoker	250366012	Ex-heavy smoker (20-39/day)
ex smoker	250364010	Ex-light smoker (1-9/day)
ex smoker	250365011	Ex-moderate smoker (10-19/day)
ex smoker	854051000006112	Ex-pipe smoker
ex smoker	250371017	Ex-smoker - amount unknown

Status	MedCodeId	Term
ex smoker	1154471000000114	Ex-smoker annual review
ex smoker	1123951000000110	Ex-smoker annual review - enhanced services administration
ex smoker	853001000006110	Ex-smoker NOS
ex smoker	250363016	Ex-trivial smoker (<1/day)
ex smoker	250367015	Ex-very heavy smoker (40+/day)
ex smoker	854111000006110	Past smoker
Non smoker	1009271000006118	Non smoker NOS
Non smoker	1154431000000112	Non smoker annual review
Non smoker	14866014	Non-smoker
Non smoker	397732011	Never smoked tobacco
Non smoker	5495921000006119	Never-smoked

K. COPD Exacerbations (CPRD GOLD)

MedCode	Term
1446	Acute exacerbation of chronic obstructive airways disease
7884	Chron obstruct pulmonary dis wth acute exacerbation, unspec

L. COPD Exacerbations (CPRD Aurum)

MedCodeId	Term
301453013	Acute exacerbation of chronic obstructive airways disease
2010061000006113	Acute non-infective exacerbation of chronic obstructive pulmonary disease
424365019	Acute infective exacerbation of chronic obstructive airways disease
553211000006119	Chron obstruct pulmonary dis wth acute exacerbation, unspec

M. COPD Exacerbation (HES)

ICD-10 Code	Term
J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection
J44.1	Chronic obstructive pulmonary disease with acute exacerbation, unspecified

N. Lower respiratory tract infections (CPRD GOLD)

medcode	readterm
68	chest infection
312	acute bronchitis
1382	acute viral bronchitis unspecified
2476	chest cold
2581	chest infection nos
3358	lower resp tract infection
5978	acute wheezy bronchitis
6124	acute lower respiratory tract infection
9043	acute pneumococcal bronchitis
11072	acute purulent bronchitis
17359	chest infection - unspecified bronchitis
20198	acute bronchitis nos
21061	chronic obstruct pulmonary dis with acute lower resp infectn
21492	acute haemophilus influenzae bronchitis
24316	chest infection with infectious disease ec
24800	acute bacterial bronchitis unspecified
29273	acute bronchitis due to parainfluenza virus
37447	acute lower respiratory tract infection
43362	acute streptococcal bronchitis
48593	acute bronchitis due to respiratory syncytial virus
49794	acute neisseria catarrhalis bronchitis
64890	acute bronchitis due to rhinovirus
65916	acute bronchitis due to echovirus
71370	acute pseudomembranous bronchitis
73100	[x]acute bronchitis due to other specified organisms
93153	acute bronchitis due to coxsackievirus
101775	acute membranous bronchitis
556	influenza
1019	acute bronchiolitis
2157	flu like illness
5947	influenza like illness
6181	obliterating fibrous bronchiolitis
8980	influenza-like symptoms
14791	influenza with gastrointestinal tract involvement
15774	influenza with laryngitis
16388	influenza nos
17185	acute bronchiolitis with bronchospasm
17917	acute bronchiolitis nos
18451	acute bronchiolitis due to respiratory syncytial virus
21145	acute croupous bronchitis
23488	influenza with respiratory manifestations nos

medcode	readterm
26125	bronchiolitis obliterans
29617	influenza with pharyngitis
29669	acute bronchitis and bronchiolitis
31363	influenza with other manifestations nos
41137	acute bronchitis or bronchiolitis nos
41589	acute obliterating bronchiolitis
43625	influenza with other respiratory manifestation
46157	influenza with encephalopathy
47472	influenza with other manifestations
54533	acute capillary bronchiolitis
63697	avian influenza virus nucleic acid detection
66228	acute bronchiolitis due to other specified organisms
66397	[x]other acute lower respiratory infections
69192	acute exudative bronchiolitis
91123	parainfluenza type 3 nucleic acid detection
94130	parainfluenza type 1 nucleic acid detection
94858	parainfluenza type 2 nucleic acid detection
94930	avian influenza
96017	influenza b virus detected
96018	influenza h3 virus detected
96019	influenza h1 virus detected
96286	human parainfluenza virus detected
97062	influenza a virus, other or untyped strain detected
97279	[x]influenza+other manifestations, virus not identified
97605	[x]influenza+oth respiratory manifestatns,virus not identifd
97936	[x]influenza+other manifestations,influenza virus identified
98102	influenza a (h1n1) swine flu
98103	possible influenza a virus h1n1 subtype
98115	suspected swine influenza
98125	suspected influenza a virus subtype h1n1 infection
98129	influenza due to influenza a virus subtype h1n1
98143	influenza a virus h1n1 subtype detected
98156	influenza h5 virus detected
98257	[x]flu+oth respiratory manifestations,'flu virus identified
99214	[x]acute bronchiolitis due to other specified organisms
102918	influenza h2 virus detected

O. Lower respiratory tract infections (CPRD Aurum)

MedCodeId	Term
460161011	Influenza-like symptoms
1122831000000118	Suspected influenza A virus subtype H1N1 infection
1122841000000110	Suspected swine influenza
1135701000000110	Possible influenza A virus H1N1 subtype
312571000000119	Avian influenza virus nucleic acid detection
353561000000111	Parainfluenza type 1 nucleic acid detection
353591000000117	Parainfluenza type 2 nucleic acid detection
353621000000119	Parainfluenza type 3 nucleic acid detection
1126371000000114	Influenza A virus H1N1 subtype detected
676781000000110	Influenza H1 virus detected
676841000000114	Influenza H2 virus detected
676901000000115	Influenza H3 virus detected
676961000000116	Influenza H5 virus detected
677021000000113	Influenza A virus, other or untyped strain detected
677081000000114	Influenza B virus detected
689941000000115	Human parainfluenza virus detected
301095014	Acute bronchitis and bronchiolitis
18268014	Acute bronchitis
411490016	Acute wheezy bronchitis
301101010	Acute membranous bronchitis
2475601016	Acute pseudomembranous bronchitis
301103013	Acute purulent bronchitis
2475602011	Acute croupous bronchitis
301105018	Acute pneumococcal bronchitis
301106017	Acute streptococcal bronchitis
301108016	Acute haemophilus influenzae bronchitis
301109012	Acute neisseria catarrhalis bronchitis
455991000006112	Acute bronchitis due to coxsackievirus
456021000006115	Acute bronchitis due to parainfluenza virus
456031000006117	Acute bronchitis due to respiratory syncytial virus
301116013	Acute bronchitis due to rhinovirus
456001000006113	Acute bronchitis due to echovirus
301120012	Acute viral bronchitis unspecified
301121011	Acute bacterial bronchitis unspecified
301122016	Acute bronchitis NOS
10187013	Acute bronchiolitis
2478755014	Acute capillary bronchiolitis
99508014	Acute obliterating bronchiolitis
25801011	Acute bronchiolitis with bronchospasm
301126018	Acute exudative bronchiolitis
301127010	Obliterating fibrous bronchiolitis

MedCodeId	Term
301128017	Acute bronchiolitis due to respiratory syncytial virus
301129013	Acute bronchiolitis due to other specified organisms
301130015	Acute bronchiolitis NOS
457801000006117	Acute lower respiratory tract infection
301132011	Acute bronchitis or bronchiolitis NOS
396090018	Chest infection NOS
546411000006111	Chest infection
733471000006110	Lower resp tract infection
579878017	Acute lower respiratory tract infection
301143015	Chest cold
546511000006112	Chest infection with infectious disease EC
11203012	Influenza
301415015	Influenza with other respiratory manifestation
301416019	Influenza with laryngitis
301417011	Influenza with pharyngitis
301418018	Influenza with respiratory manifestations NOS
301421016	Influenza with other manifestations
123962018	Influenza with encephalopathy
301423018	Influenza with gastrointestinal tract involvement
301424012	Influenza with other manifestations NOS
396106019	Influenza NOS
762181000006116	Flu like illness
778711000006116	Influenza like illness
92429016	Avian influenza
2820795016	Influenza due to Influenza A virus subtype H1N1
1128141000000118	Influenza A (H1N1) swine flu
350041018	Chest infection - unspecified bronchitis
492443010	Bronchiolitis obliterans
555461000006119	Chronic obstruct pulmonary dis with acute lower resp infectn
387051000006110	[X]Flu+oth respiratory manifestations,'flu virus identified
389901000006115	[X]Influenza+other manifestations,influenza virus identified
389881000006117	[X]Influenza+oth respiratory manifestatns,virus not identifd
389891000006119	[X]Influenza+other manifestations, virus not identified
301819015	[X]Other acute lower respiratory infections
301820014	[X]Acute bronchitis due to other specified organisms
301821013	[X]Acute bronchiolitis due to other specified organisms

P. COPD therapies (CPRD GOLD)

Drug Class	prodcode	Product name
AZITHRO	743	azithromycin 500mg tablets
AZITHRO	4165	zithromax 250mg capsules (pfizer ltd)
AZITHRO	5057	azithromycin 200mg/5ml oral suspension
AZITHRO	5116	azithromycin 250mg capsules
AZITHRO	5335	zithromax 500mg tablets (pfizer ltd)
AZITHRO	14514	zithromax 200mg/5ml oral suspension (pfizer ltd)
AZITHRO	33888	azithromycin 250mg tablets
AZITHRO	40218	azithromycin 500mg tablets (teva uk ltd)
AZITHRO	43400	clamelle 500mg tablets (actavis uk ltd)
AZITHRO	46695	azithromycin 500mg tablet (hillcross pharmaceuticals ltd)
AZITHRO	49530	azithromycin 200mg/5ml oral suspension (sandoz ltd)
AZITHRO	52029	zithromax 250mg capsules (mawdsley-brooks & company ltd)
AZITHRO	53850	azithromycin 200mg/5ml oral suspension (a a h pharmaceuticals ltd)
AZITHRO	58206	azithromycin 250mg tablets (teva uk ltd)
AZITHRO	58426	azithromycin 500mg tablets (sandoz ltd)
AZITHRO	60382	azithromycin 250mg capsules (de pharmaceuticals)
AZITHRO	60814	azithromycin 500mg tablets (de pharmaceuticals)
AZITHRO	61810	azithromycin 500mg tablets (a a h pharmaceuticals ltd)
AZITHRO	62785	azithromycin 250mg capsules (a a h pharmaceuticals ltd)
AZITHRO	65486	azithromycin 200mg/5ml oral suspension (alliance healthcare (distribution) ltd)
AZITHRO	65855	azithromycin 200mg/5ml oral suspension sugar free
AZITHRO	66034	azithromycin 250mg tablets (sandoz ltd)
AZITHRO	69438	zithromax 200mg/5ml oral suspension (waymade healthcare plc)

Drug Class	prodcode	Product name
AZITHRO	69613	azithromycin 250mg capsules (teva uk ltd)
AZITHRO	70783	azithromycin 500mg tablets (kent pharmaceuticals ltd)
ICS	38	beclometasone 100micrograms/dose inhaler
ICS	99	becotide 100 inhaler (glaxosmithkline uk ltd)
ICS	454	pulmicort 200microgram inhaler (astrazeneca uk ltd)
ICS	883	becodisks 200microgram disc (allen & hanburys ltd)
ICS	895	beclazone 100 easi-breathe inhaler (teva uk ltd)
ICS	896	becotide easi-breathe 100microgram/actuation pressurised inhalation (allen & hanburys ltd)
ICS	908	pulmicort 400 turbohaler (astrazeneca uk ltd)
ICS	909	budesonide 200micrograms/dose inhaler
ICS	911	flixotide accuhaler 250 250microgram/inhalation inhalation powder (allen & hanburys ltd)
ICS	947	budesonide 50micrograms/actuation refill canister
ICS	956	pulmicort 200 turbohaler (astrazeneca uk ltd)
ICS	959	budesonide 50micrograms/dose inhaler
ICS	960	pulmicort 100 turbohaler (astrazeneca uk ltd)
ICS	1100	beclazone 100 inhaler (teva uk ltd)
ICS	1236	becloforte 250micrograms/dose inhaler (glaxosmithkline uk ltd)
ICS	1242	beclometasone 250micrograms/dose inhaler
ICS	1243	beclazone 250 easi-breathe inhaler (teva uk ltd)
ICS	1258	becotide 200 inhaler (glaxosmithkline uk ltd)
ICS	1259	beclometasone 200micrograms/dose inhaler
ICS	1406	becotide 50 inhaler (glaxosmithkline uk ltd)
ICS	1412	flixotide 250microgram/actuation inhalation powder (allen & hanburys ltd)
ICS	1424	flixotide 250microgram disc (allen & hanburys ltd)
ICS	1426	flixotide 500microgram disc (allen & hanburys ltd)
ICS	1518	flixotide 50microgram/actuation inhalation powder (allen & hanburys ltd)

Drug Class	prodcode	Product name
ICS	1537	becotide 200microgram rotacaps (glaxosmithkline uk ltd)
ICS	1551	beclazone 250 inhaler (teva uk ltd)
ICS	1552	becloforte easi-breathe 250microgram/actuation pressurised inhalation (allen & hanburys ltd)
ICS	1642	budesonide 400micrograms/dose dry powder inhaler
ICS	1676	flixotide 125microgram/actuation inhalation powder (allen & hanburys ltd)
ICS	1680	pulmicort ls 50micrograms/dose inhaler (astrazeneca uk ltd)
ICS	1725	beclazone 50 easi-breathe inhaler (teva uk ltd)
ICS	1727	becotide easi-breathe 50microgram/actuation pressurised inhalation (allen & hanburys ltd)
ICS	1734	beclometasone 100micrograms/dose breath actuated inhaler
ICS	1861	aerobec 100 autohaler (meda pharmaceuticals ltd)
ICS	1885	beclazone 200 inhaler (teva uk ltd)
ICS	1951	becodisks 400microgram disc (allen & hanburys ltd)
ICS	1956	pulmicort 1mg respules (astrazeneca uk ltd)
ICS	1959	pulmicort 0.5mg respules (astrazeneca uk ltd)
ICS	2092	budesonide 200micrograms/dose dry powder inhaler
ICS	2124	pulmicort refil 200 mcg inh
ICS	2125	pulmicort 200microgram refill canister (astrazeneca uk ltd)
ICS	2148	beclometasone 400microgram disc
ICS	2159	aerobec 50 autohaler (meda pharmaceuticals ltd)
ICS	2160	beclometasone 50micrograms/dose breath actuated inhaler
ICS	2229	becodisks 100microgram disc (allen & hanburys ltd)
ICS	2282	fluticasone propionate 500micrograms/dose dry powder inhaler
ICS	2335	qvar 100 inhaler (teva uk ltd)
ICS	2440	flixotide accuhaler 500 500microgram/inhalation inhalation powder (allen & hanburys ltd)
ICS	2600	beclometasone 250micrograms/dose breath actuated inhaler
ICS	2723	fluticasone 25micrograms/dose inhaler

Drug Class	prodcode	Product name
ICS	2892	becloforte 400microgram disks (glaxosmithkline uk ltd)
ICS	2893	beclometasone 200micrograms disc
ICS	2951	fluticasone 250microgram/actuation pressurised inhalation
ICS	2992	beclazone 50 inhaler (teva uk ltd)
ICS	3018	beclometasone 50micrograms/dose inhaler
ICS	3065	bextasol inhalation powder (allen & hanburys ltd)
ICS	3075	becotide 400microgram rotacaps (glaxosmithkline uk ltd)
ICS	3119	becloforte integra 250microgram/actuation inhaler with compact spacer (glaxo laboratories ltd)
ICS	3150	beclometasone 100micrograms/actuation extrafine particle cfc free inhaler
ICS	3188	pulmicort complete 50 mcg inh
ICS	3220	qvar 50 autohaler (teva uk ltd)
ICS	3289	flixotide 25micrograms/dose inhaler (glaxosmithkline uk ltd)
ICS	3363	becloforte 400microgram disks with diskhaler (glaxosmithkline uk ltd)
ICS	3437	becotide rotahaler type 4 insufflator inhalation powder (allen and hanburys ltd)
ICS	3442	pulmicort complete 200 mcg inh
ICS	3546	qvar 50 inhaler (teva uk ltd)
ICS	3570	budesonide 200micrograms/actuation refill canister
ICS	3743	filair 50 inhaler (meda pharmaceuticals ltd)
ICS	3753	flixotide diskhaler-community pack 250 mcg
ICS	3898	budesonide 3mg gastro-resistant modified-release capsules
ICS	3927	filair 100 inhaler (meda pharmaceuticals ltd)
ICS	3947	becotide 100microgram rotacaps (glaxosmithkline uk ltd)
ICS	3988	flixotide diskhaler-community pack 100 mcg
ICS	3989	flixotide 100microgram disc (allen & hanburys ltd)
ICS	3993	filair forte 250micrograms/dose inhaler (meda pharmaceuticals ltd)
ICS	4131	fluticasone 100microgram disc

Drug Class	prodcode	Product name
ICS	4132	fluticasone 125microgram/actuation pressurised inhalation
ICS	4365	beclometasone 100micrograms disc
ICS	4413	qvar 100 autohaler (teva uk ltd)
ICS	4499	aerobec 250microgram/actuation pressurised inhalation (meda pharmaceuticals ltd)
ICS	4545	pulmicort ls 50microgram refill canister (astrazeneca uk ltd)
ICS	4601	asmabec 100 clickhaler (focus pharmaceuticals ltd)
ICS	4688	fluticasone 50microgram/actuation pressurised inhalation
ICS	4759	beclometasone 100microgram inhalation powder capsules
ICS	4803	beclazone 250microgram/actuation inhalation powder (actavis uk ltd)
ICS	4926	flixotide accuhaler 100 100microgram/inhalation inhalation powder (allen & hanburys ltd)
ICS	5223	fluticasone 50micrograms/dose inhaler cfc free
ICS	5309	flixotide 50micrograms/dose evohaler (glaxosmithkline uk ltd)
ICS	5521	beclometasone 200micrograms/dose dry powder inhaler
ICS	5522	beclometasone 100micrograms/dose dry powder inhaler
ICS	5551	flixotide 0.5mg/2ml nebules (glaxosmithkline uk ltd)
ICS	5580	flixotide accuhaler 50 50microgram/inhalation inhalation powder (allen & hanburys ltd)
ICS	5683	flixotide 250micrograms/dose evohaler (glaxosmithkline uk ltd)
ICS	5718	flixotide 125micrograms/dose evohaler (glaxosmithkline uk ltd)
ICS	5804	beclometasone 250micrograms/dose dry powder inhaler
ICS	5822	fluticasone 250micrograms/dose inhaler cfc free
ICS	5885	fluticasone propionate 100micrograms/dose dry powder inhaler
ICS	5975	fluticasone 125micrograms/dose inhaler cfc free
ICS	5992	beclometasone 50micrograms/dose dry powder inhaler
ICS	6095	budesonide 3mg gastro-resistant capsules
ICS	7602	fluticasone 50microgram disc
ICS	7638	fluticasone 250microgram disc

Drug Class	prodcode	Product name
ICS	7653	beclometasone 400microgram inhalation powder capsules
ICS	7724	betamethasone valerate 100micrograms/actuation inhaler
ICS	7788	budesonide 100micrograms/dose dry powder inhaler
ICS	7891	fluticasone 500microgram disc
ICS	7948	fluticasone propionate 250micrograms/dose dry powder inhaler
ICS	8111	becloforte vm 250microgram/actuation vm pack (allen & hanburys ltd)
ICS	8251	pulmicort refil 50 mg inh
ICS	8433	budesonide 100micrograms/actuation inhaler
ICS	8450	flixotide diskhaler-community pack 50 mcg
ICS	8635	flixotide 50microgram disc (allen & hanburys ltd)
ICS	9164	fluticasone propionate 50micrograms/dose dry powder inhaler
ICS	9233	beclometasone 200microgram inhalation powder capsules
ICS	9356	becotide rotahaler insufflator inhalation powder (allen and hanburys ltd)
ICS	9477	asmabec 100microgram/actuation spacehaler (celltech pharma europe ltd)
ICS	9571	beclometasone 250micrograms/actuation vortex inhaler
ICS	9577	asmabec 50 clickhaler (focus pharmaceuticals ltd)
ICS	9599	beclazone 50microgram/actuation inhalation powder (actavis uk ltd)
ICS	9921	beclometasone 100micrograms/dose breath actuated inhaler cfc free
ICS	10090	beclometasone 50micrograms/actuation extrafine particle cfc free inhaler
ICS	10254	mometasone 400micrograms/dose dry powder inhaler
ICS	10321	budesonide 400microgram inhalation powder capsules
ICS	11149	betnelan 500microgram tablets (focus pharmaceuticals ltd)
ICS	11198	beclometasons 50 micrograms/actuation vortex inhaler
ICS	11497	beclometasone 400micrograms/dose dry powder inhaler
ICS	11732	beclometasone 50micrograms/dose breath actuated inhaler cfc free
ICS	13037	pulvinal beclometasone dipropionate 200micrograms/dose dry powder inhaler (chiesi ltd)

Drug Class	prodcode	Product name
ICS	13290	clenil modulite 100micrograms/dose inhaler (chiesi ltd)
ICS	13815	beclazone 100microgram/actuation inhalation powder (actavis uk ltd)
ICS	14294	qvar 50micrograms/dose easi-breathe inhaler (teva uk ltd)
ICS	14321	beclometasone 200micrograms/dose inhaler cfc free
ICS	14524	bdp 250microgram/actuation spacehaler (celltech pharma europe ltd)
ICS	14567	asmabec 250 clickhaler (focus pharmaceuticals ltd)
ICS	14590	asmabec 250microgram/actuation spacehaler (celltech pharma europe ltd)
ICS	14700	budesonide 400micrograms/actuation inhaler
ICS	14736	pulvinal beclometasone dipropionate 400micrograms/dose dry powder inhaler (chiesi ltd)
ICS	14757	pulvinal beclometasone dipropionate 100micrograms/dose dry powder inhaler (chiesi ltd)
ICS	15326	beclometasone 100micrograms/dose inhaler cfc free
ICS	15706	beclometasone 100 micrograms/actuation vortex inhaler
ICS	16018	mometasone 200micrograms/dose dry powder inhaler
ICS	16054	budesonide 200micrograms/actuation breath actuated powder inhaler
ICS	16148	clenil modulite 250micrograms/dose inhaler (chiesi ltd)
ICS	16151	clenil modulite 200micrograms/dose inhaler (chiesi ltd)
ICS	16158	clenil modulite 50micrograms/dose inhaler (chiesi ltd)
ICS	16305	flixotide 2mg/2ml nebules (glaxosmithkline uk ltd)
ICS	16584	beclometasone 50micrograms/dose inhaler cfc free
ICS	17654	easyhaler beclometasone 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
ICS	17670	easyhaler budesonide 100micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
ICS	18394	bdp 50microgram/actuation spacehaler (celltech pharma europe ltd)
ICS	18537	budesonide 200microgram inhalation powder capsules
ICS	18848	qvar 100micrograms/dose easi-breathe inhaler (teva uk ltd)
ICS	19031	bdp 100microgram/actuation spacehaler (celltech pharma europe ltd)
ICS	19389	asmabec 50microgram/actuation spacehaler (celltech pharma europe ltd)

Drug Class	prodcode	Product name
ICS	19401	beclometasone 250micrograms/actuation inhaler and compact spacer
ICS	19736	becotide susp for nebulisation
ICS	20707	becotide 100
ICS	20763	becloforte
ICS	20812	pulmicort refill
ICS	20825	spacehaler bdp 250microgram/actuation spacehaler (celltech pharma europe ltd)
ICS	21005	beclometasone 250micrograms/dose inhaler cfc free
ICS	21482	beclometasone 100micrograms/dose inhaler (mylan)
ICS	23675	pulmicort l.s. refil
ICS	23741	novolizer budesonide 200microgram/actuation pressurised inhalation (meda pharmaceuticals ltd)
ICS	24219	becotide rotacaps
ICS	24660	betamethasone valerate
ICS	24898	spacehaler bdp 100microgram/actuation spacehaler (celltech pharma europe ltd)
ICS	25204	beclometasone 100micrograms/dose inhaler (a a h pharmaceuticals ltd)
ICS	26063	beclometasone 100micrograms/dose inhaler (teva uk ltd)
ICS	26665	pulmicort complete
ICS	27188	easyhaler budesonide 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
ICS	27525	becotide 50
ICS	27583	pulmicort
ICS	27679	beclometasone 100microgram/actuation pressurised inhalation (approved prescription services ltd)
ICS	27915	fluticasone prop disk refill
ICS	28073	beclometasone 250microgram/actuation pressurised inhalation (approved prescription services ltd)
ICS	28640	beclometasone 100microgram/actuation inhalation powder (actavis uk ltd)

Drug Class	prodcode	Product name
ICS	28761	spacehaler bdp 50microgram/actuation spacehaler (celltech pharma europe ltd)
ICS	29325	beclometasone 250micrograms/dose inhaler (mylan)
ICS	30210	beclometasone 250micrograms/dose inhaler (teva uk ltd)
ICS	30238	beclometasone 50microgram/actuation pressurised inhalation (approved prescription services ltd)
ICS	30649	easyhaler budesonide 400micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
ICS	31774	beclometasone 50micrograms/dose inhaler (mylan)
ICS	32874	beclometasone 50microgram/actuation inhalation powder (actavis uk ltd)
ICS	33258	beclometasone 250micrograms/dose inhaler (a a h pharmaceuticals ltd)
ICS	33849	beclometasone 100microgram/actuation inhalation powder (neo laboratories ltd)
ICS	34315	beclometasone 250microgram/actuation inhalation powder (actavis uk ltd)
ICS	34428	beclometasone 50microgram/actuation inhalation powder (neo laboratories ltd)
ICS	34739	beclometasone 50micrograms/dose inhaler (teva uk ltd)
ICS	34794	beclometasone 200micrograms/dose inhaler (a a h pharmaceuticals ltd)
ICS	34859	beclometasone 250microgram/actuation inhalation powder (neo laboratories ltd)
ICS	34919	beclometasone 50micrograms/dose inhaler (a a h pharmaceuticals ltd)
ICS	35071	becodisks 200microgram (glaxosmithkline uk ltd)
ICS	35106	becodisks 100microgram with diskhaler (glaxosmithkline uk ltd)
ICS	35107	beclometasone 400microgram inhalation powder blisters with device
ICS	35113	beclometasone 200microgram inhalation powder blisters
ICS	35118	becodisks 400microgram with diskhaler (glaxosmithkline uk ltd)
ICS	35225	flixotide 100microgram disks with diskhaler (glaxosmithkline uk ltd)
ICS	35288	beclometasone 400microgram inhalation powder blisters
ICS	35293	beclometasone 200microgram inhalation powder blisters with device
ICS	35299	becodisks 400microgram (glaxosmithkline uk ltd)
ICS	35374	flixotide 500microgram disks (glaxosmithkline uk ltd)

Drug Class	prodcode	Product name
ICS	35392	flixotide 500microgram disks with diskhaler (glaxosmithkline uk ltd)
ICS	35408	becodisks 100microgram (glaxosmithkline uk ltd)
ICS	35430	becodisks 200microgram with diskhaler (glaxosmithkline uk ltd)
ICS	35461	flixotide 250microgram disks with diskhaler (glaxosmithkline uk ltd)
ICS	35510	budesonide 200micrograms/dose dry powder inhalation cartridge with device
ICS	35580	beclometasone 100microgram inhalation powder blisters with device
ICS	35602	budesonide 200micrograms/dose dry powder inhalation cartridge
ICS	35611	flixotide 250microgram disks (glaxosmithkline uk ltd)
ICS	35631	budelin novolizer 200micrograms/dose inhalation powder (meda pharmaceuticals ltd)
ICS	35638	fluticasone propionate 100microgram inhalation powder blisters with device
ICS	35652	beclometasone 100microgram inhalation powder blisters
ICS	35700	fluticasone propionate 500microgram inhalation powder blisters with device
ICS	35724	budelin novolizer 200micrograms/dose inhalation powder refill (meda pharmaceuticals ltd)
ICS	35772	fluticasone propionate 100microgram inhalation powder blisters
ICS	35905	fluticasone propionate 250microgram inhalation powder blisters
ICS	35986	flixotide 50microgram disks (glaxosmithkline uk ltd)
ICS	36021	fluticasone propionate 50microgram inhalation powder blisters with device
ICS	36090	flixotide 100microgram disks (glaxosmithkline uk ltd)
ICS	36290	flixotide 50microgram disks with diskhaler (glaxosmithkline uk ltd)
ICS	36401	fluticasone propionate 250microgram inhalation powder blisters with device
ICS	36462	fluticasone propionate 500microgram inhalation powder blisters
ICS	37203	beclometasone 5mg gastro-resistant modified-release tablets
ICS	37447	fluticasone propionate 50microgram inhalation powder blisters
ICS	39067	clipper 5mg gastro-resistant modified-release tablets (chiesi ltd)
ICS	39099	pulmicort 100micrograms/dose inhaler cfc free (astrazeneca uk ltd)
ICS	39102	budesonide 100micrograms/dose inhaler cfc free

Drug Class	prodcode	Product name
ICS	39200	aerobec forte 250 autohaler (meda pharmaceuticals ltd)
ICS	39879	budesonide 200micrograms/dose inhaler cfc free
ICS	40057	pulmicort 200micrograms/dose inhaler cfc free (astrazeneca uk ltd)
ICS	41269	beclometasone 400 cyclocaps (teva uk ltd)
ICS	41412	beclometasone 400micrograms/actuation inhaler
ICS	42928	flixotide 100micrograms/dose accuhaler (glaxosmithkline uk ltd)
ICS	42985	flixotide 50micrograms/dose accuhaler (glaxosmithkline uk ltd)
ICS	42994	flixotide 250micrograms/dose accuhaler (glaxosmithkline uk ltd)
ICS	43074	flixotide 500micrograms/dose accuhaler (glaxosmithkline uk ltd)
ICS	46157	beclometasone 200 cyclocaps (teva uk ltd)
ICS	47225	budesonide 9mg gastro-resistant granules sachets
ICS	47943	beclazone easi-breathe (roi) 100microgram/actuation pressurised inhalation (ivax pharmaceuticals ireland)
ICS	48088	budenofalk 9mg gastro-resistant granules sachets (dr. falk pharma uk ltd)
ICS	48340	clenil modulite 100micrograms/dose inhaler (mawdsley-brooks & company ltd)
ICS	48709	qvar 100micrograms/dose easi-breathe inhaler (sigma pharmaceuticals plc)
ICS	49367	clenil modulite 50micrograms/dose inhaler (mawdsley-brooks & company ltd)
ICS	49412	clenil modulite 200micrograms/dose inhaler (mawdsley-brooks & company ltd)
ICS	49711	pulmicort 200micrograms/dose inhaler (astrazeneca uk ltd)
ICS	49772	fluticasone 250micrograms/dose evohaler (sigma pharmaceuticals plc)
ICS	50037	pulmicort 0.5mg respules (waymade healthcare plc)
ICS	50129	qvar 100micrograms/dose easi-breathe inhaler (de pharmaceuticals)
ICS	50287	qvar 100 inhaler (de pharmaceuticals)
ICS	50701	becotide rotahaler (glaxosmithkline uk ltd)
ICS	51234	qvar 100 inhaler (waymade healthcare plc)
ICS	51415	qvar 50 inhaler (mawdsley-brooks & company ltd)

Drug Class	prodcode	Product name
ICS	51480	qvar 100 autohaler (de pharmaceuticals)
ICS	51681	qvar 100 inhaler (sigma pharmaceuticals plc)
ICS	51815	flixotide 250micrograms/dose evohaler (waymade healthcare plc)
ICS	51997	budesonide 9mg gastro-resistant granules sachets
ICS	52732	pulmicort 0.5mg respules (necessity supplies ltd)
ICS	52806	qvar 100 autohaler (lexon (uk) ltd)
ICS	53057	flixotide 50micrograms/dose evohaler (lexon (uk) ltd)
ICS	53480	qvar 100 autohaler (stephar (u.k.) ltd)
ICS	54207	qvar 50 inhaler (de pharmaceuticals)
ICS	54399	qvar 100 autohaler (sigma pharmaceuticals plc)
ICS	56144	budenofalk 9mg gastro-resistant granules sachets (dr. falk pharma uk ltd)
ICS	56462	becodisks 400microgram (waymade healthcare plc)
ICS	56471	becodisks 200microgram (mawdsley-brooks & company ltd)
ICS	56474	flixotide 125micrograms/dose evohaler (de pharmaceuticals)
ICS	56475	flixotide 50micrograms/dose accuhaler (sigma pharmaceuticals plc)
ICS	56477	flixotide 100micrograms/dose accuhaler (waymade healthcare plc)
ICS	56484	flixotide 250micrograms/dose accuhaler (waymade healthcare plc)
ICS	56493	qvar 50micrograms/dose easi-breathe inhaler (sigma pharmaceuticals plc)
ICS	56498	pulmicort 200 turbohaler (waymade healthcare plc)
ICS	56499	flixotide 500micrograms/dose accuhaler (waymade healthcare plc)
ICS	57525	flixotide 250micrograms/dose accuhaler (stephar (u.k.) ltd)
ICS	57555	flixotide 125micrograms/dose evohaler (dowelhurst ltd)
ICS	57579	flixotide 50micrograms/dose accuhaler (de pharmaceuticals)
ICS	57589	becloforte 250micrograms/dose inhaler (dowelhurst ltd)
ICS	60937	pulmicort 200 turbohaler (dowelhurst ltd)
ICS	60946	entocort cr 3mg capsules (waymade healthcare plc)

Drug Class	prodcode	Product name
ICS	61664	clenil modulite 250micrograms/dose inhaler (waymade healthcare plc)
ICS	62341	becotide 50 inhaler (dowelhurst ltd)
ICS	62518	beclometasone 100micrograms/dose inhaler cfc free (ennogen healthcare ltd)
ICS	63585	beclometasone 50micrograms/dose inhaler (almus pharmaceuticals ltd)
ICS	63893	budesonide 9mg modified-release tablets
ICS	64557	cortiment 9mg modified-release tablets (ferring pharmaceuticals ltd)
ICS	67234	becotide 100 inhaler (waymade healthcare plc)
ICS	67237	flixotide 125micrograms/dose evohaler (lexon (uk) ltd)
ICS	67239	pulmicort 400 turbohaler (waymade healthcare plc)
ICS	67253	flixotide 50micrograms/dose accuhaler (mawdsley-brooks & company ltd)
ICS	67261	pulmicort 1mg respules (sigma pharmaceuticals plc)
ICS	67265	becodisks 200microgram (lexon (uk) ltd)
ICS	67315	budesonide 400micrograms/dose turbohaler (waymade healthcare plc)
ICS	67319	flixotide 0.5mg/2ml nebules (waymade healthcare plc)
ICS	67322	pulmicort 100 turbohaler (waymade healthcare plc)
ICS	67735	beclazone easi-breathe (roi) 250microgram/actuation pressurised inhalation (ivax pharmaceuticals ireland)
ICS	70015	beclometasone 100micrograms/dose inhaler (almus pharmaceuticals ltd)
ICS	70749	budesonide 400micrograms/dose turbohaler (dowelhurst ltd)
ICS	71109	flixotide 250micrograms/dose accuhaler (de pharmaceuticals)
ICS	71337	qvar 100 inhaler (mawdsley-brooks & company ltd)
ICS	71338	pulmicort 200 turbohaler (de pharmaceuticals)
ICS	71341	flixotide 100micrograms/dose accuhaler (necessity supplies ltd)
ICS	71345	budesonide 200micrograms/dose turbohaler (dowelhurst ltd)
ICS	71347	pulmicort 400 turbohaler (sigma pharmaceuticals plc)
ICS	71356	clenil modulite 250micrograms/dose inhaler (mawdsley-brooks & company ltd)

Drug Class	prodcode	Product name
ICS	71366	flixotide 500micrograms/dose accuhaler (de pharmaceuticals)
ICS	71368	pulmicort 200 turbohaler (lexon (uk) ltd)
ICS	71380	flixotide 250micrograms/dose accuhaler (necessity supplies ltd)
ICS	71427	budesonide 100micrograms/dose turbohaler (dowelhurst ltd)
ICS	71467	beclometasone 50micrograms/dose inhaler cfc free (j m mcgill ltd)
ICS	72292	flixotide 250micrograms/dose accuhaler (mawdsley-brooks & company ltd)
ICS	73691	flixotide 100micrograms/dose accuhaler (de pharmaceuticals)
LABA	465	salmeterol 25micrograms/dose inhaler
LABA	549	serevent 25micrograms/dose inhaler (glaxosmithkline uk ltd)
LABA	719	salmeterol 50micrograms/dose dry powder inhaler
LABA	910	serevent diskhaler 50microgram inhalation powder (glaxo wellcome uk ltd)
LABA	1974	oxis 12 turbohaler (astrazeneca uk ltd)
LABA	1975	oxis 6 turbohaler (astrazeneca uk ltd)
LABA	2224	serevent 50micrograms/dose accuhaler (glaxosmithkline uk ltd)
LABA	3297	salmeterol 50micrograms disc
LABA	6526	formoterol 12microgram inhalation powder capsules with device
LABA	7133	formoterol 12micrograms/dose dry powder inhaler
LABA	7268	serevent 25micrograms/dose evohaler (glaxosmithkline uk ltd)
LABA	7270	salmeterol 25micrograms/dose inhaler cfc free
LABA	9711	formoterol 6micrograms/dose dry powder inhaler
LABA	10968	foradil 12microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)
LABA	14306	formoterol 12micrograms/dose inhaler cfc free
LABA	19799	tulobuterol 2mg
LABA	22663	respacal 2mg tablet (ucb pharma ltd)
LABA	25784	atimos modulite 12micrograms/dose inhaler (chiesi ltd)
LABA	26829	brelomax 2mg tablet (abbott laboratories ltd)

Drug Class	prodcode	Product name
LABA	35165	serevent 50microgram disks with diskhaler (glaxosmithkline uk ltd)
LABA	35503	salmeterol 50microgram inhalation powder blisters
LABA	35542	salmeterol 50microgram inhalation powder blisters with device
LABA	35725	formoterol easyhaler 12micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
LABA	35825	serevent 50microgram disks (glaxosmithkline uk ltd)
LABA	43738	indacaterol 150microgram inhalation powder capsules with device
LABA	43893	onbrez breezhaler 150microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)
LABA	44064	onbrez breezhaler 300microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)
LABA	45610	indacaterol 300microgram inhalation powder capsules with device
LABA	47638	neovent 25micrograms/dose inhaler cfc free (kent pharmaceuticals ltd)
LABA	50051	serevent 25micrograms/dose evohaler (waymade healthcare plc)
LABA	54742	salmeterol 25micrograms/dose inhaler cfc free (a a h pharmaceuticals ltd)
LABA	56478	serevent 50micrograms/dose accuhaler (de pharmaceuticals)
LABA	56482	oxis 12 turbohaler (waymade healthcare plc)
LABA	57544	serevent 50micrograms/dose accuhaler (waymade healthcare plc)
LABA	57558	oxis 6 turbohaler (lexon (uk) ltd)
LABA	57694	vertine 25micrograms/dose inhaler cfc free (teva uk ltd)
LABA	62662	olodaterol 2.5micrograms/dose solution for inhalation cartridge with device cfc free
LABA	62667	ultibro breezhaler 85microgram/43microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)
LABA	62739	indacaterol 85micrograms/dose / glycopyrronium bromide 54micrograms/dose inhalation powder capsules with device
LABA	65431	striverdi respimat 2.5micrograms/dose solution for inhalation cartridge with device (boehringer ingelheim ltd)
LABA	66547	oxis 12 turbohaler (de pharmaceuticals)

Drug Class	prodcode	Product name
LABA	67238	foradil 12microgram inhalation powder capsules with device (sigma pharmaceuticals plc)
LABA	67800	serevent 25micrograms/dose evohaler (lexon (uk) ltd)
LABA	67823	salmeterol 50microgram diskhaler (dowelhurst ltd)
LABA	68260	serevent 50micrograms/dose accuhaler (mawdsley-brooks & company ltd)
LABA	68483	soltel 25micrograms/dose inhaler cfc free (kent pharmaceuticals ltd)
LABA	71394	serevent 50microgram disks with diskhaler (dowelhurst ltd)
LABA	71597	serevent 25micrograms/dose evohaler (sigma pharmaceuticals plc)
LABA	72949	serevent 25micrograms/dose evohaler (de pharmaceuticals)
LABA_ICS	638	seretide 250 accuhaler (glaxosmithkline uk ltd)
LABA_ICS	665	seretide 100 accuhaler (glaxosmithkline uk ltd)
LABA_ICS	3666	seretide 500 accuhaler (glaxosmithkline uk ltd)
LABA_ICS	5143	seretide 50 evohaler (glaxosmithkline uk ltd)
LABA_ICS	5161	seretide 125 evohaler (glaxosmithkline uk ltd)
LABA_ICS	5172	seretide 250 evohaler (glaxosmithkline uk ltd)
LABA_ICS	5558	salmeterol 50micrograms with fluticasone 500micrograms cfc free inhaler
LABA_ICS	5864	salmeterol 25micrograms with fluticasone 250micrograms cfc free inhaler
LABA_ICS	5942	salmeterol 50micrograms with fluticasone 250micrograms cfc free inhaler
LABA_ICS	6325	symbicort 200/6 turbohaler (astrazeneca uk ltd)
LABA_ICS	6569	salmeterol 25micrograms with fluticasone 125micrograms cfc free inhaler
LABA_ICS	6616	salmeterol 25micrograms with fluticasone 50micrograms cfc free inhaler
LABA_ICS	6746	budesonide 400micrograms/dose / formoterol 12micrograms/dose dry powder inhaler
LABA_ICS	6780	symbicort 400/12 turbohaler (astrazeneca uk ltd)
LABA_ICS	6796	budesonide 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler
LABA_ICS	6938	salmeterol 50micrograms with fluticasone 100micrograms dry powder inhaler
LABA_ICS	7013	symbicort 100/6 turbohaler (astrazeneca uk ltd)
LABA_ICS	10218	budesonide 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler

Drug Class	prodcode	Product name
LABA_ICS	11410	fluticasone propionate 500micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler
LABA_ICS	11588	fluticasone 125micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free
LABA_ICS	11618	fluticasone 250micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free
LABA_ICS	12994	fluticasone 50micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free
LABA_ICS	13040	fluticasone propionate 250micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler
LABA_ICS	13273	fluticasone propionate 100micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler
LABA_ICS	37432	fostair 100micrograms/dose / 6micrograms/dose inhaler (chiesi ltd)
LABA_ICS	37470	beclometasone 100micrograms/dose / formoterol 6micrograms/dose inhaler cfc free
LABA_ICS	48666	flutiform 250micrograms/dose / 10micrograms/dose inhaler (napp pharmaceuticals ltd)
LABA_ICS	48739	seretide 250 evohaler (de pharmaceuticals)
LABA_ICS	49000	seretide 250 evohaler (waymade healthcare plc)
LABA_ICS	49114	symbicort 100/6 turbohaler (sigma pharmaceuticals plc)
LABA_ICS	49868	fluticasone 250micrograms/dose / formoterol 10micrograms/dose inhaler cfc free
LABA_ICS	50036	flutiform 125micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd)
LABA_ICS	50560	seretide 250 accuhaler (sigma pharmaceuticals plc)
LABA_ICS	50689	flutiform 50micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd)
LABA_ICS	50739	symbicort 400/12 turbohaler (mawdsley-brooks & company ltd)
LABA_ICS	50886	seretide 250 evohaler (stephar (u.k.) ltd)
LABA_ICS	50945	symbicort 100/6 turbohaler (mawdsley-brooks & company ltd)
LABA_ICS	51027	seretide 125 evohaler (de pharmaceuticals)
LABA_ICS	51151	seretide 125 evohaler (lexon (uk) ltd)
LABA_ICS	51209	fluticasone 125micrograms/dose / formoterol 5micrograms/dose inhaler cfc free
LABA_ICS	51270	fluticasone 50micrograms/dose / formoterol 5micrograms/dose inhaler cfc free

Drug Class	prodcode	Product name
LABA_ICS	51394	seretide 500 accuhaler (waymade healthcare plc)
LABA_ICS	51570	symbicort 200/6 turbohaler (de pharmaceuticals)
LABA_ICS	51593	seretide 500 accuhaler (de pharmaceuticals)
LABA_ICS	51759	symbicort 200/6 turbohaler (mawdsley-brooks & company ltd)
LABA_ICS	51861	seretide 500 accuhaler (mawdsley-brooks & company ltd)
LABA_ICS	51909	seretide 250 evohaler (necessity supplies ltd)
LABA_ICS	53230	seretide 250 accuhaler (de pharmaceuticals)
LABA_ICS	53237	symbicort 400/12 turbohaler (de pharmaceuticals)
LABA_ICS	53283	seretide 100 accuhaler (waymade healthcare plc)
LABA_ICS	53491	symbicort 200/6 turbohaler (sigma pharmaceuticals plc)
LABA_ICS	55677	seretide 500 accuhaler (lexon (uk) ltd)
LABA_ICS	59327	relvar ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)
LABA_ICS	59439	fluticasone furoate 92micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler
LABA_ICS	59573	relvar ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)
LABA_ICS	59899	fluticasone furoate 184micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler
LABA_ICS	61280	seretide 250 accuhaler (waymade healthcare plc)
LABA_ICS	61644	fostair nexthaler 100micrograms/dose / 6micrograms/dose dry powder inhaler (chiesi ltd)
LABA_ICS	61666	duoresp spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler (teva uk ltd)
LABA_ICS	61782	duoresp spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (teva uk ltd)
LABA_ICS	62030	beclometasone 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler
LABA_ICS	62126	seretide 100 accuhaler (de pharmaceuticals)
LABA_ICS	63252	seretide 250 evohaler (lexon (uk) ltd)
LABA_ICS	63945	seretide 250 accuhaler (lexon (uk) ltd)
LABA_ICS	64372	sirdupla 25micrograms/dose / 125micrograms/dose inhaler (mylan)

Drug Class	prodcode	Product name
LABA_ICS	64373	sirdupla 25micrograms/dose / 250micrograms/dose inhaler (mylan)
LABA_ICS	64638	flutiform 125micrograms/dose / 5micrograms/dose inhaler (waymade healthcare plc)
LABA_ICS	65117	seretide 125 evohaler (mawdsley-brooks & company ltd)
LABA_ICS	65596	fostair 200micrograms/dose / 6micrograms/dose inhaler (chiesi ltd)
LABA_ICS	65658	fostair nexthaler 200micrograms/dose / 6micrograms/dose dry powder inhaler (chiesi ltd)
LABA_ICS	65677	airflusal forspiro 50micrograms/dose / 500micrograms/dose dry powder inhaler (sandoz ltd)
LABA_ICS	65758	beclometasone 200micrograms/dose / formoterol 6micrograms/dose inhaler cfc free
LABA_ICS	65894	beclometasone 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler
LABA_ICS	66448	flutiform 250micrograms/dose / 10micrograms/dose inhaler (waymade healthcare plc)
LABA_ICS	66453	sirdupla 25micrograms/dose / 250micrograms/dose inhaler (waymade healthcare plc)
LABA_ICS	67055	fluticasone 250micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free (a a h pharmaceuticals ltd)
LABA_ICS	67101	fluticasone propionate 500micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler (a a h pharmaceuticals ltd)
LABA_ICS	67677	symbicort 200micrograms/dose / 6micrograms/dose pressurised inhaler (astrazeneca uk ltd)
LABA_ICS	67958	budesonide 200micrograms/dose / formoterol 6micrograms/dose inhaler cfc free
LABA_ICS	68034	symbicort 200/6 turbohaler (necessity supplies ltd)
LABA_ICS	68175	flutiform 50micrograms/dose / 5micrograms/dose inhaler (waymade healthcare plc)
LABA_ICS	68453	seretide 125 evohaler (waymade healthcare plc)
LABA_ICS	68495	seretide 500 accuhaler (necessity supplies ltd)
LABA_ICS	68983	aerivio spiromax 50micrograms/dose / 500micrograms/dose dry powder inhaler (teva uk ltd)
LABA_ICS	69436	sereflo 25micrograms/dose / 125micrograms/dose inhaler (kent pharmaceuticals ltd)
LABA_ICS	69538	sereflo 25micrograms/dose / 250micrograms/dose inhaler (kent pharmaceuticals ltd)
LABA_ICS	69827	airflusal 25micrograms/dose / 250micrograms/dose inhaler (sandoz ltd)
LABA_ICS	70250	airflusal 25micrograms/dose / 125micrograms/dose inhaler (sandoz ltd)
LABA_ICS	70711	trimbow 87micrograms/dose / 5micrograms/dose / 9micrograms/dose inhaler (chiesi ltd)

Drug Class	prodcode	Product name
LABA_ICS	71260	generic trimbow 87micrograms/dose / 5micrograms/dose / 9micrograms/dose inhaler
LABA_ICS	71284	fobumix easyhaler 320micrograms/dose / 9micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
LABA_ICS	71354	symbicort 400/12 turbohaler (necessity supplies ltd)
LABA_ICS	71371	symbicort 100/6 turbohaler (waymade healthcare plc)
LABA_ICS	71409	seretide 50 evohaler (waymade healthcare plc)
LABA_ICS	71763	trelegy ellipta 92micrograms/dose / 55micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)
LABA_ICS	71915	fobumix easyhaler 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
LABA_ICS	72310	generic trelegy ellipta 92micrograms/dose / 55micrograms/dose / 22micrograms/dose dry powder inhaler
LABA_ICS	72400	fobumix easyhaler 80micrograms/dose / 4.5micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
LABA_ICS	72564	aloflute 25micrograms/dose / 125micrograms/dose inhaler (mylan)
LABA_ICS	73527	aloflute 25micrograms/dose / 250micrograms/dose inhaler (mylan)
LABA_ICS	73849	fusacomb easyhaler 50micrograms/dose / 500micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
LABA_LAMA	61176	anoro ellipta 55micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)
LABA_LAMA	61490	umeclidinium bromide 65micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler
LABA_LAMA	62535	duaklir 340micrograms/dose / 12micrograms/dose genuair (astrazeneca uk ltd)
LABA_LAMA	62838	aclidinium bromide 396micrograms/dose / formoterol 11.8micrograms/dose dry powder inhaler
LABA_LAMA	64509	tiotropium bromide 2.5micrograms/dose / olodaterol 2.5micrograms/dose solution for inhalation cartridge with device cfc free
LABA_LAMA	64523	spiolto respimat 2.5micrograms/dose / 2.5micrograms/dose solution for inhalation cartridge with device (boehringer ingelheim ltd)

Drug Class	prodcode	Product name
LABA_LAMA	69556	aclidinium bromide 396micrograms/dose / formoterol 11.8micrograms/dose dry powder inhaler (colorama pharmaceuticals ltd)
LAMA	746	tiotropium 18 microgram capsule
LAMA	6050	spiriva 18 microgram capsule (boehringer ingelheim ltd)
LAMA	34995	spiriva 18microgram inhalation powder capsules with handihaler (boehringer ingelheim ltd)
LAMA	35000	spiriva 18microgram inhalation powder capsules (boehringer ingelheim ltd)
LAMA	35011	tiotropium bromide 18microgram inhalation powder capsules
LAMA	35014	tiotropium bromide 18microgram inhalation powder capsules with device
LAMA	36864	tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device cfc free
LAMA	36869	spiriva respimat 2.5micrograms/dose solution for inhalation cartridge with device (boehringer ingelheim ltd)
LAMA	49227	aclidinium bromide 375micrograms/dose dry powder inhaler
LAMA	49228	eklira 322micrograms/dose genuair (astrazeneca uk ltd)
LAMA	50103	spiriva 18microgram inhalation powder capsules with handihaler (waymade healthcare plc)
LAMA	50292	spiriva 18microgram inhalation powder capsules (sigma pharmaceuticals plc)
LAMA	50577	spiriva 18microgram inhalation powder capsules with handihaler (de pharmaceuticals)
LAMA	51967	spiriva 18microgram inhalation powder capsules (mawdsley-brooks & company ltd)
LAMA	53761	glycopyrronium bromide 55microgram inhalation powder capsules with device
LAMA	53982	seebri breezhaler 44microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)
LAMA	59638	spiriva 18microgram inhalation powder capsules with handihaler (sigma pharmaceuticals plc)
LAMA	61582	spiriva respimat 2.5micrograms/dose solution for inhalation cartridge with device (waymade healthcare plc)
LAMA	61879	incruse ellipta 55micrograms/dose dry powder inhaler (glaxosmithkline uk ltd)
LAMA	62109	umeclidinium bromide 65micrograms/dose dry powder inhaler
LAMA	63992	eklira 322micrograms/dose genuair (waymade healthcare plc)

Drug Class	prodcode	Product name
LAMA	64232	tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device cfc free (am distributions (yorkshire) ltd)
LAMA	67531	glycopyrronium bromide 55microgram inhalation powder capsules with device (j m mcgill ltd)
LAMA	68530	tiotropium bromide 10microgram inhalation powder capsules with device
LAMA	68729	braltus 10microgram inhalation powder capsules with zonda inhaler (teva uk ltd)
LAMA	69109	glycopyrronium bromide 400micrograms/ml oral solution sugar free
LAMA	72031	glycopyrronium bromide 55microgram inhalation powder capsules with device (ennogen healthcare ltd)
MUCOLYTICS	752	carbocisteine 375mg capsules
MUCOLYTICS	6276	carbocisteine 250mg/5ml oral solution
MUCOLYTICS	6802	mucodyne 375mg capsules (sanofi)
MUCOLYTICS	6920	mecysteine 100mg gastro-resistant tablets
MUCOLYTICS	8968	acetylcysteine 200mg granules sachets
MUCOLYTICS	9018	mucodyne 375mg capsule (aventis pharma)
MUCOLYTICS	9642	mucodyne 250mg/5ml oral solution (aventis pharma)
MUCOLYTICS	9906	mucodyne 250mg/5ml syrup (sanofi)
MUCOLYTICS	9943	visclair 100mg gastro-resistant tablets (ranbaxy (uk) ltd)
MUCOLYTICS	10808	mucodyne paediatric 125mg/5ml syrup (sanofi)
MUCOLYTICS	12529	fabrol 200mg granules (novartis consumer health uk ltd)
MUCOLYTICS	15301	carbocisteine 125mg/5ml oral solution
MUCOLYTICS	18312	bisolvon 4mg/5ml oral solution (boehringer ingelheim ltd)
MUCOLYTICS	22828	carbocisteine 750mg/5ml forte oral solution
MUCOLYTICS	24456	carbocisteine 375mg tablets
MUCOLYTICS	27301	bromhexine hcl 8mg tablets
MUCOLYTICS	32632	fluimucil n 200mg granules sachets (imported (germany))
MUCOLYTICS	35015	erdosteine 300mg capsules

Drug Class	prodcode	Product name
MUCOLYTICS	35178	erdotin 300mg capsules (galen ltd)
MUCOLYTICS	37666	acetylcysteine 600mg tablets
MUCOLYTICS	41662	bisolvon 8mg tablet (boehringer ingelheim ltd)
MUCOLYTICS	43794	nebusal 7% inhalation solution 4ml ampoules (forest laboratories uk ltd)
MUCOLYTICS	43870	sodium chloride 7% inhalation solution 4ml ampoules
MUCOLYTICS	45133	acetylcysteine 600mg capsules
MUCOLYTICS	47297	solgar nac 600mg capsules (solgar vitamin and herb)
MUCOLYTICS	49016	sodium chloride 7% inhalation solution 4ml vials
MUCOLYTICS	49045	nebusal 7% inhalation solution 4ml vials (forest laboratories uk ltd)
MUCOLYTICS	49357	acetylcysteine 600mg effervescent tablets
MUCOLYTICS	50508	mucodyne 250mg/5ml syrup (sigma pharmaceuticals plc)
MUCOLYTICS	53303	carbocisteine 375mg capsules (accord healthcare ltd)
MUCOLYTICS	53747	oronac 600 capsules (rhodes pharma ltd)
MUCOLYTICS	54092	a-cys 600mg capsules (ennogen healthcare ltd)
MUCOLYTICS	56741	ivacaftor 150mg tablets
MUCOLYTICS	56987	en-cys 600mg tablets (ennogen healthcare ltd)
MUCOLYTICS	57237	acetylcysteine 100mg granules sachets
MUCOLYTICS	57365	oronac 600 tablets (rhodes pharma ltd)
MUCOLYTICS	57820	n-acetylcysteine 600mg tablets (special order)
MUCOLYTICS	60524	acetylcysteine 100mg/5ml oral solution
MUCOLYTICS	61502	bronchitol 40mg inhalation powder capsules with device (chiesi ltd)
MUCOLYTICS	61509	mannitol 40mg inhalation powder capsules with device
MUCOLYTICS	63490	a-cys 200mg granules sachets (ennogen healthcare ltd)
MUCOLYTICS	65004	carbocisteine 750mg/10ml oral solution 10ml sachets sugar free
MUCOLYTICS	65672	carbocisteine 750mg/10ml oral solution 10ml sachets sugar free (intrapharm laboratories ltd)
MUCOLYTICS	66874	mucodyne 250mg/5ml syrup (de pharmaceuticals)

Drug Class	prodcode	Product name
MUCOLYTICS	68393	resp-ease 7% inhalation solution 4ml vials (venture healthcare ltd)
MUCOLYTICS	71422	carbocisteine 375mg capsules (a a h pharmaceuticals ltd)
MUCOLYTICS	72610	orkambi 200mg/125mg tablets (vertex pharmaceuticals (uk) ltd)
OCS	44	prednisolone 5mg gastro-resistant tablets
OCS	95	prednisolone 5mg tablets
OCS	557	prednisolone 2.5mg gastro-resistant tablets
OCS	578	prednisolone 1mg tablets
OCS	955	prednisolone 5mg soluble tablets
OCS	1063	prednesol 5mg tablet (sovereign medical ltd)
OCS	2044	prednisone 2.5 mg tab
OCS	2368	prednisolone 2.5mg tablet
OCS	2390	prednisolone e/c 1 mg tab
OCS	2704	prednisolone 25mg tablets
OCS	2799	prednisolone 10 mg tab
OCS	2949	prednisone 5mg tablets
OCS	3059	prednisolone 50 mg tab
OCS	3345	sintisone tablet (pharmacia ltd)
OCS	3557	prednisone 1mg tablets
OCS	5490	deltacortril 5mg gastro-resistant tablets (alliance pharmaceuticals ltd)
OCS	5913	deltacortril 2.5mg gastro-resistant tablets (alliance pharmaceuticals ltd)
OCS	7584	prednisolone 4 mg tab
OCS	7710	prednisolone 15 mg tab
OCS	7934	prednisone 30 mg tab
OCS	9727	prednisolone 50mg tablets
OCS	13522	prednisolone 2 mg tab
OCS	13615	prednisone 10 mg tab

Drug Class	prodcode	Product name
OCS	16724	prednisone 50 mg tab
OCS	19141	prednisolone 5mg soluble tablets (amco)
OCS	20095	precortisyl forte 25mg tablet (aventis pharma)
OCS	20670	prednisolone e/c
OCS	21417	prednisolone 5mg tablets (a a h pharmaceuticals ltd)
OCS	21833	decortisyl 5mg tablet (roussel laboratories ltd)
OCS	23512	precortisyl 5mg tablet (hoechst marion roussel)
OCS	24716	prednisolone e/c
OCS	25272	precortisyl 1mg tablet (hoechst marion roussel)
OCS	27889	prednisolone
OCS	27959	prednisolone
OCS	27962	deltastab 1mg tablet (waymade healthcare plc)
OCS	28375	prednisolone 2.5mg gastro-resistant tablets (a a h pharmaceuticals ltd)
OCS	28376	prednisolone 2.5mg gastro-resistant tablet (biorex laboratories ltd)
OCS	28859	deltastab 5mg tablet (waymade healthcare plc)
OCS	29333	prednisolone 5mg tablets (actavis uk ltd)
OCS	30390	deltastab 2 mg tab
OCS	30971	decortisyl 25 mg tab
OCS	31327	prednisolone steaglate 6.65mg tablet
OCS	31532	prednisolone 5mg gastro-resistant tablets (a a h pharmaceuticals ltd)
OCS	32803	prednisolone 5mg gastro-resistant tablets (actavis uk ltd)
OCS	32835	prednisolone 5mg tablets (wockhardt uk ltd)
OCS	33691	prednisolone 5mg gastro-resistant tablet (biorex laboratories ltd)
OCS	33988	prednisolone 5mg tablet (co-pharma ltd)
OCS	33990	prednisolone 5mg tablet (ivax pharmaceuticals uk ltd)
OCS	34109	prednisolone 5 mg gastro-resistant tablet

Drug Class	prodcode	Product name
OCS	34393	prednisolone 5mg gastro-resistant tablets (teva uk ltd)
OCS	34404	prednisolone 1mg tablets (actavis uk ltd)
OCS	34452	prednisolone 1mg tablets (a a h pharmaceuticals ltd)
OCS	34461	prednisolone 2.5mg gastro-resistant tablets (actavis uk ltd)
OCS	34631	prednisolone 1mg tablet (co-pharma ltd)
OCS	34660	prednisolone 1mg tablets (kent pharmaceuticals ltd)
OCS	34748	prednisolone 1mg tablets (teva uk ltd)
OCS	34781	prednisolone 5mg tablets (kent pharmaceuticals ltd)
OCS	34914	prednisolone 1mg tablet (celltech pharma europe ltd)
OCS	34978	prednisolone 1mg tablets (wockhardt uk ltd)
OCS	38407	prednisolone 20mg tablet
OCS	41515	prednisolone 5mg tablets (teva uk ltd)
OCS	41745	prednisolone 25mg tablets (zentiva)
OCS	43544	prednisone 5mg tablet (knoll ltd)
OCS	44380	prednisone 1mg modified-release tablets
OCS	44723	prednisone 5mg modified-release tablets
OCS	44802	lodotra 5mg modified-release tablets (napp pharmaceuticals ltd)
OCS	44803	lodotra 2mg modified-release tablets (napp pharmaceuticals ltd)
OCS	45302	prednisolone 5mg tablet (biorex laboratories ltd)
OCS	46711	prednisone 2mg modified-release tablets
OCS	47142	prednisolone 5mg soluble tablet (amdipharm plc)
OCS	51753	prednisolone 1mg tablets (strides shasun (uk) ltd)
OCS	53313	prednisolone 20mg/5ml oral suspension
OCS	53336	prednisolone 25mg tablets (a a h pharmaceuticals ltd)
OCS	54118	prednisolone 25mg/5ml oral suspension
OCS	54432	lodotra 1mg modified-release tablets (napp pharmaceuticals ltd)

Drug Class	prodcode	Product name
OCS	54434	prednisolone 2.5mg/5ml oral suspension
OCS	55024	prednisolone 5mg/5ml oral solution
OCS	55480	prednisolone 2.5mg gastro-resistant tablets (alliance pharmaceuticals ltd)
OCS	56891	prednisolone 1mg tablets (waymade healthcare plc)
OCS	58000	prednisolone 5mg tablets (almus pharmaceuticals ltd)
OCS	58061	prednisone 50mg tablets
OCS	58234	prednisolone 10mg/5ml oral solution
OCS	58369	prednisolone 5mg tablets (boston healthcare ltd)
OCS	58384	prednisolone 1mg tablets (almus pharmaceuticals ltd)
OCS	58987	prednisolone 5mg gastro-resistant tablets (phoenix healthcare distribution ltd)
OCS	59229	dilacort 5mg gastro-resistant tablets (auden mckenzie (pharma division) ltd)
OCS	59283	dilacort 2.5mg gastro-resistant tablets (auden mckenzie (pharma division) ltd)
OCS	59338	prednisolone 1mg/5ml oral solution
OCS	59912	prednisolone 5mg gastro-resistant tablets (waymade healthcare plc)
OCS	60421	prednisolone 5mg tablets (strides shasun (uk) ltd)
OCS	61132	prednisolone 1mg tablets (boston healthcare ltd)
OCS	61162	prednisolone 5mg tablets (waymade healthcare plc)
OCS	61689	prednisolone 5mg soluble tablets (a a h pharmaceuticals ltd)
OCS	62656	prednisone 5mg tablet (hillcross pharmaceuticals ltd)
OCS	63066	prednisolone 2.5mg tablets
OCS	63082	prednisolone 20mg tablets
OCS	63172	prednisolone 10mg tablets
OCS	63214	prednisolone 5mg soluble tablets (alliance healthcare (distribution) ltd)
OCS	63549	prednisolone 1mg/ml oral solution (logixx pharma solutions ltd)
OCS	63791	prednisolone 5mg/5ml oral solution unit dose
OCS	64007	pevanti 10mg tablets (amco)

Drug Class	prodcode	Product name
OCS	64008	pevanti 2.5mg tablets (amco)
OCS	64128	pevanti 5mg tablets (amco)
OCS	64221	prednisolone 5mg/5ml oral suspension
OCS	64416	prednisolone 10mg/ml oral solution sugar free
OCS	65020	prednisolone 25mg/5ml oral solution
OCS	65626	prednisolone 10mg/5ml oral suspension
OCS	66015	prednisolone dompe 5mg/5ml oral solution unit dose (logixx pharma solutions ltd)
OCS	66550	prednisolone 5mg gastro-resistant tablets (alliance healthcare (distribution) ltd)
OCS	66645	prednisolone 5mg/5ml oral solution unit dose (logixx pharma solutions ltd)
OCS	66914	prednisolone 1mg gastro-resistant tablets
OCS	67076	prednisolone 20mg/5ml oral solution
OCS	67107	prednisolone 5mg gastro-resistant tablets (alliance pharmaceuticals ltd)
OCS	67507	prednisolone 30mg tablets
OCS	67559	prednisolone 5mg/5ml oral solution unit dose (a a h pharmaceuticals ltd)
OCS	68497	prednisolone 2.5mg gastro-resistant tablets (waymade healthcare plc)
OCS	69811	prednisolone 30mg tablets (actavis uk ltd)
OCS	70603	prednisolone 5mg soluble tablets (focus pharmaceuticals ltd)
OCS	72421	prednisolone 1mg gastro-resistant tablets (a a h pharmaceuticals ltd)
OCS	73294	prednisolone 2.5mg/5ml oral solution
OCS	73553	prednisolone 1mg tablets (alliance healthcare (distribution) ltd)
OCS	73678	prednisolone 5mg gastro-resistant tablets (de pharmaceuticals)
OXYG	1972	oxygen bp size af lightweight gas 1360 litres
OXYG	2510	oxygen bp gas 1280 litres
OXYG	3347	oxygen bp size f gas 1360 litres
OXYG	4412	oxygen bp size g gas 3400 litres
OXYG	4538	oxygen bp size pd gas 300 litres

Drug Class	prodcode	Product name
OXYG	4791	oxygen bp size c gas 170 litres
OXYG	5584	oxygen cylinders size pd (boc ltd)
OXYG	5773	oxygen bp size dd gas 460 litres
OXYG	5780	oxygen cylinders size af (boc ltd)
OXYG	5976	oxygen bp size dd 460 litre inhalation gas (boc ltd)
OXYG	6419	oxygen cylinders size f (boc ltd)
OXYG	6420	oxygen bp size d gas 340 litres
OXYG	6423	oxygen bp with integral headset 1360 litre inhalation gas (boc ltd)
OXYG	6556	oxygen cylinders size c (boc ltd)
OXYG	6619	oxygen bp size cd gas 460 litres
OXYG	6768	oxygen bp size cd 460 litre inhalation gas (boc ltd)
OXYG	6848	oxygen cylinders size dd with integral headset 2 and 4litres/minute flow rate (boc ltd)
OXYG	6976	oxygen bp with integral headset gas 430 litres
OXYG	7031	oxygen bp size e gas 680 litres
OXYG	7042	oxygen cylinders size e (boc ltd)
OXYG	7239	oxygen cylinders size b10s (air products plc)
OXYG	8183	oxygen bp gas 640 litres
OXYG	8505	oxygen bp gas 6400 litres
OXYG	8757	oxygen bp gas 3200 litres
OXYG	9889	oxygen cylinders size g (boc ltd)
OXYG	9895	oxygen bp size df with integral headset gas 1360 litres
OXYG	10043	oxygen composite cylinders size b10c with integral headset (air products plc)
OXYG	10053	oxygen connection cubing 1.8m
OXYG	11659	oxygen bp size dd with integral headset gas 460 litres
OXYG	13206	oxygen bp with integral headset gas 300 litres
OXYG	15214	oxygen bp size pd 300 litre inhalation gas (medigas ltd)

Drug Class	prodcode	Product name
OXYG	15281	oxygen cylinders size pa2 with integral headset (air products plc)
OXYG	15979	oxygen bp with integral headset 300 litre inhalation gas (boc ltd)
OXYG	16124	oxygen cylinders (medigas ltd)
OXYG	16523	oxygen cylinders size cd with integral headset 0-15litres/minute flow rate (boc ltd)
OXYG	17005	oxygen bp size cd with integral headset gas 460 litres
OXYG	17644	oxygen bp with integral headset gas 2122 litres
OXYG	21330	oxygen composite cylinders size if2 with integral headset (medigas ltd)
OXYG	21331	oxygen composite cylinders with integral headset (air products plc)
OXYG	21402	oxygen cylinders size pd (air products plc)
OXYG	23337	oxygen cylinder f size 1280 litres
OXYG	23905	oxygen cylinders size d (boc ltd)
OXYG	35566	oxygen bp with set gas 1360 litres
OXYG	38479	heliox 1780 litre (size hx) inhalation gas (boc ltd)
OXYG	49123	oxygen 95% / carbon dioxide 5%
OXYG	49379	oxygen
OXYG	49566	oxygen composite cylinders size df with integral headset (boc ltd)
OXYG	50993	medical oxygen cylinders size d (linde gas uk ltd)
OXYG	51001	medical oxygen cylinders size f (linde gas uk ltd)
OXYG	51450	oxygen cylinders size af (linde gas uk ltd)
OXYG	51781	helium 79% / oxygen 21%
OXYG	53462	medical oxygen cylinders size ad 200 (linde gas uk ltd)
OXYG	57708	oxygen cylinders size cd 300 with integral headset (linde gas uk ltd)
OXYG	60928	oxygen composite cylinders size f with integral headset (medigas ltd)
OXYG	64137	medical oxygen cylinders size c (linde gas uk ltd)
ROFLUM	44173	roflumilast 500microgram tablets
ROFLUM	44431	daxas 500microgram tablets (astrazeneca uk ltd)

Drug Class	prodcode	Product name
SABA	8	salbutamol 100micrograms/dose inhaler
SABA	17	salbutamol 100micrograms/dose inhaler cfc free
SABA	31	ventolin 100microgram/inhalation inhalation powder (glaxo wellcome uk ltd)
SABA	235	bricanyl 250micrograms/dose inhaler (astrazeneca uk ltd)
SABA	282	salbutamol 2mg/5ml oral solution sugar free
SABA	510	ventolin 5mg/ml respirator solution (glaxosmithkline uk ltd)
SABA	674	ventolin 2.5mg nebules (glaxosmithkline uk ltd)
SABA	696	salbutamol 8mg modified-release capsules
SABA	856	ventolin 2mg/5ml syrup (glaxosmithkline uk ltd)
SABA	860	salbutamol 4mg tablets
SABA	862	salbulin inhalation powder (3m health care ltd)
SABA	881	salbutamol 2mg tablets
SABA	882	salbutamol 200microgram inhalation powder capsules
SABA	898	ventolin evohaler 100 100microgram/inhalation pressurised inhalation (glaxo wellcome uk ltd)
SABA	907	bricanyl turbohaler 500 500microgram turbohaler (astrazeneca uk ltd)
SABA	957	salamol easi-breathe 100microgram/actuation pressurised inhalation (ivax pharmaceuticals uk ltd)
SABA	958	ventolin easi-breathe 100microgram/actuation pressurised inhalation (allen & hanburys ltd)
SABA	987	ventolin 4mg tablet (allen & hanburys ltd)
SABA	1087	asmasal 95micrograms/dose clickhaler (focus pharmaceuticals ltd)
SABA	1093	salamol 100microgram/actuation inhalation powder (ivax pharmaceuticals uk ltd)
SABA	1619	terbutaline 500micrograms/dose dry powder inhaler
SABA	1620	terbutaline 250micrograms/dose inhaler
SABA	1628	terbutaline 250micrograms/actuation refill canister
SABA	1635	salbuvent 2mg/5ml oral solution (pharmacia ltd)
SABA	1698	salbutamol 100micrograms/dose breath actuated inhaler

Drug Class	prodcode	Product name
SABA	1741	salbutamol 100micrograms/dose breath actuated inhaler cfc free
SABA	1794	berotec 100microgram/actuation inhalation powder (boehringer ingelheim ltd)
SABA	1882	ventodisks 200microgram/blister disc (allen & hanburys ltd)
SABA	1950	ventodisks 400microgram/blister disc (allen & hanburys ltd)
SABA	1952	ventolin 400microgram rotacaps (glaxosmithkline uk ltd)
SABA	1957	ventolin 5mg nebules (glaxosmithkline uk ltd)
SABA	1960	volmax 8mg modified-release tablets (glaxosmithkline uk ltd)
SABA	1961	volmax 4mg modified-release tablets (glaxosmithkline uk ltd)
SABA	2020	berotec 200micrograms/dose inhaler (boehringer ingelheim ltd)
SABA	2149	steri-neb salamol 2.5 mg inh
SABA	2395	salbutamol 2 mg/5ml syr
SABA	2655	airomir 100micrograms/dose inhaler (teva uk ltd)
SABA	2758	bricanyl refill canister (astrazeneca uk ltd)
SABA	2850	salbutamol 400microgram inhalation powder capsules
SABA	2851	ventolin 200microgram rotacaps (glaxosmithkline uk ltd)
SABA	2869	salbutamol 8mg modified-release tablets
SABA	2978	salbutamol 200micrograms/dose dry powder inhaler
SABA	3163	salbutamol 200micrograms disc
SABA	3189	salbuvent inh inh
SABA	3254	salbulin 4mg tablet (3m health care ltd)
SABA	3443	salbutamol 100microgram/inhalation spacehaler (celltech pharma europe ltd)
SABA	3534	bricanyl 5mg tablets (astrazeneca uk ltd)
SABA	3584	bricanyl 1.5mg/5ml syrup (astrazeneca uk ltd)
SABA	3758	pulmadil inhalation powder (3m health care ltd)
SABA	3763	terbutaline respules inh
SABA	3764	bricanyl respules (5mg/2ml) 2.5 mg/ml inh

Drug Class	prodcode	Product name
SABA	3838	salbutamol 400mcg/beclometh.100mcg r/cap inh
SABA	3994	salbutamol 4mg modified-release tablets
SABA	4055	salbulin 2mg/5ml oral solution (3m health care ltd)
SABA	4171	ventolin 2mg tablet (allen & hanburys ltd)
SABA	4222	bricanyl 10mg/ml respirator solution (astrazeneca uk ltd)
SABA	4497	ventolin accuhaler 200 200microgram/actuation inhalation powder (glaxo wellcome uk ltd)
SABA	4541	bricanyl sa 7.5mg tablets (astrazeneca uk ltd)
SABA	4665	salbulin 100micrograms/dose inhaler (3m health care ltd)
SABA	4842	fenoterol 100microgram/actuation inhaler
SABA	4908	ventolin rotahaler (glaxosmithkline uk ltd)
SABA	5170	salamol 100micrograms/dose inhaler cfc free (teva uk ltd)
SABA	5185	fenoterol 200micrograms/dose inhaler
SABA	5516	salamol 100micrograms/dose easi-breathe inhaler (teva uk ltd)
SABA	5740	airomir 100micrograms/dose autohaler (teva uk ltd)
SABA	5753	salbutamol 400micrograms disc
SABA	5889	salamol 100microgram/inhalation inhalation powder (kent pharmaceuticals ltd)
SABA	6462	salbutamol 95micrograms/dose dry powder inhaler
SABA	7017	salbutamol 100micrograms/dose dry powder inhaler
SABA	7192	bambuterol 10mg tablets
SABA	7452	ventolin .25 mg inj
SABA	7711	terbutaline 250micrograms/dose inhaler with spacer
SABA	7935	maxivent 100microgram/inhalation inhalation powder (ashbourne pharmaceuticals ltd)
SABA	7953	terbutaline 1.5mg/5ml oral solution sugar free
SABA	7954	bricanyl 250micrograms/dose spacer inhaler (astrazeneca uk ltd)
SABA	8012	exirel 15mg capsule (3m health care ltd)
SABA	8252	pirbuterol 15mg capsule

Drug Class	prodcode	Product name
SABA	8339	fenoterol hydrobromide complete unit inh
SABA	8429	ventolin i/v 5 mg inj
SABA	8504	exirel 15 mg tab
SABA	8522	terbutaline 7.5mg modified-release tablets
SABA	8572	rimiterol inhaler
SABA	8636	ventolin s/r 8 mg spa
SABA	9384	salbutamol 4mg modified-release capsules
SABA	9651	asmasal 100microgram/inhalation spacehaler (celltech pharma europe ltd)
SABA	10353	salbuvent rondo
SABA	10458	ventolin cr 4mg tablet (allen & hanburys ltd)
SABA	10825	terbutaline 5mg tablets
SABA	10858	pulmadil auto inhalation powder (3m health care ltd)
SABA	10958	salbutamol .25 mg inj
SABA	12042	ventolin cr 8mg tablet (allen & hanburys ltd)
SABA	12144	bambuterol 20mg tablets
SABA	12463	pirbuterol 15 mg tab
SABA	12486	bronchodil 500microgram/dose inhalation powder (viatris pharmaceuticals ltd)
SABA	12563	exirel inhalation powder (3m health care ltd)
SABA	13038	pulvinal salbutamol 200micrograms/dose dry powder inhaler (chiesi ltd)
SABA	13181	easyhaler salbutamol sulfate 100micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
SABA	13575	bambec 20mg tablets (astrazeneca uk ltd)
SABA	13996	salamol 100microgram/inhalation inhalation powder (sandoz ltd)
SABA	14482	bricanyl 2.5 mg inj
SABA	14525	salbutamol 100micrograms/inhalation vortex inhaler
SABA	14527	bambec 10mg tablets (astrazeneca uk ltd)
SABA	15075	bronchodil 20mg tablet (viatris pharmaceuticals ltd)

Drug Class	prodcode	Product name
SABA	15165	reproterol 500micrograms/dose inhaler
SABA	15441	fenoterol hydrobromide .5 % sol
SABA	16236	pirbuterol acetate inhaler
SABA	16577	easyhaler salbutamol sulfate 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
SABA	17696	ventmax sr 4mg capsules (chiesi ltd)
SABA	17874	monovent 1.5mg/5ml oral solution (lagap)
SABA	17901	bricanyl nebule 2.5 ml
SABA	18622	salbulin 2mg tablet (3m health care ltd)
SABA	19642	ventolin nebules
SABA	19649	ventolin rotahaler
SABA	19653	ventolin respirator
SABA	19726	ventolin s/r
SABA	19732	cobutolin inh
SABA	20675	salbutamol rotahaler complete unit
SABA	20781	salbutamol u.dose nebulising 2.5mg/2.5ml
SABA	20838	salbuvent 2mg tablet (pharmacia ltd)
SABA	21102	salbutamol 2mg/5ml oral solution (lagap)
SABA	21859	asmaven 100microgram inhalation powder (berk pharmaceuticals ltd)
SABA	22225	beclomethasone /salbutamol
SABA	22313	ventmax sr 8mg capsules (chiesi ltd)
SABA	22430	spacehaler salbutamol 100microgram/inhalation spacehaler (celltech pharma europe ltd)
SABA	22467	salbutamol respirator soln
SABA	22512	salbutamol inhaler
SABA	22550	duovent
SABA	22661	pirbuterol 10mg capsule
SABA	22790	reproterol 10mg/ml respirator solution

Drug Class	prodcode	Product name
SABA	23688	ventolin rotacaps
SABA	23787	exirel 10mg capsule (3m health care ltd)
SABA	25073	salbutamol
SABA	25218	salbutamol cfc/free b/a
SABA	25820	bronchodil 10mg/5ml oral solution (viatris pharmaceuticals ltd)
SABA	25821	exirel 7.5mg/5ml oral solution (3m health care ltd)
SABA	25829	pirbuterol 7.5mg/5ml oral solution
SABA	26420	exirel 10 mg tab
SABA	26525	ventolin
SABA	26716	airomir autohaler cfc free b/a
SABA	26873	cobutolin 2mg tablet (actavis uk ltd)
SABA	27573	ventolin
SABA	27793	salbutamol cyclohaler type 5 insufflator inhalation powder (bristol-myers squibb pharmaceuticals ltd)
SABA	28508	salbutamol 100microgram/inhalation inhalation powder (ivax pharmaceuticals uk ltd)
SABA	28881	salbutamol 2mg/5ml oral solution sugar free (a a h pharmaceuticals ltd)
SABA	29267	salbuvent 4mg tablet (pharmacia ltd)
SABA	30118	salbutamol 100micrograms/dose inhaler cfc free (teva uk ltd)
SABA	30204	salbutamol 200micrograms inahalation capsules
SABA	30212	salbutamol cyclohaler
SABA	30230	salbutamol 100micrograms/actuation breath actuated inhaler
SABA	31082	salbuvent 5mg/ml respirator solution (pharmacia ltd)
SABA	31290	salbulin cfc free
SABA	31845	salapin 2mg/5ml syrup (pinewood healthcare)
SABA	31933	salbutamol 100micrograms/dose inhaler (a a h pharmaceuticals ltd)
SABA	32050	salbutamol 400 cyclocaps (teva uk ltd)

Drug Class	prodcode	Product name
SABA	32102	salbutamol 4mg tablets (a a h pharmaceuticals ltd)
SABA	32812	numotac 10mg tablet (3m health care ltd)
SABA	33089	salbutamol 100micrograms/dose inhaler (kent pharmaceuticals ltd)
SABA	33373	salbutamol 200 cyclocaps (teva uk ltd)
SABA	33588	salbutamol 100micrograms/dose inhaler (mylan)
SABA	33817	salbutamol 100micrograms/dose inhaler cfc free (actavis uk ltd)
SABA	34029	salbutamol 400micrograms inahalation capsules
SABA	34310	salbutamol 100micrograms/dose inhaler cfc free (a a h pharmaceuticals ltd)
SABA	34311	salbutamol 100microgram/inhalation inhalation powder (berk pharmaceuticals ltd)
SABA	34618	salbutamol 2mg tablets (actavis uk ltd)
SABA	34619	salbutamol 100microgram/inhalation inhalation powder (kent pharmaceuticals ltd)
SABA	34702	salbutamol 100microgram/inhalation inhalation powder (c p pharmaceuticals ltd)
SABA	34938	salbutamol 4mg tablets (actavis uk ltd)
SABA	36677	reproterol 10mg/5ml oral solution
SABA	38079	salbutamol 100micrograms/dose dry powder inhalation cartridge with device
SABA	38097	salbutamol cyclocaps 200microgram inhalation powder (dupont pharmaceuticals ltd)
SABA	38136	salbulin novolizer 100micrograms/dose inhalation powder (meda pharmaceuticals ltd)
SABA	38214	salbutamol 100micrograms/dose dry powder inhalation cartridge
SABA	38226	salbulin novolizer 100micrograms/dose inhalation powder refill (meda pharmaceuticals ltd)
SABA	38416	salbutamol cyclocaps 400microgram inhalation powder (dupont pharmaceuticals ltd)
SABA	38419	terbutaline 1.5mg/5ml oral solution sugar free (a a h pharmaceuticals ltd)
SABA	40655	salbuvent 100microgram/actuation inhalation powder (pharmacia ltd)
SABA	41548	salbutamol 2mg tablets (approved prescription services ltd)
SABA	41549	salbutamol 2mg tablet (c p pharmaceuticals ltd)
SABA	41691	salbutamol 2mg/5ml oral solution sugar free (sandoz ltd)
SABA	41832	monovent 1.5mg/5ml syrup (sandoz ltd)

Drug Class	prodcode	Product name
SABA	42497	salbutamol 8mg tablet
SABA	42830	ventolin 100micrograms/dose evohaler (glaxosmithkline uk ltd)
SABA	42858	ventolin 200micrograms/dose accuhaler (glaxosmithkline uk ltd)
SABA	42867	terbutaline 1.5mg/5ml oral solution (sandoz ltd)
SABA	42886	bricanyl 500micrograms/dose turbohaler (astrazeneca uk ltd)
SABA	43085	bricanyl 5mg/2ml respules (astrazeneca uk ltd)
SABA	44713	salbutamol 100microgram/inhalation inhalation powder (celltech pharma europe ltd)
SABA	46551	salbutamol 100microgram/inhalation inhalation powder (neo laboratories ltd)
SABA	48490	ventolin 100micrograms/dose evohaler (de pharmaceuticals)
SABA	48519	ventolin 100micrograms/dose evohaler (waymade healthcare plc)
SABA	48547	salamol 100micrograms/dose inhaler cfc free (arrow generics ltd)
SABA	48741	ventolin 100micrograms/dose evohaler (mawdsley-brooks & company ltd)
SABA	48742	ventodisks 400microgram (glaxosmithkline uk ltd)
SABA	48809	ventodisks 400microgram with diskhaler (glaxosmithkline uk ltd)
SABA	49368	ventodisks 200microgram with diskhaler (glaxosmithkline uk ltd)
SABA	49369	salbutamol 200microgram inhalation powder blisters
SABA	49370	ventodisks 200microgram (glaxosmithkline uk ltd)
SABA	49591	salbutamol 100micrograms/dose inhaler cfc free (sandoz ltd)
SABA	50315	salbutamol 200microgram inhalation powder blisters with device
SABA	50503	ventolin 200micrograms/dose accuhaler (mawdsley-brooks & company ltd)
SABA	50557	ventolin 200micrograms/dose accuhaler (lexon (uk) ltd)
SABA	50956	ventolin 200micrograms/dose accuhaler (de pharmaceuticals)
SABA	52410	bricanyl 500micrograms/dose turbohaler (necessity supplies ltd)
SABA	52543	salbutamol 400microgram inhalation powder blisters
SABA	52799	salbutamol 400microgram inhalation powder blisters with device
SABA	53019	ventolin 2.5mg nebules (mawdsley-brooks & company ltd)

Drug Class	prodcode	Product name
SABA	53297	ventolin 200micrograms/dose accuhaler (sigma pharmaceuticals plc)
SABA	57249	asmavent 100micrograms/dose inhaler cfc free (kent pharmaceuticals ltd)
SABA	57524	ventolin 200micrograms/dose accuhaler (dowelhurst ltd)
SABA	58269	airsalb 100micrograms/dose inhaler cfc free (sandoz ltd)
SABA	59409	salbutamol 100micrograms/dose inhaler cfc free (waymade healthcare plc)
SABA	60923	salamol 100micrograms/dose easi-breathe inhaler (de pharmaceuticals)
SABA	61591	salbutamol 100micrograms/dose inhaler cfc free (phoenix healthcare distribution ltd)
SABA	64801	salbutamol 100micrograms/dose inhaler cfc free (mylan)
SABA	65376	salbutamol 2mg/5ml oral solution sugar free (pinewood healthcare)
SABA	66395	salbutamol 100micrograms/dose inhaler cfc free (mawdsley-brooks & company ltd)
SABA	66793	salbutamol rondo 100micrograms/actuation inhaler and spacer
SABA	66924	salbutamol 100micrograms/dose inhaler cfc free (de pharmaceuticals)
SABA	66972	salbutamol 100micrograms/dose inhaler cfc free (am distributions (yorkshire) ltd)
SABA	67040	salbutamol 100micrograms/dose inhaler cfc free (alliance healthcare (distribution) ltd)
SABA	67326	bricanyl 500micrograms/dose turbohaler (de pharmaceuticals)
SABA	67543	bricanyl 500micrograms/dose turbohaler (waymade healthcare plc)
SABA	69238	ventolin 200micrograms/dose accuhaler (waymade healthcare plc)
SABA	70750	ventolin 100micrograms/dose evohaler (dowelhurst ltd)
SABA	73812	bricanyl 500micrograms/dose turbohaler (lexon (uk) ltd)
SABA_CROMO	8267	sodium cromoglicate 1mg/dose / salbutamol 100micrograms/dose inhaler
SABA_CROMO	10360	aerocrom inhaler (castlemead healthcare ltd)
SABA_CROMO	18314	aerocrom syncroner with spacer (castlemead healthcare ltd)
SABA_CROMO	24380	sodium cromoglicate 1mg/dose / salbutamol 100micrograms/dose inhaler with spacer
SABA_ICS	1801	ventide inhaler (glaxosmithkline uk ltd)
SABA_ICS	3556	beclometasone 50micrograms with salbutamol 100micrograms/inhalation inhaler
SABA_ICS	11307	salbutamol 100micrograms/dose / beclometasone 50micrograms/dose inhaler

Drug Class	prodcode	Product name
SABA_ICS	14561	salbutamol 400microgram / beclometasone 200microgram inhalation powder capsules
SABA_ICS	16625	ventide rotacaps (glaxosmithkline uk ltd)
SABA_ICS	18456	salbutamol 200microgram / beclometasone 100microgram inhalation powder capsules
SABA_ICS	18484	ventide paediatric rotacaps (glaxosmithkline uk ltd)
SABA_ICS	19121	beclometasone 100micrograms with salbutamol 200micrograms inhalation capsules
SABA_ICS	19376	beclometasone 200micrograms with salbutamol 400micrograms inhalation capsules
SABA_SAMA	556	combivent inhaler (boehringer ingelheim ltd)
SABA_SAMA	2152	ipratropium bromide with salbutamol 20mcg + 100mcg
SABA_SAMA	2722	duovent inhaler (boehringer ingelheim ltd)
SABA_SAMA	2862	duovent autohaler (boehringer ingelheim ltd)
SABA_SAMA	3786	fenoterol 100micrograms/dose / ipratropium 40micrograms/dose inhaler
SABA_SAMA	9270	ipratropium bromide with fenoterol hydrobromide 500micrograms + 1.25mg/4ml
SABA_SAMA	11046	ipratropium bromide with salbutamol 500micrograms + 2.5mg/2.5ml
SABA_SAMA	12808	fenoterol 100micrograms/dose / ipratropium bromide 40micrograms/dose breath actuated inhaler
SABA_SAMA	12822	salbutamol 2.5mg with ipratropium bromide 500micrograms/2.5ml unit dose nebuilser solution
SABA_SAMA	12909	salbutamol 100micrograms/dose / ipratropium 20micrograms/dose inhaler
SABA_SAMA	26616	ipratropium bromide with fenoterol hydrobromide 0micrograms + 100micrograms/actuation
SABA_SAMA	27505	ipratropium bromide with fenoterol hydrobromide 40micrograms + 100micrograms/actuation
SAMA	534	atrovent 20micrograms/dose inhaler (boehringer ingelheim ltd)
SAMA	1409	ipratropium bromide 20micrograms/dose inhaler
SAMA	1410	ipratropium bromide 0.25mg/ml
SAMA	1411	ipratropium bromide 250micrograms/ml
SAMA	1697	atrovent 20micrograms/dose autohaler (boehringer ingelheim ltd)
SAMA	2437	oxitropium bromide 100micrograms/dose inhaler
SAMA	2994	atrovent aerocaps 40microgram inhalation powder (boehringer ingelheim ltd)

Drug Class	prodcode	Product name
SAMA	3039	oxivent 100micrograms/dose inhaler (boehringer ingelheim ltd)
SAMA	3306	atrovent forte 40micrograms/dose inhaler (boehringer ingelheim ltd)
SAMA	3850	oxivent 100micrograms/dose autohaler (boehringer ingelheim ltd)
SAMA	4268	ipratropium bromide 40micrograms/dose inhaler
SAMA	6081	ipratropium bromide 20micrograms/dose breath actuated inhaler
SAMA	6512	atrovent 20micrograms/dose inhaler cfc free (boehringer ingelheim ltd)
SAMA	6522	ipratropium bromide 20micrograms/dose inhaler cfc free
SAMA	8333	ipratropium bromide 40microgram inhalation powder capsules
SAMA	9658	oxitropium bromide 100micrograms/dose breath actuated inhaler
SAMA	9681	atrovent aerohaler 40microgram inhalation powder (boehringer ingelheim ltd)
SAMA	11779	ipratropium bromide 40microgram inhalation powder capsules with device
SAMA	18140	respontin 500micrograms/2ml nebules (glaxosmithkline uk ltd)
SAMA	19805	atrovent
SAMA	20720	atrovent forte
SAMA	23567	respontin 250micrograms/1ml nebules (glaxosmithkline uk ltd)
SAMA	23961	ipratropium bromide 250microgram/ml inhalation vapour (galen ltd)
SAMA	25020	ipratropium bromide (forte)
SAMA	37791	ipratropium bromide 250microgram/ml
SAMA	43090	atrovent 40microgram aerocaps (boehringer ingelheim ltd)
SAMA	43105	atrovent 40microgram aerocaps with aerohaler (boehringer ingelheim ltd)
SAMA	50810	atrovent 20micrograms/dose inhaler cfc free (de pharmaceuticals)
SAMA	57557	atrovent 20micrograms/dose inhaler cfc free (lexon (uk) ltd)
SAMA	60920	atrovent 20micrograms/dose inhaler cfc free (sigma pharmaceuticals plc)
THEOPH	180	phyllocontin sup
THEOPH	218	aminophylline 100 mg cap
THEOPH	273	theophylline 200 mg cap

Drug Class	prodcode	Product name
THEOPH	555	aminophylline 225mg modified-release tablets
THEOPH	590	phyllocontin continus 225mg tablets (napp pharmaceuticals ltd)
THEOPH	863	slo-phyllin 125mg capsule (lipha pharmaceuticals ltd)
THEOPH	879	theophylline 125mg modified-release capsules
THEOPH	880	theophylline 60mg modified-release capsules
THEOPH	1097	slo-phyllin 60mg capsule (lipha pharmaceuticals ltd)
THEOPH	1423	uniphyllin continus 200mg tablets (napp pharmaceuticals ltd)
THEOPH	1832	theograd 350mg tablet (abbott laboratories ltd)
THEOPH	1833	theophylline 200mg modified-release tablets
THEOPH	1834	theophylline 400mg modified-release tablets
THEOPH	2147	theophylline 250mg modified-release capsules
THEOPH	2757	slo-phyllin 250mg capsule (lipha pharmaceuticals ltd)
THEOPH	2995	nuelin sa 175mg tablets (meda pharmaceuticals ltd)
THEOPH	3388	theophylline 175mg modified-release tablets
THEOPH	4514	aminophylline 350mg modified-release tablets
THEOPH	4593	theophylline 125mg tablets
THEOPH	5261	nuelin sa 250 tablets (meda pharmaceuticals ltd)
THEOPH	5453	uniphyllin continus 400mg tablets (napp pharmaceuticals ltd)
THEOPH	5941	uniphyllin continus 300mg tablets (napp pharmaceuticals ltd)
THEOPH	6315	slo-phyllin 250mg capsules (merck serono ltd)
THEOPH	6988	aminophylline hydrate 100mg modified-release tablets
THEOPH	7730	theo-dur 300mg tablets (astrazeneca uk ltd)
THEOPH	7731	theo-dur 200mg tablets (astrazeneca uk ltd)
THEOPH	7732	theophylline 300mg modified-release tablets
THEOPH	7733	theophylline 250mg modified-release tablets
THEOPH	7832	choline theophyllinate 200mg tablets

Drug Class	prodcode	Product name
THEOPH	7841	nuelin 125mg tablets (3m health care ltd)
THEOPH	8056	aminophylline 100mg tablets
THEOPH	8057	aminophylline 100mg modified-release tablets
THEOPH	8470	aminophylline 225 mg sup
THEOPH	8610	aminophylline 1 gm sup
THEOPH	8653	aminophylline 360 mg sup
THEOPH	8806	phyllocontin continus 350mg tablet (napp pharmaceuticals ltd)
THEOPH	8955	theophylline 100 mg tab
THEOPH	9092	theophylline 350mg modified release tablets
THEOPH	10289	aminophylline 200 mg sup
THEOPH	10331	nuelin 60mg/5ml liquid (3m health care ltd)
THEOPH	10407	phyllocontin paediatric continus 100mg tablets (napp pharmaceuticals ltd)
THEOPH	10432	theophylline 300 mg sup
THEOPH	10433	theophylline 60mg/5ml oral solution
THEOPH	10723	theophylline 125mg/5ml syrup
THEOPH	10744	theophylline 80 mg eli
THEOPH	10831	biophylline 125mg/5ml oral solution (lorex synthelabo ltd)
THEOPH	11719	slo-phyllin 60mg capsules (merck serono ltd)
THEOPH	11993	pro-vent 300mg capsule (wellcome medical division)
THEOPH	12240	theophylline 300mg modified release capsules
THEOPH	12699	pecram 225mg modified-release tablet (novartis consumer health uk ltd)
THEOPH	13529	amnivent-225 sr tablets (ashbourne pharmaceuticals ltd)
THEOPH	14739	norphyllin sr 225mg tablets (teva uk ltd)
THEOPH	15025	aminophylline 25 mg sup
THEOPH	15284	slo-phyllin 125mg capsules (merck serono ltd)
THEOPH	15365	theophylline 10mg/5ml sf elixir

Drug Class	prodcode	Product name
THEOPH	15409	theophylline 3 mg sol
THEOPH	16994	aminophylline hydrate 350mg modified-release tablets
THEOPH	17002	aminophylline hydrate 225mg modified-release tablets
THEOPH	17140	aminophylline 200mg tablets
THEOPH	18288	choline theophyllinate 100mg tablets
THEOPH	18308	aminophylline 100 mg sup
THEOPH	18937	sabidal sr 270 270 mg tab
THEOPH	18988	choline theophyllinate 62.5mg/5ml oral solution
THEOPH	19350	aminophylline 62.5 mg sup
THEOPH	19735	uniphyllin continus
THEOPH	20171	aminophylline 180 mg sup
THEOPH	20225	aminophylline 500 mg inj
THEOPH	21769	lasma 300mg tablet (pharmax ltd)
THEOPH	22080	aminophylline 20 ml inj
THEOPH	22669	choline theophyllinate 270 mg tab
THEOPH	23572	aminophylline sr 225mg modified-release tablet (ivax pharmaceuticals uk ltd)
THEOPH	24117	aminophylline 300 mg sup
THEOPH	24207	aminophylline paed 50 mg sup
THEOPH	24418	biophylline 350mg tablet (lorex synthelabo ltd)
THEOPH	24674	biophylline 500mg tablet (lorex synthelabo ltd)
THEOPH	25022	aminophylline 150 mg sup
THEOPH	25093	theophylline s/r
THEOPH	26079	uniphyllin paediatric continus
THEOPH	27040	phyllocontin continus
THEOPH	27558	choledyl
THEOPH	27593	aminophylline 350 mg sup

Drug Class	prodcode	Product name
THEOPH	27842	aminophylline 2 ml inj
THEOPH	29273	aminophylline 225mg modified-release tablet (hillcross pharmaceuticals ltd)
THEOPH	30596	aminophylline 225mg modified-release tablet (actavis uk ltd)
THEOPH	31758	uniphyllin continus
THEOPH	32461	choline theophyllinate 90 mg tab
THEOPH	32893	theophylline 100mg/lysine 74mg mg tab
THEOPH	38120	theophylline 500mg modified release tablets
THEOPH	39040	phyllocontin forte continus 350mg tablets (napp pharmaceuticals ltd)
THEOPH	48484	theophylline 250mg/5ml oral suspension
THEOPH	51430	theophylline 60mg/5ml oral suspension
THEOPH	73738	sabidal slow release 270 tablet (novartis consumer health uk ltd)

Q. COPD Therapies(CPRD Aurum)

Drug Class	ProdCodeId	Term from EMIS
AZITHRO	96941000033113	Azithromycin 250mg capsules
AZITHRO	98441000033116	Azithromycin 200mg/5ml oral suspension
AZITHRO	1553141000033111	Zithromax 250mg capsules (Pfizer Ltd)
AZITHRO	1557141000033118	Zithromax 200mg/5ml oral suspension (Pfizer Ltd)
AZITHRO	1572841000033112	Azithromycin 500mg tablets
AZITHRO	1713741000033116	Zithromax 500mg tablets (Pfizer Ltd)
AZITHRO	3955441000033115	Azithromycin 250mg tablets
AZITHRO	4823141000033118	Clamelle 500mg tablets (Actavis UK Ltd)
ICS	20141000033118	AeroBec 50 Autohaler (Meda Pharmaceuticals Ltd)
ICS	20241000033113	AeroBec Forte 250 Autohaler (Meda Pharmaceuticals Ltd)
ICS	20341000033115	AeroBec 100 Autohaler (Meda Pharmaceuticals Ltd)
ICS	121641000033112	Becloforte 250micrograms/dose inhaler (GlaxoSmithKline UK Ltd)
ICS	123241000033110	Beclazone 100 Easi-Breathe inhaler (Teva UK Ltd)
ICS	123341000033117	Beclazone 50 Easi-Breathe inhaler (Teva UK Ltd)
ICS	123441000033111	Beclazone 250 Easi-Breathe inhaler (Teva UK Ltd)
ICS	126641000033118	Becloforte 400microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
ICS	126741000033110	Becodisks 100microgram with Diskhaler (GlaxoSmithKline UK Ltd)
ICS	126841000033117	Becodisks 200microgram with Diskhaler (GlaxoSmithKline UK Ltd)
ICS	126941000033113	Becodisks 400microgram with Diskhaler (GlaxoSmithKline UK Ltd)
ICS	129041000033117	Beclazone 100 inhaler (Teva UK Ltd)
ICS	129141000033118	Beclazone 50 inhaler (Teva UK Ltd)
ICS	129241000033113	Beclazone 250 inhaler (Teva UK Ltd)
ICS	129841000033112	Becotide 100 inhaler (GlaxoSmithKline UK Ltd)
ICS	129941000033116	Becotide 50 inhaler (GlaxoSmithKline UK Ltd)
ICS	131441000033112	Becotide 200 inhaler (GlaxoSmithKline UK Ltd)

Drug Class	ProdCodeId	Term from EMIS
ICS	136641000033115	Becloforte 400microgram disks (GlaxoSmithKline UK Ltd)
ICS	136941000033110	Becodisks 100microgram (GlaxoSmithKline UK Ltd)
ICS	137041000033111	Becodisks 200microgram (GlaxoSmithKline UK Ltd)
ICS	137241000033115	Becodisks 400microgram (GlaxoSmithKline UK Ltd)
ICS	137641000033117	Becotide 100microgram Rotacaps (GlaxoSmithKline UK Ltd)
ICS	137741000033114	Becotide 200microgram Rotacaps (GlaxoSmithKline UK Ltd)
ICS	138041000033110	Becotide 400microgram Rotacaps (GlaxoSmithKline UK Ltd)
ICS	576141000033117	Filair 100 inhaler (Meda Pharmaceuticals Ltd)
ICS	576241000033112	Filair 50 inhaler (Meda Pharmaceuticals Ltd)
ICS	576341000033119	Filair Forte 250micrograms/dose inhaler (Meda Pharmaceuticals Ltd)
ICS	1571041000033110	Asmabec 100 Clickhaler (Focus Pharmaceuticals Ltd)
ICS	1571141000033114	Asmabec 250 Clickhaler (Focus Pharmaceuticals Ltd)
ICS	1571241000033119	Asmabec 50 Clickhaler (Focus Pharmaceuticals Ltd)
ICS	1577941000033118	Beclazone 200 inhaler (Teva UK Ltd)
ICS	1671041000033116	Qvar 50 inhaler (Teva UK Ltd)
ICS	1671141000033117	Qvar 100 inhaler (Teva UK Ltd)
ICS	1671241000033112	Qvar 50 Autohaler (Teva UK Ltd)
ICS	1671341000033119	Qvar 100 Autohaler (Teva UK Ltd)
ICS	2623141000033115	Pulvinal Beclometasone Dipropionate 100micrograms/dose dry powder inhaler (Chiesi Ltd)
ICS	2623241000033110	Pulvinal Beclometasone Dipropionate 200micrograms/dose dry powder inhaler (Chiesi Ltd)
ICS	2623341000033117	Pulvinal Beclometasone Dipropionate 400micrograms/dose dry powder inhaler (Chiesi Ltd)
ICS	2725541000033116	Beclometasone 100 Cyclocaps (Teva UK Ltd)
ICS	2725641000033115	Beclometasone 200 Cyclocaps (Teva UK Ltd)
ICS	2725741000033112	Beclometasone 400 Cyclocaps (Teva UK Ltd)
ICS	3080441000033114	Beclometasone 250micrograms/dose inhaler

Drug Class	ProdCodeId	Term from EMIS
ICS	3080541000033110	Beclometasone 250micrograms/dose breath actuated inhaler
ICS	3080641000033111	Beclometasone 50micrograms/dose breath actuated inhaler
ICS	3080741000033119	Beclometasone 100micrograms/dose breath actuated inhaler
ICS	3081041000033114	Beclometasone 100microgram inhalation powder blisters with device
ICS	3081141000033113	Beclometasone 200microgram inhalation powder blisters with device
ICS	3081241000033118	Beclometasone 400microgram inhalation powder blisters with device
ICS	3081341000033111	Beclometasone 100microgram inhalation powder blisters
ICS	3081441000033117	Beclometasone 200microgram inhalation powder blisters
ICS	3081541000033116	Beclometasone 400microgram inhalation powder blisters
ICS	3081641000033115	Beclometasone 200micrograms/dose inhaler
ICS	3081741000033112	Beclometasone 100micrograms/dose inhaler
ICS	3081841000033119	Beclometasone 50micrograms/dose inhaler
ICS	3081941000033110	Beclometasone 400microgram inhalation powder capsules
ICS	3082041000033116	Beclometasone 100microgram inhalation powder capsules
ICS	3082141000033117	Beclometasone 200microgram inhalation powder capsules
ICS	3082241000033112	Beclometasone 50micrograms/dose dry powder inhaler
ICS	3082341000033119	Beclometasone 100micrograms/dose dry powder inhaler
ICS	3082441000033113	Beclometasone 250micrograms/dose dry powder inhaler
ICS	3082541000033114	Beclometasone 400micrograms/dose dry powder inhaler
ICS	3082641000033110	Beclometasone 200micrograms/dose dry powder inhaler
ICS	3082741000033118	Beclometasone 50micrograms/dose inhaler CFC free
ICS	3082841000033111	Beclometasone 100micrograms/dose inhaler CFC free
ICS	3082941000033115	Beclometasone 50micrograms/dose breath actuated inhaler CFC free
ICS	3083041000033113	Beclometasone 100micrograms/dose breath actuated inhaler CFC free
ICS	3199241000033112	Qvar 50micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
ICS	3199341000033119	Qvar 100micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
ICS	3343041000033119	Easyhaler Beclometasone 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)

Drug Class	ProdCodeId	Term from EMIS
ICS	3942841000033114	Beclometasone 200micrograms/dose inhaler CFC free
ICS	3942941000033118	Beclometasone 250micrograms/dose inhaler CFC free
ICS	3943041000033111	Clenil Modulite 50micrograms/dose inhaler (Chiesi Ltd)
ICS	3943341000033113	Clenil Modulite 100micrograms/dose inhaler (Chiesi Ltd)
ICS	3943441000033119	Clenil Modulite 200micrograms/dose inhaler (Chiesi Ltd)
ICS	3943641000033117	Clenil Modulite 250micrograms/dose inhaler (Chiesi Ltd)
ICS	163741000033113	Budesonide 200micrograms/dose inhaler
ICS	163841000033115	Budesonide 50micrograms/dose inhaler
ICS	169341000033114	Budesonide 3mg gastro-resistant modified-release capsules
ICS	521541000033116	Entocort CR 3mg capsules (Tillotts Pharma Ltd)
ICS	1143041000033117	Pulmicort 200micrograms/dose inhaler (AstraZeneca UK Ltd)
ICS	1143141000033118	Pulmicort LS 50micrograms/dose inhaler (AstraZeneca UK Ltd)
ICS	1145141000033119	Pulmicort 200 Turbohaler (AstraZeneca UK Ltd)
ICS	1145241000033114	Pulmicort 400 Turbohaler (AstraZeneca UK Ltd)
ICS	1145341000033116	Pulmicort 100 Turbohaler (AstraZeneca UK Ltd)
ICS	2725841000033119	Budesonide 200microgram inhalation powder capsules
ICS	2725941000033110	Budesonide 400microgram inhalation powder capsules
ICS	2726041000033117	Budesonide 200 Cyclocaps (Teva UK Ltd)
ICS	2726141000033118	Budesonide 400 Cyclocaps (Teva UK Ltd)
ICS	2798341000033112	Pulmicort 200micrograms/dose inhaler with Nebuchamber (AstraZeneca UK Ltd)
ICS	3141341000033112	Budesonide 200micrograms/dose dry powder inhalation cartridge with device
ICS	3256341000033119	Budesonide 200micrograms/dose dry powder inhalation cartridge
ICS	3871541000033110	Budesonide 100micrograms/dose dry powder inhaler
ICS	3871641000033111	Budesonide 200micrograms/dose dry powder inhaler
ICS	3871741000033119	Budesonide 400micrograms/dose dry powder inhaler
ICS	3871841000033112	Easyhaler Budesonide 100micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)

Drug Class	ProdCodeId	Term from EMIS
ICS	3871941000033116	Easyhaler Budesonide 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
ICS	3872041000033110	Easyhaler Budesonide 400micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
ICS	4815041000033111	Budesonide 100micrograms/dose inhaler CFC free
ICS	4815141000033110	Budesonide 200micrograms/dose inhaler CFC free
ICS	4815241000033115	Pulmicort 100micrograms/dose inhaler CFC free (AstraZeneca UK Ltd)
ICS	4815341000033113	Pulmicort 200micrograms/dose inhaler CFC free (AstraZeneca UK Ltd)
ICS	5393341000033118	Budelin Novolizer 200micrograms/dose inhalation powder (Meda Pharmaceuticals Ltd)
ICS	5393441000033112	Budelin Novolizer 200micrograms/dose inhalation powder refill (Meda Pharmaceuticals Ltd)
ICS	576741000033118	Flixotide 100micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
ICS	576841000033111	Flixotide 250micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
ICS	576941000033115	Flixotide 50micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
ICS	577041000033119	Flixotide 500micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
ICS	581241000033110	Flixotide 100microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
ICS	581341000033117	Flixotide 250microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
ICS	581441000033111	Flixotide 50microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
ICS	581841000033114	Flixotide 500microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
ICS	585741000033118	Flixotide 25micrograms/dose inhaler (GlaxoSmithKline UK Ltd)
ICS	586041000033113	Fluticasone 25micrograms/dose inhaler
ICS	590841000033115	Flixotide 100microgram disks (GlaxoSmithKline UK Ltd)
ICS	590941000033111	Flixotide 250microgram disks (GlaxoSmithKline UK Ltd)
ICS	591041000033118	Flixotide 50microgram disks (GlaxoSmithKline UK Ltd)
ICS	591141000033119	Fluticasone propionate 100microgram inhalation powder blisters
ICS	591241000033114	Fluticasone propionate 250microgram inhalation powder blisters
ICS	591341000033116	Fluticasone propionate 50microgram inhalation powder blisters

Drug Class	ProdCodeId	Term from EMIS
ICS	591441000033110	Flixotide 500microgram disks (GlaxoSmithKline UK Ltd)
ICS	591541000033111	Fluticasone propionate 500microgram inhalation powder blisters
ICS	1914341000033112	Fluticasone propionate 50micrograms/dose dry powder inhaler
ICS	1914441000033118	Fluticasone propionate 100micrograms/dose dry powder inhaler
ICS	1914541000033117	Fluticasone propionate 250micrograms/dose dry powder inhaler
ICS	1914641000033116	Fluticasone propionate 500micrograms/dose dry powder inhaler
ICS	1914741000033113	Fluticasone propionate 50microgram inhalation powder blisters with device
ICS	1914841000033115	Fluticasone propionate 100microgram inhalation powder blisters with device
ICS	1914941000033111	Fluticasone propionate 250microgram inhalation powder blisters with device
ICS	1915041000033111	Fluticasone propionate 500microgram inhalation powder blisters with device
ICS	2067541000033118	Flixotide 125micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
ICS	2067641000033117	Flixotide 250micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
ICS	2067741000033114	Fluticasone 125micrograms/dose inhaler CFC free
ICS	2067841000033116	Fluticasone 250micrograms/dose inhaler CFC free
ICS	2148441000033115	Fluticasone 50micrograms/dose inhaler CFC free
ICS	2148541000033119	Flixotide 50micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
ICS	5811241000033111	Mometasone 200micrograms/dose dry powder inhaler
ICS	5811341000033118	Mometasone 400micrograms/dose dry powder inhaler
ICS	5811441000033112	Asmanex 200micrograms/dose Twisthaler (Merck Sharp & Dohme Ltd)
ICS	5811541000033113	Asmanex 400micrograms/dose Twisthaler (Merck Sharp & Dohme Ltd)
ICS	3227441000033112	Ciclesonide 80micrograms/dose inhaler CFC free
ICS	4823241000033113	Ciclesonide 160micrograms/dose inhaler CFC free
ICS	3227641000033114	Alvesco 80 inhaler (AstraZeneca UK Ltd)
ICS	4823341000033115	Alvesco 160 inhaler (AstraZeneca UK Ltd)
ICS	3256441000033113	Novolizer Budesonide Inhalation Cartridge Refill 200 micrograms/dose, 100 doses
ICS	3141441000033118	Novolizer Budesonide Inhalation Cartridge + Device 200 micrograms/dose, 100 doses
ICS	2798441000033118	Budesonide Inhaler with spacer device 200 micrograms/dose

Drug Class	ProdCodeId	Term from EMIS
ICS	1580041000033111	Budesonide Breath-Actuated Dry Powder Inhaler 400 micrograms/dose
ICS	1579941000033112	Budesonide Breath-Actuated Dry Powder Inhaler 200 micrograms/dose
ICS	1579841000033116	Budesonide Breath-Actuated Dry Powder Inhaler 100 micrograms/dose
ICS	174641000033114	Budesonide Turbohaler 100 micrograms/dose
ICS	174541000033113	Budesonide Turbohaler 400 micrograms/dose
ICS	171741000033119	Budesonide Spacer inhaler 200 micrograms/dose
ICS	174441000033112	Budesonide Turbohaler 200 micrograms/dose
ICS	171641000033111	Budesonide Spacer inhaler 50 micrograms/dose
ICS	171541000033110	Budesonide Respules 1 mg/2 ml single dose unit
ICS	171441000033114	Budesonide Respules 500 micrograms/2 ml single dose unit
ICS	171341000033115	Budesonide Refill canister 50 micrograms/dose
ICS	171241000033113	Budesonide Refill canister 200 micrograms/dose
ICS	577141000033115	Fluticasone Propionate Accuhaler 100 micrograms/dose
ICS	577241000033110	Fluticasone Propionate Accuhaler 250 micrograms/dose
ICS	577341000033117	Fluticasone Propionate Accuhaler 50 micrograms/dose
ICS	577441000033111	Fluticasone Propionate Accuhaler 500 micrograms/dose
ICS	581541000033112	Fluticasone Propionate Disks with diskhaler 100 micrograms/dose
ICS	581641000033113	Fluticasone Propionate Disks with diskhaler 250 micrograms/dose
ICS	581741000033116	Fluticasone Propionate Disks with diskhaler 50 micrograms/dose
ICS	581941000033118	Fluticasone Propionate Disks with diskhaler 500 micrograms/puff
ICS	585941000033115	Fluticasone Propionate Inhaler 125 micrograms/puff
ICS	586341000033110	Fluticasone Propionate Inhaler 250 micrograms/puff
ICS	586141000033112	Fluticasone Propionate Inhaler 50 micrograms/puff
ICS	121941000033117	Betamethasone Valerate Aerosol inhalation 100 micrograms/metered inhalation
LABA	1252041000033114	Salmeterol 50microgram inhalation powder blisters
LABA	1267441000033114	Serevent 50micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
LABA	1268941000033117	Serevent 50microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
LABA	1272941000033113	Serevent 50microgram disks (GlaxoSmithKline UK Ltd)

Drug Class	ProdCodeId	Term from EMIS
LABA	1914141000033114	Salmeterol 50micrograms/dose dry powder inhaler
LABA	1914241000033119	Salmeterol 50microgram inhalation powder blisters with device
LABA	1206341000033118	Salmeterol 25micrograms/dose inhaler
LABA	1267641000033111	Serevent 25micrograms/dose inhaler (GlaxoSmithKline UK Ltd)
LABA	3855941000033115	Salmeterol 25micrograms/dose inhaler CFC free
LABA	3856041000033113	Serevent 25micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
LABA	6456541000033118	Neovent 25micrograms/dose inhaler CFC free (Teva UK Ltd)
LABA	8536141000033111	Vertine 25micrograms/dose inhaler CFC free (Teva UK Ltd)
LABA	11782841000033117	Soltel 25micrograms/dose inhaler CFC free (Kent Pharmaceuticals Ltd)
LABA	9299341000033119	Olodaterol 2.5micrograms/dose solution for inhalation cartridge with device CFC free
LABA	9299441000033113	Striverdi Respimat 2.5micrograms/dose solution for inhalation cartridge with device (Boehringer Ingelheim Ltd)
LABA	5707041000033111	Indacaterol 150microgram inhalation powder capsules with device
LABA	5707141000033110	Indacaterol 300microgram inhalation powder capsules with device
LABA	5707341000033113	Onbrez Breezhaler 300microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
LABA	5707241000033115	Onbrez Breezhaler 150microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
LABA	599641000033111	Foradil 12microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
LABA	1022341000033117	Oxis 12 Turbohaler (AstraZeneca UK Ltd)
LABA	1022441000033111	Oxis 6 Turbohaler (AstraZeneca UK Ltd)
LABA	3089641000033116	Formoterol 6micrograms/dose dry powder inhaler
LABA	3089741000033113	Formoterol 12micrograms/dose dry powder inhaler
LABA	3347141000033113	Atimos Modulite 12micrograms/dose inhaler (Chiesi Ltd)
LABA	4063541000033116	Formoterol Easyhaler 12micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
LABA	3089841000033115	Formoterol 12microgram inhalation powder capsules with device

Drug Class	ProdCodeId	Term from EMIS
LABA	3347041000033114	Formoterol 12micrograms/dose inhaler CFC free
LABA_ICS	1752341000033119	Seretide 500 Accuhaler (GlaxoSmithKline UK Ltd)
LABA_ICS	4418141000033112	Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose inhaler CFC free
LABA_ICS	4418241000033117	Fostair 100micrograms/dose / 6micrograms/dose inhaler (Chiesi Ltd)
LABA_ICS	9531441000033113	Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
LABA_ICS	9537441000033115	Fostair NEXThaler 100micrograms/dose / 6micrograms/dose dry powder inhaler (Chiesi Ltd)
LABA_ICS	10735041000033115	Beclometasone 200micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
LABA_ICS	10735141000033116	Fostair NEXThaler 200micrograms/dose / 6micrograms/dose dry powder inhaler (Chiesi Ltd)
LABA_ICS	10740041000033111	Beclometasone 200micrograms/dose / Formoterol 6micrograms/dose inhaler CFC free
LABA_ICS	10740141000033110	Fostair 200micrograms/dose / 6micrograms/dose inhaler (Chiesi Ltd)
LABA_ICS	2905641000033115	Symbicort 400/12 Turbohaler (AstraZeneca UK Ltd)
LABA_ICS	3164341000033116	Budesonide 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
LABA_ICS	3164541000033111	Budesonide 400micrograms/dose / Formoterol 12micrograms/dose dry powder inhaler
LABA_ICS	3164441000033110	Budesonide 200micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
LABA_ICS	9342841000033118	DuoResp Spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler (Teva UK Ltd)
LABA_ICS	9342741000033111	DuoResp Spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (Teva UK Ltd)
LABA_ICS	11707241000033115	Budesonide 200micrograms/dose / Formoterol 6micrograms/dose inhaler CFC free
LABA_ICS	11707341000033113	Symbicort 200micrograms/dose / 6micrograms/dose pressurised inhaler (AstraZeneca UK Ltd)
LABA_ICS	12403741000033110	Fobumix 320/9 Easyhaler (Orion Pharma (UK) Ltd)

Drug Class	ProdCodeId	Term from EMIS
LABA_ICS	8102141000033110	Flutiform 250micrograms/dose / 10micrograms/dose inhaler (Napp Pharmaceuticals Ltd)
LABA_ICS	8102041000033111	Flutiform 125micrograms/dose / 5micrograms/dose inhaler (Napp Pharmaceuticals Ltd)
LABA_ICS	8101941000033117	Flutiform 50micrograms/dose / 5micrograms/dose inhaler (Napp Pharmaceuticals Ltd)
LABA_ICS	8101841000033113	Fluticasone 250micrograms/dose / Formoterol 10micrograms/dose inhaler CFC free
LABA_ICS	8101741000033115	Fluticasone 125micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free
LABA_ICS	8101641000033112	Fluticasone 50micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free
LABA_ICS	1752141000033117	Seretide 100 Accuhaler (GlaxoSmithKline UK Ltd)
LABA_ICS	1752241000033112	Seretide 250 Accuhaler (GlaxoSmithKline UK Ltd)
LABA_ICS	2147241000033117	Seretide 50 Evohaler (GlaxoSmithKline UK Ltd)
LABA_ICS	2147341000033110	Seretide 125 Evohaler (GlaxoSmithKline UK Ltd)
LABA_ICS	3163741000033118	Fluticasone 50micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free
LABA_ICS	2147441000033116	Seretide 250 Evohaler (GlaxoSmithKline UK Ltd)
LABA_ICS	3163941000033115	Fluticasone 250micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free
LABA_ICS	3163841000033111	Fluticasone 125micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free
LABA_ICS	3164041000033118	Fluticasone propionate 100micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler
LABA_ICS	3164241000033114	Fluticasone propionate 500micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler
LABA_ICS	3164141000033119	Fluticasone propionate 250micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler
LABA_ICS	10387141000033115	Sirdupla 25micrograms/dose / 125micrograms/dose inhaler (Mylan Ltd)
LABA_ICS	10387241000033110	Sirdupla 25micrograms/dose / 250micrograms/dose inhaler (Mylan Ltd)
LABA_ICS	10715041000033111	AirFluSal Forspiro 50micrograms/dose / 500micrograms/dose dry powder inhaler (Sandoz Ltd)

Drug Class	ProdCodeId	Term from EMIS
LABA_ICS	11899741000033117	Aerivio Spiromax 50micrograms/dose / 500micrograms/dose dry powder inhaler (Teva UK Ltd)
LABA_ICS	12046641000033114	Sereflo 25micrograms/dose / 125micrograms/dose inhaler (Kent Pharmaceuticals Ltd)
LABA_ICS	12197841000033113	AirFluSal 25micrograms/dose / 125micrograms/dose inhaler (Sandoz Ltd)
LABA_ICS	12046741000033117	Sereflo 25micrograms/dose / 250micrograms/dose inhaler (Kent Pharmaceuticals Ltd)
LABA_ICS	12197941000033117	AirFluSal 25micrograms/dose / 250micrograms/dose inhaler (Sandoz Ltd)
LABA_ICS	12370841000033110	Aloflute 25micrograms/dose / 125micrograms/dose inhaler (Mylan Ltd)
LABA_ICS	12370941000033119	Aloflute 25micrograms/dose / 250micrograms/dose inhaler (Mylan Ltd)
LABA_ICS	8946841000033112	Fluticasone furoate 184micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler
LABA_ICS	8946941000033116	Fluticasone furoate 92micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler
LABA_ICS	8947041000033115	Relvar Ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)
LABA_ICS	8947141000033116	Relvar Ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)
LABA_ICS	2587541000033118	Symbicort 100/6 Turbohaler (AstraZeneca UK Ltd)
LABA_ICS	2587641000033117	Symbicort 200/6 Turbohaler (AstraZeneca UK Ltd)
LABA_ICS	5140541000033119	Symbicort Turbuhaler 80/4.5 micrograms/dose
LABA_ICS	5140741000033110	Symbicort Turbuhaler 160/4.5 micrograms/dose
LABA_ICS	8028941000033114	Symbicort Turbuhaler 320/9 micrograms/dose
LABA_LAMA	9293241000033114	Umeclidinium bromide 65micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler
LABA_LAMA	9293341000033116	Anoro Ellipta 55micrograms/dose / 22micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)
LABA_LAMA	10589141000033112	Tiotropium bromide 2.5micrograms/dose / Olodaterol 2.5micrograms/dose solution for inhalation cartridge with device CFC free

Drug Class	ProdCodeId	Term from EMIS
LABA_LAMA	10589241000033117	Spiolto Respimat 2.5micrograms/dose / 2.5micrograms/dose solution for inhalation cartridge with device (Boehringer Ingelheim Ltd)
LABA_LAMA	9995741000033115	Duaklir 340micrograms/dose / 12micrograms/dose Genuair (AstraZeneca UK Ltd)
LABA_LAMA	9995641000033112	Aclidinium bromide 396micrograms/dose / Formoterol 11.8micrograms/dose dry powder inhaler
LAMA	2793541000033114	Tiotropium bromide 18microgram inhalation powder capsules with device
LAMA	2793641000033110	Tiotropium bromide 18microgram inhalation powder capsules
LAMA	2793741000033118	Spiriva 18microgram inhalation powder capsules with HandiHaler (Boehringer Ingelheim Ltd)
LAMA	4270641000033112	Tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device CFC free
LAMA	2793841000033111	Spiriva 18microgram inhalation powder capsules (Boehringer Ingelheim Ltd)
LAMA	4270741000033115	Spiriva Respimat 2.5micrograms/dose solution for inhalation cartridge with device (Boehringer Ingelheim Ltd)
LAMA	11789041000033118	Braltus 10microgram inhalation powder capsules with Zonda inhaler (Teva UK Ltd)
LAMA	11788941000033110	Tiotropium bromide 10microgram inhalation powder capsules with device
LAMA	8141741000033112	Glycopyrronium bromide 55microgram inhalation powder capsules with device
LAMA	8141841000033119	Seebri Breezhaler 44microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
LAMA	9703441000033119	Umeclidinium bromide 65micrograms/dose dry powder inhaler
LAMA	9703641000033117	Incruse Ellipta 55micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)
LAMA	8056941000033114	Aclidinium bromide 375micrograms/dose dry powder inhaler
LAMA	8057341000033112	Eklira 322micrograms/dose Genuair (AstraZeneca UK Ltd)
MUCOLYTICS	177041000033113	Carbocisteine 375mg capsules
MUCOLYTICS	208341000033117	Carbocisteine 125mg/5ml oral solution
MUCOLYTICS	208641000033113	Carbocisteine 250mg/5ml oral solution
MUCOLYTICS	941641000033113	Mucodyne 375mg capsules (Sanofi)
MUCOLYTICS	942941000033113	Mucodyne Paediatric 125mg/5ml syrup (Sanofi)

Drug Class	ProdCodeId	Term from EMIS
MUCOLYTICS	943341000033118	Mucodyne 250mg/5ml syrup (Sanofi)
MUCOLYTICS	10598741000033115	Carbocisteine 750mg/10ml oral solution 10ml sachets sugar free
MUCOLYTICS	11909241000033119	Mucodyne Paediatric 250mg/5ml syrup (Sanofi)
MUCOLYTICS	1524641000033117	Visclair 100mg gastro-resistant tablets (Ranbaxy (UK) Ltd)
MUCOLYTICS	3098941000033119	Mecysteine 100mg gastro-resistant tablets
MUCOLYTICS	5941000033115	Acetylcysteine 200mg granules sachets
MUCOLYTICS	4133741000033111	Acetylcysteine 600mg capsules
MUCOLYTICS	4199841000033114	Acetylcysteine 600mg tablets
MUCOLYTICS	4425341000033110	Acetylcysteine 600mg effervescent tablets
MUCOLYTICS	8048541000033118	Solgar NAC 600mg capsules (Solgar Vitamin and Herb)
MUCOLYTICS	8133041000033114	Siran 600mg effervescent tablets (Imported (Germany))
MUCOLYTICS	8233241000033116	OroNAC 600 tablets (Rhodes Pharma Ltd)
MUCOLYTICS	8233341000033114	OroNAC 600 capsules (Rhodes Pharma Ltd)
MUCOLYTICS	8299741000033115	ACC-600 effervescent tablets (Imported (Germany))
MUCOLYTICS	9109541000033113	Fluimucil 600 effervescent tablets (Imported (Austria))
MUCOLYTICS	11693541000033118	YourNAC 600mg capsules (Your Products Ltd)
MUCOLYTICS	11899941000033119	YourNAC 600mg tablets (Your Products Ltd)
MUCOLYTICS	12037041000033119	Acetylcysteine 200mg oral powder sachets sugar free
MUCOLYTICS	12315041000033116	Aceteff 600mg effervescent tablets (Dunelm Pharmaceuticals Ltd)
MUCOLYTICS	12315141000033117	Acetylcysteine 600mg effervescent tablets sugar free
MUCOLYTICS	10043841000033113	OroNAC 600 effervescent tablets (Rhodes Pharma Ltd)
MUCOLYTICS	1819241000033111	Saline nebuliser liquid 20ml unit dose Steripoule vials (Galen Ltd)
MUCOLYTICS	1751641000033115	Saline Steripoules nebuliser liquid 2.5ml unit dose ampoules (Galen Ltd)
MUCOLYTICS	1382141000033113	Saline 0.9% nebuliser liquid 2.5ml Steri-Neb unit dose ampoules (Teva UK Ltd)
MUCOLYTICS	10252141000033118	Sodium chloride 0.9% nebuliser liquid 2.5ml unit dose ampoules
MUCOLYTICS	6066641000033116	Sodium chloride 3% nebuliser liquid
MUCOLYTICS	5378441000033113	Sodium chloride 7% nebuliser liquid
MUCOLYTICS	6066541000033117	Sodium chloride 3% nebuliser liquid 10ml unit dose vials

Drug Class	ProdCodeId	Term from EMIS
MUCOLYTICS	4088041000033117	Sodium chloride 3% nebuliser liquid 20ml unit dose vials
MUCOLYTICS	4042841000033118	Sodium chloride 5% nebuliser liquid 20ml vials
MUCOLYTICS	3929941000033112	Sodium chloride 7% nebuliser liquid 5ml bottles
MUCOLYTICS	7861741000033115	Bronchitol 40mg inhalation powder capsules with two devices (Chiesi Ltd)
MUCOLYTICS	7861641000033112	Bronchitol 40mg inhalation powder capsules with device (Chiesi Ltd)
MUCOLYTICS	3985641000033111	Erdosteine 300mg capsules
MUCOLYTICS	3985741000033119	Erdotin 300mg capsules (Galen Ltd)
OCS	431541000033114	Deltacortril 2.5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)
OCS	431641000033110	Deltacortril 5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)
OCS	1114241000033116	Prednisolone 2.5mg gastro-resistant tablets
OCS	1114341000033114	Prednisolone 5mg gastro-resistant tablets
OCS	8494441000033110	Dilacort 2.5mg gastro-resistant tablets (Crescent Pharma Ltd)
OCS	8494541000033111	Dilacort 5mg gastro-resistant tablets (Crescent Pharma Ltd)
OCS	11507841000033115	Prednisolone 1mg gastro-resistant tablets
OCS	9119141000033118	Prednisolone 15mg/5ml oral solution
OCS	10266841000033117	Prednisolone 5mg/5ml oral solution unit dose
OCS	10494341000033117	Prednisolone 10mg/ml oral solution sugar free
OCS	1130741000033110	Prednisolone 25mg tablets
OCS	1131741000033117	Prednisolone 1mg tablets
OCS	1131841000033110	Prednisolone 2.5mg tablets
OCS	1131941000033119	Prednisolone 5mg tablets
OCS	10212141000033111	Prednisolone 10mg tablets
OCS	10212341000033114	Prednisolone 20mg tablets
OCS	10212441000033115	Pevanti 2.5mg tablets (AMCo)
OCS	10212541000033119	Pevanti 5mg tablets (AMCo)
OCS	10212641000033118	Pevanti 10mg tablets (AMCo)
OCS	10212741000033110	Pevanti 20mg tablets (AMCo)
OCS	10212941000033113	Pevanti 25mg tablets (AMCo)

Drug Class	ProdCodeId	Term from EMIS
OCS	11664841000033116	Prednisolone 30mg tablets
OCS	2509341000033118	*Prednisolone Tablets
OCS	1130841000033117	Prednisolone Steaglate Tablets 6.65 mg
OCS	2509741000033117	*Prednisolone Pills (Sucrose)
OCS	10988941000033111	Prednisolone Dompe Oral solution 5 mg/5 ml unit dose
OCS	1127341000033111	Prednisolone 5mg soluble tablets
OCS	1132041000033113	Prednisone Tablets 1 mg
OCS	1132141000033112	Prednisone Tablets 5 mg
OCS	5990141000033115	Prednisone 1mg modified-release tablets
OCS	5990241000033110	Prednisone 2mg modified-release tablets
OCS	5990341000033117	Prednisone 5mg modified-release tablets
OCS	5990641000033113	Lodotra 1mg modified-release tablets (Napp Pharmaceuticals Ltd)
OCS	5990741000033116	Lodotra 2mg modified-release tablets (Napp Pharmaceuticals Ltd)
OCS	5990841000033114	Lodotra 5mg modified-release tablets (Napp Pharmaceuticals Ltd)
SABA	116241000033112	Bambec 10mg tablets (AstraZeneca UK Ltd)
SABA	116341000033119	Bambec 20mg tablets (AstraZeneca UK Ltd)
SABA	116441000033113	Bambuterol 10mg tablets
SABA	116541000033114	Bambuterol 20mg tablets
SABA	130441000033115	Berotec 200micrograms/dose inhaler (Boehringer Ingelheim Ltd)
SABA	567541000033119	Fenoterol 200micrograms/dose inhaler
SABA	20041000033117	Aerolin 100micrograms/dose Autohaler (3M Health Care Ltd)
SABA	20441000033114	Aerocrom inhaler (Castlemead Healthcare Ltd)
SABA	20541000033110	Aerocrom Syncroner with spacer (Castlemead Healthcare Ltd)
SABA	22741000033118	Airomir 100micrograms/dose inhaler (Teva UK Ltd)
SABA	82541000033119	Asmasal 95micrograms/dose Clickhaler (Focus Pharmaceuticals Ltd)
SABA	1221441000033112	Salbutamol 100micrograms/dose breath actuated inhaler
SABA	1222341000033110	Salbutamol 100micrograms/dose inhaler CFC free
SABA	1228841000033115	Salbutamol 200microgram inhalation powder blisters with device

Drug Class	ProdCodeId	Term from EMIS
SABA	1228941000033111	Salbutamol 400microgram inhalation powder blisters with device
SABA	1241341000033116	Salbulin 100micrograms/dose inhaler (3M Health Care Ltd)
SABA	1241441000033110	Salbutamol 100micrograms/dose inhaler
SABA	1241641000033112	Salbutamol 500micrograms/1ml solution for injection ampoules
SABA	1242941000033112	Salbutamol 5mg/5ml solution for infusion ampoules
SABA	1245741000033117	Salbutamol 5mg/2.5ml nebuliser liquid unit dose vials
SABA	1246041000033112	Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials
SABA	1250141000033112	Salbutamol 200microgram inhalation powder blisters
SABA	1250241000033117	Salbutamol 400microgram inhalation powder blisters
SABA	1250341000033110	Salbutamol 5mg/ml nebuliser liquid
SABA	1255441000033110	Salbutamol 4mg modified-release tablets
SABA	1255541000033111	Salbutamol 8mg modified-release tablets
SABA	1256141000033114	Salbutamol 2mg/5ml oral solution sugar free
SABA	1257641000033118	Salbutamol 2mg tablets
SABA	1257741000033110	Salbutamol 4mg tablets
SABA	1381841000033111	Salamol 2.5mg/2.5ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
SABA	1381941000033115	Salamol 5mg/2.5ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
SABA	1505741000033119	Ventolin 200micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
SABA	1505841000033112	Ventide inhaler (GlaxoSmithKline UK Ltd)
SABA	1506841000033119	Ventodisks 200microgram with Diskhaler (GlaxoSmithKline UK Ltd)
SABA	1506941000033110	Ventodisks 400microgram with Diskhaler (GlaxoSmithKline UK Ltd)
SABA	1508241000033119	Ventolin 500micrograms/1ml solution for injection ampoules (GlaxoSmithKline UK Ltd)
SABA	1508941000033111	Ventolin 5mg/5ml solution for infusion ampoules (GlaxoSmithKline UK Ltd)
SABA	1509541000033112	Ventolin 2.5mg Nebules (GlaxoSmithKline UK Ltd)
SABA	1509641000033113	Ventolin 5mg Nebules (GlaxoSmithKline UK Ltd)
SABA	1510241000033118	Ventolin 5mg/ml respirator solution (GlaxoSmithKline UK Ltd)
SABA	1510341000033111	Ventodisks 200microgram (GlaxoSmithKline UK Ltd)

Drug Class	ProdCodeId	Term from EMIS
SABA	1510441000033117	Ventodisks 400microgram (GlaxoSmithKline UK Ltd)
SABA	1510541000033116	Ventolin 200microgram Rotacaps (GlaxoSmithKline UK Ltd)
SABA	1510641000033115	Ventolin 400microgram Rotacaps (GlaxoSmithKline UK Ltd)
SABA	1510841000033119	Ventide Paediatric Rotacaps (GlaxoSmithKline UK Ltd)
SABA	1511041000033117	Ventide Rotacaps (GlaxoSmithKline UK Ltd)
SABA	1512041000033110	Ventolin 2mg/5ml syrup (GlaxoSmithKline UK Ltd)
SABA	1526541000033113	Volmax 4mg modified-release tablets (GlaxoSmithKline UK Ltd)
SABA	1526641000033114	Volmax 8mg modified-release tablets (GlaxoSmithKline UK Ltd)
SABA	1682141000033115	Salbutamol 4mg modified-release capsules
SABA	1682241000033110	Salbutamol 8mg modified-release capsules
SABA	1705441000033110	Ventolin 100micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
SABA	1705641000033112	Ventmax SR 4mg capsules (Chiesi Ltd)
SABA	1705741000033115	Ventmax SR 8mg capsules (Chiesi Ltd)
SABA	1714241000033112	Airomir 100micrograms/dose Autohaler (Teva UK Ltd)
SABA	1741541000033119	Maxivent 2.5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Ashbourne Pharmaceuticals Ltd)
SABA	1741641000033118	Maxivent 5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Ashbourne Pharmaceuticals Ltd)
SABA	1751341000033111	Salbutamol 100micrograms/dose breath actuated inhaler CFC free
SABA	1905641000033119	Salbutamol 200microgram inhalation powder capsules
SABA	1905741000033111	Salbutamol 400microgram inhalation powder capsules
SABA	1907541000033112	Salbutamol 200micrograms/dose dry powder inhaler
SABA	2086541000033119	Salamol 100micrograms/dose inhaler CFC free (Teva UK Ltd)
SABA	2174141000033117	Salbutamol 95micrograms/dose dry powder inhaler
SABA	2588241000033119	Salamol 100micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
SABA	2622741000033114	Pulvinal Salbutamol 200micrograms/dose dry powder inhaler (Chiesi Ltd)
SABA	2640741000033111	Salapin 2mg/5ml syrup (Pinewood Healthcare)
SABA	2726241000033113	Salbutamol 200 Cyclocaps (Teva UK Ltd)

Drug Class	ProdCodeId	Term from EMIS
SABA	2726341000033115	Salbutamol 400 Cyclocaps (Teva UK Ltd)
SABA	3198541000033119	Easyhaler Salbutamol sulfate 100micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
SABA	3198641000033118	Easyhaler Salbutamol sulfate 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
SABA	3343941000033118	Salbutamol 100micrograms/dose dry powder inhaler
SABA	4498841000033119	Salbutamol 100micrograms/dose dry powder inhalation cartridge with device
SABA	4498941000033110	Salbutamol 100micrograms/dose dry powder inhalation cartridge
SABA	5393141000033116	Salbulin Novolizer 100micrograms/dose inhalation powder (Meda Pharmaceuticals Ltd)
SABA	5393241000033111	Salbulin Novolizer 100micrograms/dose inhalation powder refill (Meda Pharmaceuticals Ltd)
SABA	6029541000033117	Asmavent 100micrograms/dose inhaler CFC free (Kent Pharmaceuticals Ltd)
SABA	6116941000033117	Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
SABA	6117041000033116	Salbutamol 5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
SABA	8491641000033114	AirSalb 100micrograms/dose inhaler CFC free (Sandoz Ltd)
SABA	158441000033117	Bricanyl 250micrograms/dose inhaler (AstraZeneca UK Ltd)
SABA	158541000033116	Bricanyl 500micrograms/1ml solution for injection ampoules (AstraZeneca UK Ltd)
SABA	160041000033119	Bricanyl 5mg/2ml Respules (AstraZeneca UK Ltd)
SABA	160341000033117	Bricanyl 10mg/ml respirator solution (AstraZeneca UK Ltd)
SABA	160941000033118	Bricanyl 250micrograms/dose spacer inhaler (AstraZeneca UK Ltd)
SABA	161141000033110	Bricanyl 1.5mg/5ml syrup (AstraZeneca UK Ltd)
SABA	162141000033119	Bricanyl 5mg tablets (AstraZeneca UK Ltd)
SABA	162241000033114	Bricanyl SA 7.5mg tablets (AstraZeneca UK Ltd)
SABA	163641000033116	Bricanyl 500micrograms/dose Turbohaler (AstraZeneca UK Ltd)
SABA	934741000033118	Monovent 1.5mg/5ml syrup (Sandoz Ltd)
SABA	1419341000033114	Terbutaline 250micrograms/dose inhaler
SABA	1419441000033115	Terbutaline 500micrograms/1ml solution for injection ampoules

Drug Class	ProdCodeId	Term from EMIS
SABA	1422641000033118	Terbutaline 10mg/ml nebuliser liquid
SABA	1423441000033112	Terbutaline 250micrograms/dose inhaler with spacer
SABA	1424341000033115	Terbutaline 1.5mg/5ml oral solution sugar free
SABA	1426741000033111	Terbutaline 5mg tablets
SABA	1426841000033118	Terbutaline 7.5mg modified-release tablets
SABA	1579641000033117	Bricanyl 2.5mg/5ml solution for injection ampoules (AstraZeneca UK Ltd)
SABA	1699041000033114	Terbutaline 500micrograms/dose dry powder inhaler
SABA	1699541000033116	Terbutaline 2.5mg/5ml solution for injection ampoules
SABA	1915441000033119	Terbutaline 5mg/2ml nebuliser liquid unit dose vials
SABA	1513541000033111	Ventolin Cr S/r tablets 8 mg
SABA	1513441000033110	Ventolin Cr S/r tablets 4 mg
SABA	1512641000033116	Ventolin Tablets 4 mg
SABA	1512541000033117	Ventolin Tablets 2 mg
SABA	1511441000033114	Ventolin Spandets 8 mg
SABA	1510741000033112	Ventolin Rotahaler (GlaxoSmithKline UK Ltd)
SABA	1508041000033110	Ventolin Inhaler 100 micrograms/puff
SABA	1505941000033116	Ventolin Easi-Breathe Breath-actuated inhaler 100 micrograms/puff
SABA	1206041000033115	Salbutamol Accuhaler 200 micrograms/dose
SABA	1206241000033111	Salbutamol Aerosol inhalation 100 micrograms/metered inhalation
SABA	1207741000033115	Salbutamol Autohaler 100 micrograms/puff
SABA	1221541000033113	Salbutamol Breath-actuated inhaler 95 micrograms/dose
SABA	1228341000033112	Salbutamol Cyclocaps 200 micrograms
SABA	1228441000033118	Salbutamol Cyclocaps 400 micrograms
SABA	1241941000033117	Salbutamol Inhaler with vortex generating actuator 100 micrograms/dose
SABA	1245941000033119	Salbutamol Nebules 0.1 %
SABA	1252241000033118	Salbutamol Rotacaps 200 micrograms
SABA	1252341000033111	Salbutamol Rotacaps 400 micrograms
SABA	1252441000033117	Salbutamol Rotahaler 1

Drug Class	ProdCodeId	Term from EMIS
SABA	1255041000033118	Salbutamol Spacehaler 100 micrograms/puff
SABA	1903141000033113	Salbutamol Dry powder breath-actuated inhaler 95 micrograms/dose
SABA	1907341000033117	Salbutamol Dry powder disks + disk inhaler 200 micrograms
SABA	1907441000033111	Salbutamol Dry powder disks + disk inhaler 400 micrograms
SABA	1907641000033113	Salbutamol Dry powder for inhalation 400 micrograms/dose
SABA	1913441000033115	Salbutamol Dry powder breath-actuated inhaler 200 micrograms
SABA	2864041000033119	Salbutamol Breath Actuated Pressurised Inhalation 100 micrograms/actuation
SABA	2952141000033110	Salbutamol Breath Actuated Pressurised Inhalation, Cfc-free 100 micrograms/actuation
SABA	3344041000033116	Salbutamol Dry Powder Inhaler 200 micrograms/actuation, 200 dose
SABA_SAMA	330241000033113	Combivent inhaler (Boehringer Ingelheim Ltd)
SABA_SAMA	1818641000033117	Combivent nebuliser liquid 2.5ml UDVs (Boehringer Ingelheim Ltd)
SABA_SAMA	3163441000033113	Salbutamol 100micrograms/dose / Ipratropium 20micrograms/dose inhaler
SABA_SAMA	3163541000033114	Salbutamol 2.5mg/2.5ml / Ipratropium bromide 500micrograms/2.5ml nebuliser liquid unit dose vials
SABA_SAMA	4023941000033117	Ipramol nebuliser solution 2.5ml Steri-Neb unit dose vials (Teva UK Ltd)
SABA_SAMA	5098641000033116	Salipraneb 0.5mg/2.5mg nebuliser solution 2.5ml ampoules (Actavis UK Ltd)
SABA_SAMA	5098441000033118	Salbutamol 2.5mg/2.5ml / Ipratropium bromide 500micrograms/2.5ml nebuliser liquid ampoules
SABA_SAMA	485841000033117	Duovent Autohaler (Boehringer Ingelheim Ltd)
SABA_SAMA	488041000033119	Duovent inhaler (Boehringer Ingelheim Ltd)
SABA_SAMA	491541000033117	Duovent UDVs nebuliser liquid 4ml (Boehringer Ingelheim Ltd)
SABA_SAMA	1860741000033110	Fenoterol 100micrograms/dose / Ipratropium 40micrograms/dose inhaler
SABA_SAMA	3163641000033110	Fenoterol 1.25mg/4ml / Ipratropium 500micrograms/4ml nebuliser liquid unit dose vials
SAMA	88241000033118	Atrovent 20micrograms/dose inhaler (Boehringer Ingelheim Ltd)
SAMA	88341000033111	Atrovent 40microgram Aerocaps (Boehringer Ingelheim Ltd)
SAMA	88441000033117	Atrovent 40microgram Aerocaps with Aerohaler (Boehringer Ingelheim Ltd)

Drug Class	ProdCodeId	Term from EMIS
SAMA	88541000033116	Atrovent 20micrograms/dose Autohaler (Boehringer Ingelheim Ltd)
SAMA	89441000033110	Atrovent Forte 40micrograms/dose inhaler (Boehringer Ingelheim Ltd)
SAMA	90041000033110	Atrovent 500micrograms/2ml nebuliser liquid UDVs (Boehringer Ingelheim Ltd)
SAMA	772541000033111	Ipratropium bromide 40micrograms/dose inhaler
SAMA	772641000033112	Ipratropium bromide 20micrograms/dose inhaler
SAMA	772841000033113	Ipratropium bromide 20micrograms/dose breath actuated inhaler
SAMA	772941000033117	Ipratropium bromide 40microgram inhalation powder capsules
SAMA	773041000033110	Ipratropium bromide 40microgram inhalation powder capsules with device
SAMA	773341000033112	Ipratropium bromide 21micrograms/dose nasal spray
SAMA	773741000033113	Ipratropium 250micrograms/1ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
SAMA	773841000033115	Ipratropium 500micrograms/2ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
SAMA	773941000033111	Ipratropium bromide 500micrograms/2ml nebuliser liquid unit dose vials
SAMA	1174241000033111	Rinatec 21micrograms/dose nasal spray (Boehringer Ingelheim Ltd)
SAMA	1672141000033113	Respontin 250micrograms/1ml Nebules (GlaxoSmithKline UK Ltd)
SAMA	1672241000033118	Respontin 500micrograms/2ml Nebules (GlaxoSmithKline UK Ltd)
SAMA	1702541000033116	Tropiovent 250micrograms/1ml nebuliser liquid unit dose Steripoule vials (Ashbourne Pharmaceuticals Ltd)
SAMA	1702641000033115	Tropiovent 500micrograms/2ml nebuliser liquid unit dose Steripoule vials (Ashbourne Pharmaceuticals Ltd)
SAMA	3075441000033112	Ipratropium bromide 20micrograms/dose inhaler CFC free
SAMA	3075541000033113	Atrovent 20micrograms/dose inhaler CFC free (Boehringer Ingelheim Ltd)
SAMA	4519441000033116	Ipratropium 250micrograms/1ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
SAMA	4958441000033114	Ipratropium bromide 250micrograms/1ml nebuliser liquid unit dose vials
SAMA	4958541000033110	Atrovent 250micrograms/1ml nebuliser liquid UDVs (Boehringer Ingelheim Ltd)
SAMA	5072941000033118	Ipratropium 500micrograms/2ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
SAMA	773641000033116	Ipratropium Bromide Nebuliser solution 250 micrograms/ml

Drug Class	ProdCodeId	Term from EMIS
SAMA	1022241000033110	Oxitropium Bromide Autohaler 100 micrograms/puff
SAMA	1024041000033114	Oxitropium bromide 100micrograms/dose inhaler
SAMA	1022141000033115	Oxivent 100micrograms/dose Autohaler (Boehringer Ingelheim Ltd)
SAMA	1024141000033113	Oxivent 100micrograms/dose inhaler (Boehringer Ingelheim Ltd)
THEOPH	51841000033118	Aminophylline hydrate 225mg modified-release tablets
THEOPH	54341000033112	Amnivent-225 SR tablets (Ashbourne Pharmaceuticals Ltd)
THEOPH	57441000033114	Aminophylline 100mg tablets
THEOPH	59941000033110	Aminophylline hydrate 350mg modified-release tablets
THEOPH	61441000033113	Aminophylline 225mg modified-release tablets
THEOPH	1076441000033111	Phyllocontin Paediatric Continus 100mg tablets (Napp Pharmaceuticals Ltd)
THEOPH	1080341000033111	Phyllocontin Continus 225mg tablets (Napp Pharmaceuticals Ltd)
THEOPH	1080441000033117	Phyllocontin Forte Continus 350mg tablets (Napp Pharmaceuticals Ltd)
THEOPH	2105141000033110	Norphyllin SR 225mg tablets (Teva UK Ltd)
THEOPH	1346041000033119	Slo-Phyllin 125mg capsules (Merck Serono Ltd)
THEOPH	1346141000033115	Slo-Phyllin 250mg capsules (Merck Serono Ltd)
THEOPH	1346241000033110	Slo-Phyllin 60mg capsules (Merck Serono Ltd)
THEOPH	1429541000033111	Theophylline 125mg modified-release capsules
THEOPH	1429641000033112	Theophylline 250mg modified-release capsules
THEOPH	1429741000033115	Theophylline 60mg modified-release capsules
THEOPH	993641000033117	Nuelin SA 175mg tablets (Meda Pharmaceuticals Ltd)
THEOPH	993941000033112	Nuelin SA 250 tablets (Meda Pharmaceuticals Ltd)
THEOPH	1432941000033110	Theophylline 200mg modified-release tablets
THEOPH	1433041000033117	Theo-Dur 200mg tablets (AstraZeneca UK Ltd)
THEOPH	1433141000033118	Theo-Dur 300mg tablets (AstraZeneca UK Ltd)
THEOPH	1433541000033110	Theophylline 175mg modified-release tablets
THEOPH	1436041000033110	Theophylline 400mg modified-release tablets
THEOPH	1436141000033114	Theophylline 300mg modified-release tablets
THEOPH	1489341000033112	Uniphyllin Continus 200mg tablets (Napp Pharmaceuticals Ltd)

Drug Class	ProdCodeId	Term from EMIS
THEOPH	1490441000033110	Uniphyllin Continus 300mg tablets (Napp Pharmaceuticals Ltd)
THEOPH	1490641000033112	Uniphyllin Continus 400mg tablets (Napp Pharmaceuticals Ltd)
THEOPH	1830241000033110	Theophylline 250mg modified-release tablets
THEOPH	992241000033110	Nuelin 60mg/5ml liquid (3M Health Care Ltd)
THEOPH	1431441000033113	Theophylline 60mg/5ml oral solution
THEOPH	9203041000033115	Theophylline 50mg/5ml oral solution
THEOPH	993541000033118	Nuelin 125mg tablets (3M Health Care Ltd)
THEOPH	1434741000033116	Theophylline 125mg tablets
THEOPH	48141000033117	Aminophylline Injection 25 mg/1 ml
THEOPH	48241000033112	Aminophylline Injection 250 mg/1 ml
THEOPH	49741000033110	Aminophylline 250mg/10ml solution for injection ampoules
THEOPH	53241000033116	Aminophylline Paediatric tablets 100 mg
THEOPH	54541000033117	Aminophylline Suppositories 100 mg
THEOPH	54641000033116	Aminophylline Suppositories 150 mg
THEOPH	54741000033113	Aminophylline Suppositories 180 mg
THEOPH	54841000033115	Aminophylline Suppositories 360 mg
THEOPH	54941000033111	Aminophylline Suppositories 50 mg
THEOPH	57541000033110	Aminophylline Tablets 225 mg
THEOPH	3984041000033118	Aminophylline 250mg/10ml solution for injection pre-filled syringes
THEOPH	3984141000033119	Aminophylline 250mg/10ml solution for injection Minijet pre-filled syringes (UCB Pharma Ltd)
THEOPH	1429841000033113	Theophylline Capsules 300 mg
THEOPH	1429941000033117	Theophylline S/R Capsules 300 mg
THEOPH	1431741000033118	Theophylline Paediatric tablets 200 mg
THEOPH	1432641000033115	Theophylline Hydrate Syrup 125 mg/5 ml
THEOPH	1433441000033114	Theophylline Tablets 120 mg
THEOPH	1434841000033114	Theophylline Tablets 200 mg
THEOPH	1434941000033118	Theophylline Tablets 300 mg

Drug Class	ProdCodeId	Term from EMIS
THEOPH	1435041000033118	Theophylline Tablets 350 mg
THEOPH	1435141000033119	Theophylline Tablets 400 mg
THEOPH	1435541000033111	Theophylline Tablets 250 mg
THEOPH	1436641000033116	Theophylline S/R Tablets 500 mg

R. Intestitial Lung Disease Codes (CPRD GOLD)

medcode	Term
106515	[X]Hypersensitivity pneumonitis due to other organic dusts
65060	[X]Other interstitial pulmonary diseases with fibrosis
53095	Allergic alveolitis and pneumonitis NOS
46977	Allergic alveolitis and pneumonitis NOS
62442	Allergic extrinsic alveolitis NOS
8303	Asbestosis
51410	Asbestosis NOS
22835	Bronchiolitis obliterans organising pneumonia
37365	Byssinosis
47782	Chronic pulmonary fibrosis due to chemical fumes
22536	Chronic pulmonary fibrosis following radiation
71853	Complicated silicosis
5519	cryptogenic fibrosing alveolitis
103475	Cryptogenic organising pneumonia
6051	Diffuse pulmonary fibrosis
28853	fibrosing alveolitis associated with rheumatoid arthritis
11833	Hypersensitivity pneumonitis NOS
6837	idiopathic fibrosing alveolitis
28229	idiopathic fibrosing alveolitis nos
103753	Idiopathic pulmonary fibrosis
109815	Interstitial lung disease due to collagen vascular disease
104915	Interstitial lung disease due to connective tissue disease
8317	Interstitial lung disease NEC
4910	Interstitial pneumonia
55552	Other allergic alveolitis NOS
7791	Postinflammatory pulmonary fibrosis
103472	Pulmonary fibrosis
3859	Pulmonary sarcoidosis
103785	Respiratory bronchiolitis associated interstitial lung dis
64799	Rheumatic pneumonia
33980	Sarcoidosis of lung
58841	Sarcoidosis of lung with sarcoidosis of lymph nodes
62233	Simple silicosis

S. Intestitial Lung Disease Codes (CPRD Aurum)

medcodeid	Term
301841015	[X]Hypersensitivity pneumonitis due to other organic dusts
301852014	[X]Other interstitial pulmonary diseases with fibrosis
477131000006116	Allergic alveolitis and pneumonitis NOS
301532018	Allergic alveolitis and pneumonitis NOS
301533011	Allergic extrinsic alveolitis NOS
37941013	Asbestosis
301552017	Asbestosis NOS
474828010	Bronchiolitis obliterans organising pneumonia
142162019	Byssinosis
301575012	Chronic pulmonary fibrosis due to chemical fumes
556271000006115	Chronic pulmonary fibrosis following radiation
83019014	Complicated silicosis
196654011	Cryptogenic fibrosing alveolitis
474819014	Cryptogenic organising pneumonia
621121000006112	Diffuse pulmonary fibrosis
311496011	Fibrosing alveolitis associated with rheumatoid arthritis
301534017	Hypersensitivity pneumonitis NOS
75302014	Idiopathic fibrosing alveolitis
301709019	Idiopathic fibrosing alveolitis NOS
1786131000006116	Idiopathic pulmonary fibrosis
2676188013	Interstitial lung disease due to collagen vascular disease
1747711000000111	Interstitial lung disease due to connective tissue disease
301758015	Interstitial lung disease NEC
107470010	Interstitial pneumonia
301531013	Other allergic alveolitis NOS
211391000006118	Postinflammatory pulmonary fibrosis
85960018	Pulmonary fibrosis
40879015	Pulmonary sarcoidosis
1786171000006118	Respiratory bronchiolitis associated interstitial lung dis
13455018	Rheumatic pneumonia
1223250017	Sarcoidosis of lung
287930013	Sarcoidosis of lung with sarcoidosis of lymph nodes
79212010	Simple silicosis

T. Intestitial Lung Disease Codes (HES/ONS)

ICD-10 Code	Term
J84	Other interstitial pulmonary diseases
J84.0	Alveolar and parietoalveolar conditions
J84.1	Other interstitial pulmonary diseases with fibrosis
J84.8	Other specified interstitial pulmonary diseases
J84.9	Interstitial pulmonary disease unspecified
J70.4	Drug-induced interstitial lung disorders unspecified
J70.2	Acute drug-induced interstitial lung disorders
J70.3	Chronic drug-induced interstitial lung disorders
J60	Coalworker pneumoconiosis
J61	Pneumoconiosis due to asbestos and other mineral fibres
J62	Pneumoconiosis due to dust containing silica
J62.0	Pneumoconiosis due to talc dust
J62.8	Pneumoconiosis due to other dust containing silica
J63	Pneumoconiosis due to other inorganic dusts
J63.0	Aluminosis (of lung)
J63.1	Bauxite fibrosis (of lung)
J63.2	Berylliosis
J63.3	Graphite fibrosis (of lung)
J63.4	Siderosis
J63.5	Stannosis
J63.8	Pneumoconiosis due to other specified inorganic dusts
J64	Unspecified pneumoconiosis
J65	Pneumoconiosis associated with tuberculosis
J66	Airway disease due to specific organic dust
J66.0	Byssinosis (airway disease due to cotton dust)
J66.1	Flax-dresser disease
J66.2	Cannabinosis
J66.8	Airway disease due to other specific organic dusts
J67	Hypersensitivity pneumonitis due to organic dust
J67.0	Farmer lung
J67.1	Bagassosis
J67.2	Bird fancier lung
J67.3	Suberosis
J67.4	Maltworker lung
J67.5	Mushroom-worker lung
J67.6	Maple-bark-stripper lung
J70.0	Acute pulmonary manifestations due to radiation
J70.1	Chronic and other pulmonary manifestations due to radiation
J70.2	Acute drug-induced interstitial lung disorders
J70.3	Chronic drug-induced interstitial lung disorders
J70.4	Drug-induced interstitial lung disorders, unspecified
C96.6	Unifocal Langerhans-cell histiocytosis
D86	Sarcoidosis
D86.0	Sarcoidosis of lung

D86.2	Sarcoidosis of lung with sarcodoisis of lymph nodes
J98.2	Interstitial emphysema
J98.4	Other disorders of the lung
J99	Respiratory disorders in diseases classified elsewhere
J99.0	Rheumatoid lung disease (M05.1†)

U. Bronchiectasis Codes (CPRD GOLD)

medcode	Term
2195	bronchiectasis
15693	tuberculous bronchiectasis
20364	recurrent bronchiectasis
32679	bronchiectasis nos
41491	post-infective bronchiectasis
56427	congenital bronchiectasis
109816	h/o: bronchiectasis

V. Bronchiectasis Codes (CPRD Aurum)

MedCodeId	Term
38677017	Tuberculous bronchiectasis
301524014	Recurrent bronchiectasis
301525010	Post-infective bronchiectasis
128792019	Congenital bronchiectasis
1854831000006111	Cystic fibrosis manifested by bronchiectasis
2404941000000118	H/O: bronchiectasis
21163015	Bronchiectasis
301526011	Bronchiectasis NOS

W. Bronchiectasis Codes (HES/ONS)

ICD-10 Code	Term
J47	Bronchiectasis
Q33.4	Congenital bronchiectasis
E84	Cystic fibrosis
E84.0	Cystic fibrosis with pulmonary manifestations
E84.1	Cystic fibrosis with intestinal manifestations
E84.8	Cystic fibrosis with other manifestations
E84.9	Cystic fibrosis, unspecified
Q33.0	Congenital cystic lung

X. Heart Failure Codes (CPRD GOLD)

medcode	Term
398	congestive heart failure
884	left ventricular failure
2062	heart failure
2906	congestive cardiac failure
12627	seen in heart failure clinic
8966	Left ventricular systolic dysfunction
4024	heart failure nos
17851	heart failure follow-up
12366	congestive heart failure monitoring
30779	heart failure annual review
1223	cardiac failure
9913	heart failure confirmed
13189	New York Heart Association classification - class II
11284	Echocardiogram shows left ventricular systolic dysfunction
5942	impaired left ventricular function
7251	Impaired Left Ventricular Function
18853	New York Heart Association classification - class I
19066	New York Heart Association classification - class III
12550	Left ventricular diastolic dysfunction
5255	acute left ventricular failure
83502	heart failure 6 month review
32671	chronic congestive heart failure
32945	heart failure care plan discussed with patient
11351	Echocardiogram shows left ventricular diastolic dysfunction
24503	Cardiac failure therapy
27884	decompensated cardiac failure
107397	Left ventricular cardiac dysfunction
103732	has heart failure management plan
17278	cardiac failure nos
23707	acute congestive heart failure
27964	acute heart failure
26242	New York Heart Assoc classification heart failure symptoms
51214	New York Heart Association classification - class IV
101138	heart failure with normal ejection fraction
32898	admit heart failure emergency
11424	compensated cardiac failure
106897	heart failure with preserved ejection fraction
101137	hfnef - heart failure with normal ejection fraction
94870	congestive heart failure due to valvular disease
106008	heart failure clinical pathway
62718	hypertensive heart disease nos with ccf

medcode	Term
21837	hypertensive heart&renal dis wth (congestive) heart failure
52127	benign hypertensive heart disease with ccf
57987	Hyperten heart&renal dis+both(congestv)heart and renal fail
105542	preferred place of care for next exacerbation heart failure
72668	malignant hypertensive heart disease with ccf
66306	heart failure as a complication of care
22262	Rheumatic left ventricular failure
9524	Biventricular failure
10079	Right heart failure
10154	Right ventricular failure
104275	Right ventricular failure
5695	Chronic cor pulmonale
8464	Acute cor pulmonale

Y. Heart Failure Codes (CPRD Aurum)

medcodeid	Term
1488804017	Heart failure confirmed
784191000006110	Impaired left ventricular function
2159197017	Echocardiogram shows left ventricular systolic dysfunction
2159198010	Echocardiogram shows left ventricular diastolic dysfunction
216184014	Congestive heart failure monitoring
1484918019	Heart failure annual review
2616470012	New York Heart Association classification - class I
2616471011	New York Heart Association classification - class II
2616472016	New York Heart Association classification - class III
2616473014	New York Heart Association classification - class IV
404741000000119	Heart failure 6 month review
451426015	Cardiac failure therapy
308301000000118	Heart failure care plan discussed with patient
1746171000000119	Has heart failure management plan
2205951000000117	Heart failure clinical pathway
1784061000006118	Preferred place of care for next exacerbation heart failure
2549208013	Admit heart failure emergency
1484917012	Heart failure follow-up
2549243014	Seen in heart failure clinic
72934016	Rheumatic left ventricular failure
728671000006119	Malignant hypertensive heart disease with CCF
504901000006118	Benign hypertensive heart disease with CCF
741681000006111	Hypertensive heart disease NOS with CCF
741701000006114	Hypertensive heart&renal dis wth (congestive) heart failure
789941000006117	Hyperten heart&renal dis+both(congestv)heart and renal fail
82584011	Acute cor pulmonale

medcodeid	Term
132655012	Chronic cor pulmonale
139475013	Heart failure
139482012	Cardiac failure
70653017	Congestive heart failure
493287011	Congestive cardiac failure
206703015	Right heart failure
490972013	Right ventricular failure
510016018	Biventricular failure
18472010	Acute congestive heart failure
147247018	Chronic congestive heart failure
300179017	Decompensated cardiac failure
300180019	Compensated cardiac failure
2675255018	Congestive heart failure due to valvular disease
141306010	Left ventricular failure
411506018	Impaired left ventricular function
300190010	Acute left ventricular failure
94251011	Acute heart failure
1647701000000118	Heart failure with normal ejection fraction
1661371000000112	HFNEF - heart failure with normal ejection fraction
2227501000000110	Heart failure with preserved ejection fraction
1816101000006113	Right ventricular failure
395772015	Heart failure NOS
223981000000118	Cardiac failure NOS
216207010	Left ventricular systolic dysfunction
1489358014	Left ventricular diastolic dysfunction
2694523019	Left ventricular cardiac dysfunction
350484012	Heart failure as a complication of care

Z. Heart Failure Codes (HES/ONS)

ICD-10 Code	Term
I50.0	Congestive heart failure
I50.1	Left ventricular failure
I50.9	Heart failure, unspecified
I50.2	Systolic (congestive) heart failure
I50.3	Diastolic (congestive) heart failure
I50.4	Combined systolic (congestive) and diastolic (congestive) heart failure
I11.0	Hypertensive heart disease with (congestive) heart failure
I13.0	Hypertensive heart and renal disease with (congestive) heart failure
I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
I25.5	Ischaemic cardiomyopathy

AA. Charlson Comorbidity Index (CPRD GOLD)

Category	Score
Any malignancy	2
Cerebrovascular disease	1
Chronic pulmonary disease	1
Congestive heart failure	1
Dementia	1
Diabetes (uncomplicated)	1
Diabetes with end-organ damage	2
Hemiplegia or paraplegia	2
HIV/AIDS	4
Metastatic solid tumour	4
Mild liver disease	1
Moderate or severe liver disease	3
Myocardial infarction	1
Peptic ulcer disease	1
Peripheral vascular disease	1
Renal disease	2
Rheumatic disease	1

BB. Flu Codes (CPRD GOLD)

medcode	readterm
29457	Chest infection - influenza with pneumonia
556	Influenza
15912	Influenza with pneumonia
13573	Influenza with bronchopneumonia
62632	Influenza with pneumonia, influenza virus identified
35745	Influenza with pneumonia NOS
43625	Influenza with other respiratory manifestation
15774	Influenza with laryngitis
29617	Influenza with pharyngitis
23488	Influenza with respiratory manifestations NOS
47472	Influenza with other manifestations
46157	Influenza with encephalopathy
14791	Influenza with gastrointestinal tract involvement
31363	Influenza with other manifestations NOS
16388	Influenza NOS
98129	Influenza due to Influenza A virus subtype H1N1
98102	Influenza A (H1N1) swine flu
11849	Other specified pneumonia or influenza
6094	Pneumonia or influenza NOS
97936	[X]Influenza+other manifestations,influenza virus identified
97605	[X]Influenza+oth respiratory manifestatns,virus not identifd
97279	[X]Influenza+other manifestations, virus not identified
98143	Influenza A virus H1N1 subtype detected
101845	Influenza A virus subtype H1N1 serology
96019	Influenza H1 virus detected
102918	Influenza H2 virus detected
96018	Influenza H3 virus detected
98156	Influenza H5 virus detected
97062	Influenza A virus, other or untyped strain detected
96017	Influenza B virus detected
96286	Human parainfluenza virus detected
28610	Haemophilus influenzae septicaemia
7714	Haemophilus influenzae infection
40253	H influenzae as cause/diseases classified/other chapters
112393	Sepsis due to Haemophilus influenzae
63776	[X]Haemophilus influenzae infection, unspecified
71658	Encephalitis due to influenza-virus identified

CC. Flu codes (CPRD Aurum)

medcodeid	Term
1126371000000114	Influenza A virus H1N1 subtype detected
1143141000000112	Influenza A virus subtype H1N1 serology
676781000000110	Influenza H1 virus detected
676841000000114	Influenza H2 virus detected
676901000000115	Influenza H3 virus detected
676961000000116	Influenza H5 virus detected
677021000000113	Influenza A virus, other or untyped strain detected
677081000000114	Influenza B virus detected
689941000000115	Human parainfluenza virus detected
1206286018	Haemophilus influenzae septicaemia
151462017	Haemophilus influenzae infection
808051000006112	H influenzae as cause/diseases classified/other chapters
2899948013	Sepsis due to Haemophilus influenzae
288067017	[X]Haemophilus influenzae infection, unspecified
453299013	Encephalitis due to influenza-virus identified
11203012	Influenza
778871000006116	Influenza with pneumonia
546421000006115	Chest infection - influenza with pneumonia
1229740013	Influenza with bronchopneumonia
301413010	Influenza with pneumonia, influenza virus identified
301414016	Influenza with pneumonia NOS
301415015	Influenza with other respiratory manifestation
301416019	Influenza with laryngitis
301417011	Influenza with pharyngitis
301418018	Influenza with respiratory manifestations NOS
301421016	Influenza with other manifestations
123962018	Influenza with encephalopathy
301423018	Influenza with gastrointestinal tract involvement
301424012	Influenza with other manifestations NOS
396106019	Influenza NOS
2820795016	Influenza due to Influenza A virus subtype H1N1
1128141000000118	Influenza A (H1N1) swine flu
301430012	Other specified pneumonia or influenza
301431011	Pneumonia or influenza NOS
389901000006115	[X]Influenza+other manifestations,influenza virus identified
389881000006117	[X]Influenza+oth respiratory manifestatns,virus not identifd
389891000006119	[X]Influenza+other manifestations, virus not identified

DD. Flu codes (HES/ONS)

ICD-10 Code	Term
J09	Influenza due to identified zoonotic or pandemic influenza virus
J10	influenza due to identified seasonal influenza virus
J11	Influenza, virus not identified

EE. Pneumonia Codes (CPRD GOLD)

medcode	readterm
58896	Salmonella pneumonia
70710	Primary pneumonic plague
47295	Pneumonic plague, unspecified
25462	Varicella pneumonitis
47973	Herpes simplex pneumonia
32172	Postmeasles pneumonia
50408	Ornithosis with pneumonia
45072	Cytomegaloviral pneumonitis
27641	HIV disease resulting in Pneumocystis carinii pneumonia
40299	Pneumonia - candidal
101507	Histoplasma capsulatum with pneumonia
101292	Histoplasma duboisii with pneumonia
56762	Toxoplasma pneumonitis
35220	Pneumocystosis
10086	Pneumonia and influenza
5202	Viral pneumonia
9389	Chest infection - viral pneumonia
67836	Pneumonia due to adenovirus
31269	Pneumonia due to respiratory syncytial virus
36675	Pneumonia due to parainfluenza virus
33478	Viral pneumonia NEC
46052	Severe acute respiratory syndrome
14976	Viral pneumonia NOS
1849	Lobar (pneumococcal) pneumonia
29166	Chest infection - pneumococcal pneumonia
28634	Other bacterial pneumonia
22795	Chest infection - other bacterial pneumonia
23546	Pneumonia due to klebsiella pneumoniae
30591	Pneumonia due to pseudomonas
37881	Pneumonia due to haemophilus influenzae
48804	Pneumonia due to haemophilus influenzae
12423	Pneumonia due to streptococcus
63858	Pneumonia due to streptococcus, group B
5612	Pneumonia due to staphylococcus
50867	Pneumonia due to other specified bacteria
65419	Pneumonia due to escherichia coli
60299	E.coli pneumonia
45425	Pneumonia due to proteus
12061	Pneumonia - Legionella
52384	Pneumonia due to other aerobic gram-negative bacteria
43884	Pneumonia due to bacteria NOS

medcode	readterm
23095	Bacterial pneumonia NOS
25694	Pneumonia due to other specified organisms
30653	Chest infection - pneumonia organism OS
60119	Pneumonia due to Eaton's agent
1576	Pneumonia due to mycoplasma pneumoniae
73735	Pneumonia due to pleuropneumonia like organisms
17025	Chlamydial pneumonia
34251	Pneumonia due to specified organism NOS
40498	Pneumonia with infectious diseases EC
41034	Pneumonia with measles
43286	Pneumonia with cytomegalic inclusion disease
62623	Pneumonia with ornithosis
30437	Pneumonia with whooping cough
35082	Pneumonia with pertussis
34274	Pneumonia with aspergillosis
52071	Pneumonia with candidiasis
53969	Pneumonia with systemic mycosis NOS
69782	Pneumonia with other infectious diseases EC
61623	Pneumonia with actinomycosis
67901	Pneumonia with nocardiasis
27519	Pneumonia with pneumocystis carinii
60482	Pneumonia with Q-fever
72182	Pneumonia with salmonellosis
98782	Pneumonia with toxoplasmosis
49398	Pneumonia with typhoid fever
23726	Pneumonia with varicella
70559	Pneumonia with other infectious diseases EC NOS
66362	Pneumonia with infectious diseases EC NOS
886	Bronchopneumonia due to unspecified organism
16287	Chest infection - unspecified bronchopneumonia
572	Pneumonia due to unspecified organism
19400	Chest infection - pnemonia due to unspecified organism
9639	Lobar pneumonia due to unspecified organism
8318	Lung consolidation
3683	Basal pneumonia due to unspecified organism
34300	Postoperative pneumonia
15912	Influenza with pneumonia
29457	Chest infection - influenza with pneumonia
13573	Influenza with bronchopneumonia
62632	Influenza with pneumonia, influenza virus identified
35745	Influenza with pneumonia NOS
5324	Atypical pneumonia
57667	Gangrenous pneumonia

medcode	readterm
35189	Abscess of lung with pneumonia
23333	Hypostatic pneumonia
24356	Hypostatic bronchopneumonia
22835	Bronchiolitis obliterans organising pneumonia
52520	[X]Other viral pneumonia
63763	[X]Other bacterial pneumonia
98381	[X]Pneumonia due to other specified infectious organisms
53947	[X]Pneumonia in viral diseases classified elsewhere
53753	[X]Other pneumonia, organism unspecified

FF. Pneumonia Codes (CPRD Aurum)

medcodeid	term
5303018	Salmonella pneumonia
58969011	Primary pneumonic plague
286339014	Pneumonic plague, unspecified
301400016	Varicella pneumonitis
350073012	Herpes simplex pneumonia
294997017	Postmeasles pneumonia
134668017	Ornithosis with pneumonia
1234028011	Cytomegaloviral pneumonitis
825831000006113	HIV disease resulting in Pneumocystis carinii pneumonia
219761000006111	Pneumonia - candidal
287618016	Histoplasma capsulatum with pneumonia
287630010	Histoplasma duboisii with pneumonia
287864011	Toxoplasma pneumonitis
147339015	Pneumocystosis
301357010	Pneumonia and influenza
125510013	Viral pneumonia
546491000006118	Chest infection - viral pneumonia
219801000006119	Pneumonia due to adenovirus
301362011	Pneumonia due to respiratory syncytial virus
1232627018	Pneumonia due to parainfluenza virus
301363018	Viral pneumonia NEC
1777982019	Severe acute respiratory syndrome
301364012	Viral pneumonia NOS
739941000006111	Lobar (pneumococcal) pneumonia
546451000006112	Chest infection - pneumococcal pneumonia
301368010	Other bacterial pneumonia
1222332017	Chest infection - other bacterial pneumonia
107173015	Pneumonia due to klebsiella pneumoniae
69026013	Pneumonia due to pseudomonas
219841000006117	Pneumonia due to haemophilus influenzae

medcodeid	term
219851000006115	Pneumonia due to haemophilus influenzae
56816017	Pneumonia due to streptococcus
219991000006118	Pneumonia due to streptococcus, group B
219971000006119	Pneumonia due to staphylococcus
301370018	Pneumonia due to other specified bacteria
2671161016	Pneumonia due to escherichia coli
633531000006116	E.coli pneumonia
219931000006117	Pneumonia due to proteus
219771000006116	Pneumonia - Legionella
219881000006111	Pneumonia due to other aerobic gram-negative bacteria
301375011	Pneumonia due to bacteria NOS
301376012	Bacterial pneumonia NOS
301377015	Pneumonia due to other specified organisms
1222333010	Chest infection - pneumonia organism OS
219821000006112	Pneumonia due to Eaton's agent
2164029012	Pneumonia due to mycoplasma pneumoniae
219921000006115	Pneumonia due to pleuropneumonia like organisms
350054013	Chlamydial pneumonia
301382010	Pneumonia due to specified organism NOS
396104016	Pneumonia with infectious diseases EC
220111000006113	Pneumonia with measles
220071000006117	Pneumonia with cytomegalic inclusion disease
220131000006119	Pneumonia with ornithosis
1231963019	Pneumonia with whooping cough
1231962012	Pneumonia with pertussis
1219703018	Pneumonia with aspergillosis
220051000006110	Pneumonia with candidiasis
301393012	Pneumonia with systemic mycosis NOS
301394018	Pneumonia with other infectious diseases EC
220021000006118	Pneumonia with actinomycosis
301397013	Pneumonia with nocardiasis
220181000006118	Pneumonia with pneumocystis carinii
220191000006115	Pneumonia with Q-fever
220201000006117	Pneumonia with salmonellosis
494463016	Pneumonia with toxoplasmosis
220241000006115	Pneumonia with typhoid fever
220251000006118	Pneumonia with varicella
301403019	Pneumonia with other infectious diseases EC NOS
301404013	Pneumonia with infectious diseases EC NOS
396105015	Bronchopneumonia due to unspecified organism
546481000006116	Chest infection - unspecified bronchopneumonia
301408011	Pneumonia due to unspecified organism
546441000006110	Chest infection - pnemonia due to unspecified organism

medcodeid	term
301409015	Lobar pneumonia due to unspecified organism
512123013	Lung consolidation
451130014	Basal pneumonia due to unspecified organism
459416013	Postoperative pneumonia
778871000006116	Influenza with pneumonia
546421000006115	Chest infection - influenza with pneumonia
1229740013	Influenza with bronchopneumonia
301413010	Influenza with pneumonia, influenza virus identified
301414016	Influenza with pneumonia NOS
350051017	Atypical pneumonia
12652015	Gangrenous pneumonia
301686019	Abscess of lung with pneumonia
141663013	Hypostatic pneumonia
52762016	Hypostatic bronchopneumonia
474828010	Bronchiolitis obliterans organising pneumonia
301809014	[X]Other viral pneumonia
301811017	[X]Other bacterial pneumonia
301812012	[X]Pneumonia due to other specified infectious organisms
301814013	[X]Pneumonia in viral diseases classified elsewhere
301818011	[X]Other pneumonia, organism unspecified

GG. Pneumonia Codes (HES/ONS)

ICD-10 Code	Term
J12	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J18	Pneumonia, organism unspecified
J85.1	Abscess of lung with pneumonia
U04	Severe acute respiratory syndrome [SARS]

HH. Cough Codes (CPRD GOLD)

medcode	readterm
92	cough
292	chesty cough
1025	bronchial cough
1160	[d]cough
1234	productive cough nos
1273	c/o - cough
3068	night cough present
3645	coughing up phlegm
4070	morning cough
4836	nocturnal cough / wheeze
4931	dry cough
7706	productive cough -clear sputum
7707	cough symptom nos
7708	productive cough-yellow sputum
7773	productive cough -green sputum
8239	[d]cough with haemorrhage
18907	cough with fever
22318	difficulty in coughing up sputum
29318	evening cough
60903	cough aggravates symptom
100515	cough swab

II. Cough Codes (CPRD Aurum)

MedCodeId	Term
317408012	[D]Cough with haemorrhage
252360013	Bronchial cough
252359015	Chesty cough
82824016	Cough
961781000006119	Cough
253356015	Cough aggravates symptom
384668019	Cough swab
1709261000006111	Cough swab
252366019	Cough symptom NOS
216653013	Cough with fever
598431000006113	Coughing up phlegm
442503015	Difficulty in coughing up sputum
20419011	Dry cough
252364016	Evening cough
252363010	Morning cough
252357018	Night cough present
252406018	Nocturnal cough / wheeze
252351017	Productive cough -clear sputum

MedCodeId	Term
252352012	Productive cough -green sputum
397882011	Productive cough NOS
252353019	Productive cough-yellow sputum

JJ. Cough Codes (HES)

ICD-10 Code	Term
R05	Cough
J41.0	Simple chronic bronchitis

KK. Sputum Codes (CPRD GOLD)

medcode	readterm
292	chesty cough
1025	bronchial cough
1234	productive cough nos
1251	[d]abnormal sputum
3645	Coughing up phlegm
3727	sputum sent for c/s
7706	productive cough -clear sputum
7708	productive cough-yellow sputum
7773	productive cough -green sputum
8287	sputum sample obtained
8760	[d]positive culture findings in sputum
9807	sputum - symptom
11072	acute purulent bronchitis
14271	sputum culture
14272	sputum microscopy
14273	sputum appearance
14804	sputum appears infected
15430	[d]sputum abnormal - colour
16026	sputum examination: abnormal
18964	sputum clearance
20086	[d]sputum abnormal - amount
22318	difficulty in coughing up sputum
23252	sputum microscopy nos
23582	[d]abnormal sputum nos
24181	sputum: mucopurulent
30754	yellow sputum
30904	sputum sent for examination
36515	[d]abnormal sputum - tenacious

medcode	readterm
36880	green sputum
43270	sputum evidence of infection
44214	[d]sputum abnormal - odour
49144	sputum: pus cells present
49694	sputum: organism on gram stain
54177	sputum: excessive - mucoid
100484	volume of sputum
100524	moderate sputum
100629	white sputum
100647	copious sputum
100931	brown sputum
101782	profuse sputum
103209	grey sputum

LL. Sputum Codes (CPRD Aurum)

MedCodeId	Term
371081018	Sputum - symptom
252351017	Productive cough -clear sputum
252352012	Productive cough -green sputum
252353019	Productive cough-yellow sputum
397882011	Productive cough NOS
598431000006113	Coughing up phlegm
252359015	Chesty cough
252360013	Bronchial cough
442503015	Difficulty in coughing up sputum
457227019	Sputum sample obtained
260946013	Sputum sent for examination
260949018	Sputum examination: abnormal
260954010	Sputum: excessive - mucoid
132001000006112	Sputum: mucopurulent
414646016	Yellow sputum
414647013	Green sputum
2226161000000119	Dark green sputum
2226201000000110	Pale green sputum
414639013	Sputum appearance
414649011	Brown sputum
2694247010	White sputum
371084014	Volume of sputum
371086011	Copious sputum
371085010	Profuse sputum
371087019	Moderate sputum

MedCodeId	Term
414638017	Grey sputum
260959017	Sputum microscopy
260965017	Sputum: pus cells present
260967013	Sputum: organism on gram stain
404561015	Sputum microscopy NOS
411654018	Sputum evidence of infection
131721000006111	Sputum appears infected
1803501000006112	Sputum culture
261391015	Sputum sent for C/S
301103013	Acute purulent bronchitis
317414017	[D]Abnormal sputum
317415016	[D]Sputum abnormal - amount
317417012	[D]Sputum abnormal - colour
317418019	[D]Sputum abnormal - odour
317420016	[D]Abnormal sputum - tenacious
317421017	[D]Abnormal sputum NOS
317877011	[D]Positive culture findings in sputum

MM. Sputum Codes (HES)

ICD-10 Code	Term
R09.3	Abnormal sputum

NN. Breathlessness Codes (CPRD GOLD)

medcode	readterm
735	[d]breathlessness
741	[d]shortness of breath
1429	breathlessness
2563	[d]respiratory distress
2575	short of breath on exertion
2737	respiratory distress syndrome
2931	difficulty breathing
3092	[d]dyspnoea
4822	shortness of breath
5175	breathlessness symptom
5349	shortness of breath symptom
5896	dyspnoea - symptom
6326	breathless - moderate exertion
6434	paroxysmal nocturnal dyspnoea
7000	o/e - dyspnoea
7534	o/e - respiratory distress
7683	breathless - lying flat
7932	breathless - mild exertion
9297	[d]respiratory insufficiency
18116	nocturnal dyspnoea
21801	breathlessness nos
22094	short of breath dressing/undressing
24889	breathless - strenuous exertion
31143	breathless - at rest
53771	dyspnoea on exertion
40813	Unable to complete a sentence in one breath

OO. Breathlessness Codes (CPRD Aurum)

MedCodeId	Term
198599018	Paroxysmal nocturnal dyspnoea
252386015	Breathless - mild exertion
252387012	Breathless - at rest
252412011	Breathlessness NOS
253889014	O/E - dyspnoea
317395018	[D]Dyspnoea
371012016	Nocturnal dyspnoea
397888010	Breathlessness
451467013	[D]Breathlessness
498862013	Dyspnoea on exertion

MedCodeId	Term
1484904014	Breathless - strenuous exertion
1485144011	MRC Breathlessness Scale: grade 1
1485147016	MRC Breathlessness Scale: grade 2
1485148014	MRC Breathlessness Scale: grade 3
1485149018	MRC Breathlessness Scale: grade 4
1485150018	MRC Breathlessness Scale: grade 5
1780468018	Borg Breathlessness Score: 1 very slight
1780469014	Borg Breathlessness Score: 2 slight
1780470010	Borg Breathlessness Score: 3 moderate
1780471014	Borg Breathlessness Score: 4 somewhat severe
1780473012	Borg Breathlessness Score: 5 severe
1780475017	Borg Breathlessness Score: 6 severe (+)
1780479011	Borg Breathlessness Score: 7 very severe
1780480014	Borg Breathlessness Score: 8 very severe (+)
1780482018	Borg Breathlessness Score: 10 maximal
525691000006114	Breathless - lying flat
525741000006111	Breathlessness symptom
633381000006111	Dyspnoea - symptom
910921000006114	Borg Breathlessness Score: 0.5 very, very slight
911011000006110	Borg Breathlessness Score: 9 very, very sev (almost maximal)
982351000006118	Dyspnoea
1807841000006119	O/E - dyspnoea at rest
1807851000006117	O/E - dyspnoea on exertion
1861171000006111	Breathlessness causing difficulty eating
1861181000006114	Breathlessness causing anxiety
2002191000006115	MRC (Medical Research Council) Breathlessness Scale grade 5a
2002201000006117	MRC (Medical Research Council) Breathlessness Scale grade 5b
2287071000000115	Anxiety about breathlessness
2287881000000112	Breathlessness causing difficulty eating
3400201000006115	PND - Paroxysmal nocturnal dyspnoea
3488351000006112	Breathlessness on exertion
3488371000006119	Dyspnoea on effort
3488381000006116	Exertional dyspnoea
4545421000006118	Dyspnoea at rest
5497741000006119	Breathless
6519221000006115	Medical Research Council (MRC) Breathlessness Scale: grade 1
6519231000006117	Medical Research Council Breathlessness Scale grade 1
6519271000006119	Medical Research Council (MRC) Breathlessness Scale: grade 2

MedCodeId	Term
6519281000006116	Medical Research Council Breathlessness Scale grade 2
6519301000006117	Medical Research Council Breathlessness Scale: grade 3
6519321000006110	Medical Research Council (MRC) Breathlessness Scale: grade 4
6519331000006113	Medical Research Council Breathlessness Scale grade 4
6519351000006118	Medical Research Council (MRC) Breathlessness Scale: grade 5
6519361000006116	Medical Research Council Breathlessness Scale grade 5
7563281000006118	Difficulty eating due to breathlessness
11932071000006115	MRC (Medical Research Council) Breathlessness Scale grade 5a
11932081000006117	MRC (Medical Research Council) Breathlessness Scale grade 5b
317392015	[D]Shortness of breath
397890011	Shortness of breath
140461000006116	Shortness of breath symptom
344917018	Difficulty breathing
5530001000006115	Distressed breathing
317390011	[D]Respiratory distress
317391010	[D]Respiratory insufficiency
253892013	O/E - respiratory distress
4554111000006118	On examination - respiratory distress
112574019	Adult respiratory distress syndrome
463141000006111	Adult respiratory distress syndrome
3602471000006111	ARDS - Adult respiratory distress syndrome

PP. Breathlessness Codes (HES)

ICD-10 Code	Term
R06.8	Other and unspecified abnormalities of breathing

QQ. Flu vaccine Codes (CPRD GOLD)

medcode	readterm
6	Influenza vaccination
12104	Flu vaccination administration
12336	[V]Influenza vaccination
95092	Second pandemic influenza vaccination
97941	Influenza vaccination given by other healthcare provider
104688	Seasonal influenza vaccination
105195	Seasonal influenza vaccination given by pharmacist
107156	Administration of intranasal influenza vaccination

RR. Flu vaccine Codes (CPRD Aurum)

ProdCodeId	Term
13133041000033114	Adjuvanted trivalent influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes (Seqirus Vaccines Ltd)
2641741000033118	Agrippal vaccine suspension for injection 0.5ml pre-filled syringes (Seqirus Vaccines Ltd)
147441000033115	Begrivac vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)
5199441000033117	Celvapan (H1N1) vaccine (whole virion, Vero cell derived, inactivated) suspension for injection (Baxter Healthcare Ltd)
3331741000033119	Enzira vaccine suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd)
12593041000033119	Fluad vaccine suspension for injection 0.5ml pre-filled syringes (Seqirus Vaccines Ltd)
8563041000033113	Fluarix Tetra vaccine suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd)
596641000033118	Fluarix vaccine suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd)
12884141000033117	Flucelvax Tetra vaccine suspension for injection 0.5ml pre-filled syringes (Seqirus Vaccines Ltd)
9306941000033116	Fluenz Tetra vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)
6494641000033115	Fluenz vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)
10647441000033112	FluMist Quadrivalent vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd)
588341000033111	Fluvirin vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd)
596541000033119	Fluzone Vaccine 0.5 ml
5896241000033119	Haemophilus type b / Meningococcal C conjugate vaccine powder and solvent for solution for injection 0.5ml vials
2739241000033119	Hiberix vaccine powder and solvent for solution for injection 0.5ml vials (GlaxoSmithKline UK Ltd)
3952441000033113	Imuvac vaccine suspension for injection 0.5ml pre-filled syringes (Mylan)
6452541000033117	Inflexal V vaccine suspension for injection 0.5ml pre-filled syringes (Janssen-Cilag Ltd)
12605941000033110	Influenza MYL vaccine suspension for injection 0.5ml pre-filled syringes (Mylan)

ProdCodeId	Term
12599041000033117	Influenza Tetra MYL vaccine suspension for injection 0.5ml pre-filled syringes (Mylan)
6494541000033116	Influenza vaccine (live attenuated) nasal suspension 0.2ml unit dose
5093141000033117	Influenza vaccine (split virion, inactivated) 15microgram strain suspension for injection 0.1ml pre-filled syringes
5415841000033118	Influenza vaccine (split virion, inactivated) 9microgram strain suspension for injection 0.1ml pre-filled syringes
3347241000033118	Influenza vaccine (split virion, inactivated) suspension for injection 0.25ml pre-filled syringes
770341000033117	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes
9702041000033119	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd)
2189441000033118	Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (Sanofi Pasteur)
762141000033114	Influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes
3954341000033113	Influenza vaccine (surface antigen, inactivated, virosome) suspension for injection 0.5ml pre-filled syringes
8534741000033118	Influvac Desu vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd)
12598941000033114	Influvac sub-unit Tetra vaccine suspension for injection 0.5ml pre-filled syringes (Mylan)
759741000033113	Influvac Sub-unit vaccine suspension for injection 0.5ml pre-filled syringes (Mylan)
5093241000033112	Intanza 15microgram strain vaccine suspension for injection 0.1ml pre-filled syringes (sanofi pasteur MSD Ltd)
5415741000033111	Intanza 9microgram strain vaccine suspension for injection 0.1ml pre-filled syringes (sanofi pasteur MSD Ltd)
3188641000033119	Invivac vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd)
2890941000033111	Mastaflu vaccine suspension for injection 0.5ml pre-filled syringes (Masta Ltd)
3939141000033113	Menitorix vaccine powder and solvent for solution for injection 0.5ml vials (GlaxoSmithKline UK Ltd)
8123441000033119	Optaflu vaccine suspension for injection 0.5ml pre-filled syringes (Seqirus Vaccines Ltd)
5208541000033111	Pandemrix vaccine emulsion and suspension for emulsion for injection (GlaxoSmithKline UK Ltd)

ProdCodeId	Term
6453341000033116	Preflucel vaccine suspension for injection 0.5ml pre-filled syringes (Baxter Healthcare Ltd)
12364041000033116	Quadrivalent influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (Sanofi Pasteur)
13011941000033111	Trivalent influenza vaccine (split virion, inactivated) High Dose suspension for injection 0.5ml pre-filled syringes (Sanofi Pasteur)
3954241000033115	Viroflu vaccine suspension for injection 0.5ml pre-filled syringes (Janssen-Cilag Ltd)

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