**COPD prevalence model for small populations:**

**Technical Document produced for Public Health England**

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COPD prevalence model Technical Document

# Executive Summary

TBA during editing

However will include:

The CPRD COPD prevalence model prevalence as it currently stands is therefore disappointing and certainly under-estimates actual prevalence, because we have failed to identify patients who are likely to have COPD but do not have a diagnosis from any other source. However we did not have the time or resources to investigate further. It is possible that we could use 2010 HSfE data now that we have a better method of producing local estimates than was the case in 2012. In addition there is an obvious need to look within high risk groups such as our algorithm group for other supporting evidence e.g. spirometry data. We therefore recommend that these estimates should not be used except as an interim measure which now includes HES diagnoses, and suggest that PHE considers allocating additional funding to look further for probable cases.

# Background

The Department of Primary Care & Public Health (PCPH) in the School of Public Health (SPH) at Imperial College London (ICL) has tendered successfully to Public Health England (PHE) to develop small population prevalence models for several chronic diseases. PHE has requested a prevalence model for chronic obstructive pulmonary disease (COPD), and another for asthma. As there may be some overlap between these diseases we decided to use the same data source and to develop a common diagnostic algorithm which splits into COPD and asthma.

## Previous COPD prevalence models

Respiratory function tests were included in the Health Survey for England (HSfE) 2010 data. In 2012 we were commissioned by PHE to repeat the statistical modelling used for the first prevalence model using HSfE 2010 data. For this project we decided to continue to use the British Thoracic Society (BTS) COPD definition firstly because the 2010 National Institute for Health and Clinical Excellence (NICE) guidance had reiterated it,[1] and secondly to retain continuity with the previous modelled estimates. (The NICE giuidance requires respiratory symptoms to be present as well.)

The 2001 HSfE data which we used in our first model referred to 5,269 men and 6,133 women over 15 years old with valid lung function measures.[2] In 2010, only 1,440 men and 1,966 women (65% and 67% respectively of those having a nurse visit) had usable spirometry measurements.[3] The spirometers used in 2010 differed substantially from those used previously, which enabled exclusion of inadequate spirometry measurements (referred to in the report as quality assurance).

Overall observed COPD prevalence in 2010 was 12% in males and 8.3% in females (14.3% and 9.9% respectively in over 35s). Prevalence rates were about three per cent lower in males in 2010, moreso in the quality assured data, with a smaller reduction in women, although male prevalence was still 50% higher. This may reflect falls in smoking prevalence (from 28% in 1993 to 21% in 2011), and possibly higher mortality in older people with COPD. We fitted univariate then multivariate logistic regression models to the 2010 HSfE data. Consistent with other surveys and the previous model, the final 2010 regression model shows age group and smoking history are the strongest predictors of COPD in both genders. Unlike the 2001 analysis, residence in urban areas and ethnicity are not associated with increased risk in either gender, but the numbers tested in ethnic minority groups was very small. Living in more deprived areas is still associated with increased risk in men, but not in women.

When the 2010 model was used to predict COPD caseness and compared with the actual values in an age/sex breakdown table, the modelled prevalence rates agreed closely with the observed rates. However when the expected prevalence is broken down further by smoking category, the modelled values become unstable, and tend to over-predict prevalence. We carried out extensive checking of the modelling process and formulae and came to the conclusion that the 2010 data has characteristics which compromise the use of the regression coefficients to calculate prevalence in small populations, most likely an effect from the smaller sample size in HSfE 2010, as prevalence stimates are obtained for permutations of risk factor subcategories. We therefore recommended against using estimates based on HSfE 2010 for small population prevalence modelling, which disqualified it as a data source for the 2016 model.

## COPD epidemiology and management

COPD is a chronic condition characterised by progressive airflow obstruction, which is not completely reversible.[4 ,5] COPD contributes to nearly 30,000 deaths each year in the United Kingdom (UK), corresponding to 5.7 percent of adult male and 4 percent of adult female deaths, including a significant number of premature deaths.[6] In addition, 1.4% of the population consult their GPs for COPD each year. It accounts for 2% of hospital admission spells and over three per cent of bed-days in adults,[6] costing the NHS £800 million, and leading to 24 million working days lost each year.[7]

Respiratory function indices have been shown to be predictive of mortality from respiratory disease, cardiovascular disease and all causes.[8 ,9] A UK GP database study to quantify the burden of comorbidity and to determine the risk of first acute CVD events among individuals with COPD showed that physician-diagnosed COPD was also associated with increased risks of CVD (odds ratios [OR] 4.98, 95% CI 4.85 to 5.81; p<0.001), stroke (OR 3.34, 95% CI 3.21 to 3.48; p<0.001) and DM (OR 2.04, 95% CI 1.97 to 2.12; p<0.001).[10]

Airflow limitation may precede the development of significant symptoms of COPD by many years and its progression is directly linked to the continuing exposure to risk factors, particularly tobacco smoking. As COPD is difficult to diagnose clinically (without spirometry) in its milder forms, it is often diagnosed late - the average age at diagnosis of COPD in the UK is 67 years.[5] Widespread use of spirometry allowing early detection of airflow obstruction has been increasingly advocated as it enables early management of COPD.[11]

The prevalence of COPD is higher in smokers and in men, and it increases with age.[3] Stopping smoking prevents the development of COPD, or slows its progress and reduces the risk of hospital admissions.[12] Smoking cessation programmes are highly cost-effective, and crucially, have been specifically shown to be cost-effective when directed to individuals with asymptomatic airway obstruction.[13] This is because smokers may be motivated to attempt to quit when given a diagnosis of airflow limitation.[14] The Finnish National Programme for Chronic Bronchitis and COPD was set up 1998 to reduce prevalence, and improve diagnosis and care. Prevalence remained unchanged, but smoking decreased in males from 30% to 26% and in females from 20% to 17%. Significant improvements in the quality of spirometry were obtained, hospitalisation decreased by 39.7% (p<0.001), and COPD costs were 88% lower than had been anticipated.[15]

The incremental cost effectiveness ratio (ICER) of opportunistic COPD case-finding for this purpose is a cost per life year gained of £713.16 and a cost per QALY of £814.56.[16] The magnitude of undiagnosed cases can be ascertained by comparing the model estimates with the recorded prevalence of COPD, to indicate the extent of unmet needs in COPD. In the UK this is facilitated by GP performance payments for COPD management through the QOF of the GP Contract based on an electronic register of all patients with diagnosed COPD. If this is linked to case finding and intervention, there is a potential for reducing the population burden and progression of the disease.

The English Outcomes Strategy for COPD and Asthma was published in 2011.[17] Six shared objectives are set out in the strategy:

* Objective 1: To improve the respiratory health and well-being of all communities and minimise inequalities between communities.
* Objective 2: To reduce the number of people who develop COPD by ensuring they are aware of the importance of good lung health and well-being, with risk factors understood, avoided or minimised, and proactively address health inequalities.
* Objective 3: To reduce the number of people with COPD who die prematurely through a proactive approach to early identification, diagnosis and intervention, and proactive care and management at all stages of the disease, with a particular focus on the disadvantaged groups and areas with high prevalence.
* Objective 4: To enhance quality of life for people with COPD, across all social groups, with a positive, enabling, experience of care and support right through to the end of life.
* Objective 5: To ensure that people with COPD, across all social groups, receive safe and effective care, which minimises progression, enhances recovery and promotes independence.
* Objective 6: To ensure that people with asthma, across all social groups, are free of symptoms because of prompt and accurate diagnosis, shared decision making regarding treatment, and on-going support as they self-manage their own condition and to reduce need for unscheduled health care and risk of death.

Objective 3, covering early identification, diagnosis and intervention, is obviously relevant to the prevalence models. The Strategy notes that late diagnosis has a substantial impact on symptom control, quality of life, clinical outcome and cost because undiagnosed people receive inappropriate or inadequate treatment. As mentioned below, NICE published its most recent COPD guidelines [CG101] in June 2010. [1] An update of diagnosis and management is planned by the COPD Standing Committee, but as of July 2016 no completion date had been announced.

## COPD Prevalence

There is considerable variation in the reported prevalence of COPD internationally. One reason for this is the differing definitions in use. The BTS criteria[18] are based on the post bronchodilator values of forced expiratory volume in 1 second (FEV1) and the forced vital capacity (FVC) i.e. FEV1/ FVC < 0.70 and FEV1<80% predicted, using British reference values derived from the HSfE. The NICE COPD guideline,[1] which was revised in 2010, states that the following should be used as a definition of COPD:

* Airflow obstruction is defined as a reduced FEV1/FVC ratio (where FEV1 is forced expired volume in 1 second and FVC is forced vital capacity), such that FEV1/FVC is less than 0.7.
* If FEV1 is ≥ 80% predicted normal a diagnosis of COPD should only be made in the presence of respiratory symptoms, for example breathlessness or cough.

This is the BTS definition plus the presence of symptoms. For the previous prevalence model we decided to use the BTS definition for a practical reason, because the main objective of the model was to estimate the size of practice populations in which primary care intervention for COPD was clearly justified by the evidence base. In addition we did not have reliable data from HSfE on respiratory symptoms. Finally practices did not have the resources to identify as many as possible of their patients with a broader definition; and diagnosed prevalence in most practices was and is still well below the expected BTS-definition prevalence.[19] The second BTS criterion is not part of the international Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition: FEV1 >80% is defined as mild COPD or GOLD Stage 1. Table 1 shows the GOLD criteria for severity of COPD as used in the BOLD protocol.[20]

Table : GOLD criteria for severity of COPD[20]

| Severity of COPD (GOLD scale) | FEV1 % predicted |
| --- | --- |
| Mild (GOLD 1) | ≥80 |
| Moderate (GOLD 2) | 50–79 |
| Severe (GOLD 3) | 30–49 |
| Very severe (GOLD 4) | <30 or chronic respiratory failure symptoms |

There is no consensus regarding using a fixed threshold to define airflow obstruction versus using the lower limit of normal (LLN) adjusted for age.[21] The difference between these two definitions is illustrated by the pooled prevalence estimates of an international systematic review and meta-analysis.[22] Using the GOLD definition and including GOLD (stage I)/FEV1/FVC <0.70, the population prevalence was estimated at 9.8% (95% CIs 5.9–15.8). Including only GOLD (stage II)/FEV1/FVC <0.70 and FEV1 <80% predicted and worse, the population prevalence was 5.5% (95% CIs 3.3–9.0).

However a 2013 study by Bhatt et al compared the accuracy and discrimination of the recommended fixed ratio of FEV1/FVC <0.70 with the LLN definition in diagnosing smoking-related airflow obstruction using CT-defined emphysema and gas trapping as the disease gold standard.[21] Using COPDGene data, concordance between spirometric thresholds was measured, using quantitative CT as gold standard. There was very good agreement between the two spirometric cutoffs (κ=0.85; 95% CI 0.83 to 0.86, p<0.001). Only 7.3% were discordant. Subjects with airflow obstruction by fixed ratio only had a greater degree of emphysema (4.1% versus 1.2%, p<0.001) and gas trapping (19.8% vs 7.5%, p<0.001) than those positive by LLN only, and also smoking controls without airflow obstruction (4.1% vs 1.9% and 19.8% vs 10.9%, respectively, p<0.001). On follow-up, the fixed ratio only group had more exacerbations than smoking controls. They concluded that, compared with the fixed ratio, the use of LLN fails to identify a number of patients with significant pulmonary pathology and respiratory morbidity.

The GOLD definition has also been used in a previous analysis of the 2000 HSfE data by Shahab et al, which was used for prevalence estimates by NICE and the COPD National Strategy.[23] This found a prevalence of 13.3% in over 35s (Table 2). The Department of Health *Outcomes Strategy for People with COPD and Asthma in England* uses this figure to estimate are around 835,000 people currently diagnosed with COPD in the UK and an estimated 2,200,000 people with COPD who remain undiagnosed.[17] As a result, prevalence estimates from these sources are larger, given only the one spirometric criterion. That study also calculated the prevalence directly from the survey data, differently from our previous paper, where the estimates shown were obtained from the modelled/expected estimates and extrapolated for the population of England for validation purposes. As might be expected, the latter are somewhat lower.

Table : prevalence of COPD (GOLD definition) obtained directly from HSfE 2001 by Shahab et al[23]

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total (n=8215) | Never smokers (n=3686) | Ex-smokers (n=2551) | Smokers (n=1978) |
| Mild | 5.5 (455) | 4.9 (180) | 5.5 (141) | 6.8 (134) |
| Moderate | 5.8 (480) | 3.1 (116) | 7.1 (180) | 9.3 (184) |
| Severe/very severe | 1.9 (158) | 0.7 (26) | 2.7 (68) | 3.2 (64) |
| Overall | 13.3 (1093) | 8.7 (322) | 15.2 (389) | 19.3 (382) |

Using the BTS definition the Nacul et al methodology paper[2] on the previous COPD model gave the overall expected prevalence in the English population over 15 years of age of 3.1% (3.9% in men and 2.4% in women) (Table 3). For those over 45 years old, the estimated prevalence was 5.3% (6.8% and 3.9% in men and women respectively). This corresponds to over 1.3 million people in England with COPD, of whom nearly 800 thousand or 60% are men.

Table : number and proportion of people estimated to have COPD by age group and gender in England from 2007 COPD model (estimates for 2005)[[1]](#footnote-1)[2]

|  |  |  |  |
| --- | --- | --- | --- |
| Age-group (Years) | Men Number (%)\* | Women Number (%) | Both sexes Number (%) |
| 15–44 | 137,530 (1.30) | 93,450 (0.89) | 230,980 (1.10) |
| 45–54 | 75,720 (2.38) | 64,840 (2.00) | 140,560(2.19) |
| 55–64 | 198,400(6.90) | 122,440 (4.11) | 320,840 (5.48) |
| 65–74 | 199,840(10.03) | 105,740 (4.81) | 305,580 (7.29) |
| 75+ | 172,700(11.65) | 132,400 (5.55) | 305,100 (7.89) |
| Total 15+ | 784,190 (3.89) | 518,870 (2.41) | 1,303,060(3.15) |
| Total 45+ | 646,660 (6.76) | 425,420 (3.92) | 1,072,080(5.27) |

A systematic review of good quality COPD prevalence studies quoted by Nacul et al yielded estimates for England of between 4% and 10%.[24] The 2004 UK Health Needs Assessment report suggested a prevalence of 5% for men and 3% for women of middle age and upwards.[25] The figures estimated by our first model are in general slightly lower than, but comparable with other studies on COPD using the same BTS definition, i.e. 4.5% in Norway,[26] 6.8% in the US[27] and 6.8% in white males 40–60 years old in Spain.[28] They are also similar to the overall prevalence of 6.1% found in the NICECOPD study for Belfast white population aged 40 to 69 years.[29] The slightly lower estimated prevalence in our 2007 study may be largely explained by the lower smoking prevalence in England, but also by differences in the study populations, and the larger study size of the HSfE.

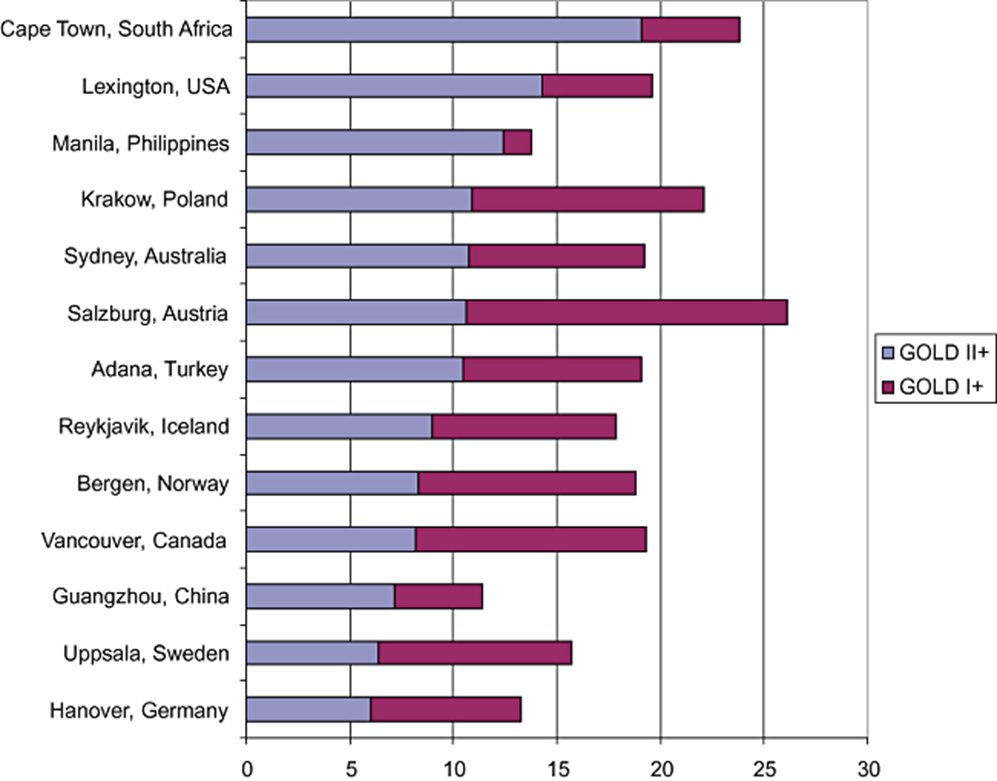
There have been many prevalence surveys published since the first prevalence model and associated documentation was published in 2007.[30-39] Most of these have used the international Burden of Obstructive Lung Disease (BOLD) protocol and study design, and hence the GOLD definition, so are not useful here unless they provide a breakdown by GOLD stages.[40] Unfortunately, moreover, relatively few contain data on risk factors other than age, gender and smoking, but nevertheless some are relevant to the UK. For example a population-based sample of adults, aged >40 years, in Maastricht, the Netherlands, found an overall prevalence of COPD of 24%, which was higher for men (28.5%) than for women (19.5%).[41] Overall prevalence of current smoking was 23%, and the prevalence of doctor-diagnosed COPD was only 8.8%. Table 4 shows estimated population prevalence of GOLD stage 2 or higher from this study.

Table : estimated population prevalence of GOLD stage 2 or higher in Maastricht, Netherlands

|  |  |  |  |
| --- | --- | --- | --- |
| Age | Male | Female | Persons |
| 40–49 | 4.4% (2.6) | 1.2% (1.2) | 2.8% (1.4) |
| 50–59 | 13.7% (3.8) | 8.2% (3.1) | 10.9% (2.4) |
| 60–69 | 18.9% (4.4) | 6.9% (2.7)[a](http://www.sciencedirect.com/science/article/pii/S0954611112000418#tbl2fna) | 12.8% (2.6) |
| 70+ | 19.9% (6.3) | 15.6% (7.2) | 17.3% (5.0) |
| Total | 13.2% (2.1) | 8.0% (2.3)[a](http://www.sciencedirect.com/science/article/pii/S0954611112000418#tbl2fna) | 10.4% (1.5) |

Another relevant BOLD study was carried out in Uppsala, Sweden.[42] COPD GOLD prevalence was 16.2%, which was the fourth lowest prevalence of COPD compared with 12 other BOLD centres. Main risk factors for COPD were increasing age [odds ratio (OR) = 2.08 per 10 years] and smoking. COPD was defined according to GOLD or according to the lower limit of normal (LLN), which is beneath the 95th percentile of population distribution for the FEV1/FVC ratio. COPD stage 2 or higher was defined as FEV1 <80% of predicted, so this is comparable with the definition we used. Figure 1 shows prevalence from this study with GOLD 2+ as the purple bar. Prevalence in other similar European countries is 6-10%.

Figure : prevalence of COPD in Uppsala, Swedish BOLD study and other countries[42]



Alternatively, the same data was published separately in 2007. Participants were aged over 40, with mean ages of male participants ranging from 52–58 years across sites and 53–60 years for female participants from the 12 sites. A total of 9,425 completed post-bronchodilator spirometry testing plus questionnaires about respiratory symptoms, health status, and exposure to COPD risk factors.[40] The prevalence of stage II or higher COPD was 10·1% (SE 4·8) overall, 11·8% (7·9) for men, and 8·5% (5·8) for women. The overall pooled OR estimate was 1·94 (1·80–2·10) per 10-year increment in age. Unfortunately data on risk factors other than smoking was not presented. Country results for GOLD stages 2-4 i.e. equivalent to the BTS definition are shown in Table 5.

Table : estimated population prevalence of COPD for GOLD stage 2-4 from BOLD multi-site study[40]

|  | Men (n,%) | | Women (n,%) | | Persons (n,%) | |
| --- | --- | --- | --- | --- | --- | --- |
| China | 236 | 9.3% | 237 | 5.1% | 473 | 7.2% |
| Turkey | 389 | 15.4% | 417 | 6.0% | 806 | 10.6% |
| Austria | 685 | 10.3% | 573 | 11.0% | 1258 | 10.6% |
| South Africa | 315 | 22.2% | 532 | 16.7% | 847 | 19.1% |
| Iceland | 402 | 8.6% | 353 | 9.4% | 755 | 8.9% |
| Germany | 349 | 8.6% | 334 | 3.7% | 683 | 5.9% |
| Poland | 266 | 13.3% | 260 | 8.6% | 526 | 10.9% |
| Norway | 324 | 11.0% | 334 | 5.9% | 658 | 8.3% |
| Canada | 344 | 9.3% | 483 | 7.3% | 827 | 25.7% |
| USA | 206 | 12.7% | 302 | 15.6% | 508 | 14.3% |
| Philippines | 378 | 18.7% | 515 | 6.8% | 893 | 12.5% |
| Australia | 265 | 9.3% | 276 | 12.2% | 541 | 10.8% |

Another Swedish study of patients 40-75 years attending an urgent primary care centre with acute respiratory tract infection, positive smoking history had a prevalence of previously undiagnosed COPD of 27%.[43] In a population database in the Netherlands, three per 1000 subjects were diagnosed with COPD per year. The incidence increased rapidly with age and was higher in men than in women. One in eight men and one in 12 women COPD free at the age of 40, will develop COPD during their life.[44] In a representative sample of the French population older than 40 years 40% had a Medical Research Council dyspnea grade of 1 or more but only 9% spontaneously reported shortness of breath. Only 220 (8%) individuals knew the term COPD and only 66% associated the term COPD with respiratory disease.[45] In summary, in the light of more recent prevalence surveys, the prevalence in our previous model appears to be somewhat lower than expected.

Table 6 shows a comparison between the age/sex specific COPD prevalence rates derived directly from the 2001 and 2010 HSfE datasets, bearing in mind that spirometry was performed differently in the two surveys, and the 2001 data shown here does not use the additional criterion of FEV1<80% predicted, although the 2010 data does. Prevalence rates are about three per cent lower in males in 2010, moreso in the quality assured data, with a smaller reduction in women, although male prevalence is still 50% higher. This may reflect falls in smoking prevalence (from 28% in 1993 to 21% in 2011), and possibly as a result of higher mortality in older people with COPD.

Table : comparison of observed COPD prevalence rates by age and sex, HSfE 2001 and 2010

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | <35 | 35-44 | 45-54 | 55-64 | 65-74 | 75+ | Total | Over 35 |
| COPD 2001 | Males | 4.6% | 6.8% | 11.9% | 18.4% | 27.6% | 34.8% | 13.6% | 16.9% |
| Females | 2.8% | 5.2% | 8.5% | 11.9% | 16.2% | 24.3% | 8.9% | 11.2% |
| COPD 2010 | Males | 3.6% | 4.6% | 7.8% | 15.9% | 25.4% | 33.1% | 12.7% | 15.1% |
| Females | 3.0% | 3.5% | 6.4% | 10.9% | 15.7% | 26.2% | 8.7% | 10.2% |
| COPD 2010 QA | Males | 3.5% | 3.8% | 8.4% | 15.8% | 25.4% | 29.8% | 12.0% | 14.3% |
| Females | 2.2% | 3.5% | 6.0% | 11.0% | 16.2% | 26.2% | 8.3% | 9.9% |

In a 2014 paper Quint et al assessed the positive predictive value (PPV) and proportion of patients diagnosed with COPD within eight algorithms which combined diagnostic, clinical, test (spirometry) and prescribing data from the Clinical Practice Research Datalink (CPRD) in various ways.[46] The results are shown in Table 7. In this study, algorithms were not exclusive, and those with a bronchitis code + COPD medication, for example, could also have had a COPD code. If the less valid algorithms are used exclusively, that is to say, for example, if a patient had a bronchitis code + COPD medication and no COPD code, the PPVs may well be significantly lower. The algorithm which included COPD Codes, spirometry and COPD medication had the highest PPV, but COPD code only gave a PPV which was almost as high. However the objective of the prevalence model is somewhat different, as it is attempting to estimate the population it would be worth reviewing because they have a high probability of having COPD. This could be determined operationally by a cost-effectiveness analysis (CEA), but a CEA is outside the scope of this project. In its absence we sought advice from an expert group of GPs to get their views as to what would be a reasonable yield for practices (views TBA).

Table : the positive predictive value (PPV) and proportion of patients diagnosed with chronic obstructive pulmonary disease (COPD) within each algorithm

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Algorithm | Number of questionnaires sent out (n=951) | Number evaluable returned (n=696) (%) | Number with confirmed COPD | PPV and 95% CI |
|  | COPD Code+spirometry+COPD medication | 119 | 85 (71.4) | 76 | 89.4, 80.7 to 94.5 |
|  | COPD Code+spirometry | 119 | 79 (66.4) | 67 | 83.8, 73.7 to 90.4 |
|  | COPD Code+COPD medication | 119 | 88 (73.9) | 77 | 87.5, 78.6 to 93.0 |
|  | COPD Code only | 119 | 89 (74.8) | 77 | 86.5, 77.5 to 92.3 |
|  | Bronchitis+COPD medication | 119 | 98 (82.4) | 44 | 44.4, 34.8 to 54.5 |
|  | Bronchitis only | 119 | 84 (70.6) | 26 | 29.5, 20.8 to 40.1 |
|  | Symptoms+spirometry | 119 | 83 (69.7) | 37 | 43.5, 33.2 to 54.4 |
|  | Symptoms only | 118 | 90 (75.6) | 11 | 12.2, 6.8 to 20.9 |

## COPD Risk Factors

A non-systematic literature search was conducted to identify recent studies which quantified the risk factors for COPD. COPD risk factors are shown in Table 8, with associated references:

Table : COPD risk factor list

|  |  |
| --- | --- |
| Risk factor | References |
| Smoking | Pirie et al, Lancet 2012 |
| Age | Afonso et al 2011[44] |
| Occupational exposure to dust and chemicals | Baur et al, J Occup Med toxicol, 2012 |
| Socioeconomic status/deprivation | Prescott & Vestbo, Thorax, 1999 |
| Sex | Sin et al, Proceedings ats, 2007 |

### Risk factor – Smoking

Active smoking is by far the most important risk factor for COPD in the UK, and alone this will explain >70% of cases globally.[2 ,37 ,39 ,42 ,47 ,48] The vast majority of those with COPD in the UK have a smoking history (>95%).[29 ,49 ,50] Exposure to active cigarette smoking is normally measured as number of “pack years”, with one pack year equating to smoking one pack (20 cigarettes) per day for one year. Generally, individuals need exposure to about 15-20 pack years before they develop COPD. Beyond this exposure level, number of pack years does not appear to be associated with higher risk of COPD. Only around 20% of smokers develop COPD, however, so genetic and perhaps environmental factors are thought to play a role in susceptibility to smoking. Most COPD in the UK is caused by tobacco smoking. However there is evidence that, shisha/water pipe, cannabis, heroin and crack cocaine smoking all cause COPD. It is difficult to assess exposure to these in large studies however. There is no definitive evidence on passive smoking at the moment.

### Risk factor- Age

COPD is very much associated with age and is very rare in those under the age of 35 (the cut-off age we have used for this prevalence model). Age is likely to interact with smoking status.[42 ,44 ,51-55]

### Risk factor – socioeconomic status/deprivation

This association could be due to early life factors and housing, other occupational or environmental exposures e.g. air pollution, or may be due to residual confounding from imperfectly measured smoking and occupational exposures. [2 ,33 ,56-59]

### Risk factor – Ethnicity

There is some evidence that ethnicity is related to risk of COPD. However much of this could be due to smoking and deprivation, depending on how well these measured. We did not find significant associations in our 2007 paper which used HSfE data. [2]. Ethnicity has also been shown to be related more to severity than incidence.[2 ,60] We therefore decided not to include it in the current models.

### Risk factor – Sex

Traditionally men have been shown to be at higher risk, taking into account smoking history, but this may be due to residual confounding from imperfectly measured smoking and occupational exposure. However with ageing of the population of women who have smoked more, evidence that this trend is disappearing and may well have reversed.[2 ,22 ,61-65] Effects of tobacco smoking are known to be higher for women. There may be an interaction with other risk factors e.g. age.

### Risk factor – Occupation

There has been increased attention on occupation recently for those exposed to dust and fumes at work.[26 ,66-68] This is likely to be different types of exposure between countries, and apparent associations may also depend on how well smoking has been measured. It is difficult to get a good occupational history from self-reports, so studies may underestimate occupation as a risk factor. However, it is likely to represent only <5% of COPD in UK. In addition, there is very little occupational data in CPRD.

Table 9 summarises COPD risk factors with their pooled, matched or adjusted odds ratios.

Table : COPD risk factors with their pooled, matched or adjusted odds ratios

| Risk factor | Type of Odds Ratio | Odds Ratio | 95% CI | Effect on Outcome |
| --- | --- | --- | --- | --- |
| Smoking status |  |  |  |  |
| Ever smoker | Pooled OR from SR and MA – incidence odds | 2.89 | 2.63-3.17 | Risk factor |
| Ex-smoker | Pooled OR from SR and MA [69] – incidence odds | 2.35 | 2.11-2.63 | Risk factor |
| Current smoker | Pooled OR from SR and MA [69] – incidence odds | 3.51 | 3.08-3.99 | Risk factor |
| Current smoker | Pooled OR from [70] (BOLD study) – prevalence odds | 1.34 | 1.12-1.61 | Risk factor |
| Passive smoking | Pooled OR from [70] (BOLD study) – prevalence odds | 1.22 | 1.06-1.41 | Risk factor |
| Smoking pack years? |  |  |  |  |
| Age |  |  |  |  |
| 40-59 |  | 1 |  |  |
| 60-69 | Adjusted HR from [44] | 3.67 | 3.23-4.17 | Risk factor |
| ≥70 | 8.55 | 7.58-9.65 | Risk factor |
| Per 10-year difference | Pooled OR from [70] (BOLD study) – prevalence odds | 1.52 | 1.35-1.71 | Risk factor |
| Sex |  |  |  |  |
| Female sex | Pooled Europe-wide OR from [70] (BOLD study) – prevalence odds | 1.10 | 0.85-1.43 | ns |
| SES |  |  |  |  |
| Education (per change in one group from none, primary, secondary, tertiary ) | Pooled OR from [70] (BOLD study) – prevalence odds | 0.76 | 0.67-0.87 | Risk factor |
| Occupation |  |  |  |  |
| Working in dusty job (per 10 years) | Pooled OR from [70] (BOLD study) – prevalence odds | 1.08 | 1.02-1.13 | ns |
| Regular exposure to dust in present job | Pooled OR from [70] (BOLD study) – prevalence odds | 0.86 | 0.61-1.21 | ns |
| Regular exposure to fumes in present job | Pooled OR from [70] (BOLD study) – prevalence odds | 0.91 | 0.67-1.24 | ns |
| Biomass exposure |  |  |  |  |
| Heating (per 10 years) | Pooled OR from [70] (BOLD study) – prevalence odds | 1.03 | 0.97-1.10 | ns |
| Cooking (per 10 years) | Pooled OR from [70] (BOLD study) – prevalence odds | 0.98 | 0.70-1.37 | ns |

As previously mentioned, COPD is a clinical diagnosis and diagnosing COPD based on spirometry alone in those with low pre-test probability (such as the general population) is likely to result in significant over-diagnosis, notably because of misdiagnosis with asthma. Many epidemiological studies have, however, used spirometry alone as a definition of COPD, therefore making estimates of population prevalence of COPD difficult. A 2015 study by Raluy-Callado reported the prevalence of COPD both from doctor diagnosed COPD in the UK, and spirometrically defined COPD worldwide. Raluy-Callado 2015, UK, Physician diagnosed COPD from EHR records, 3.3% (3.1-3.6%), -, -, 64 (SD, 11)

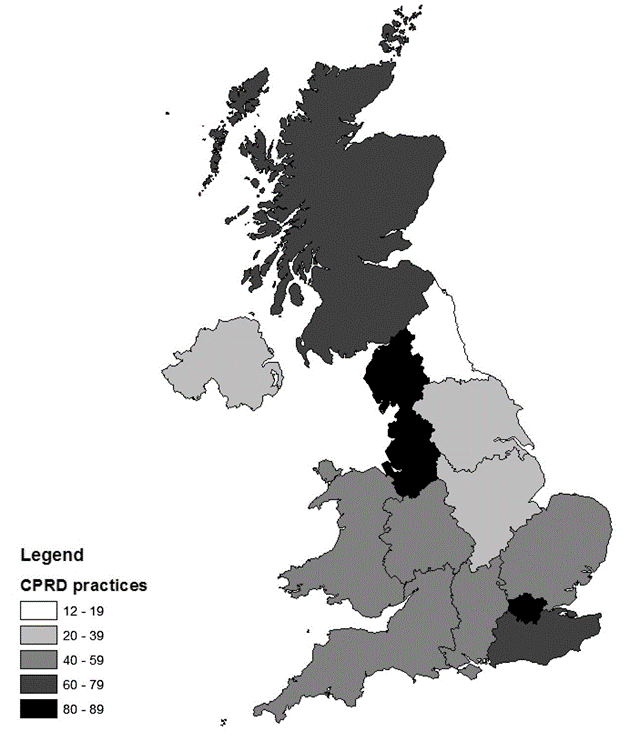
# Methods

## COPD prevalence from UK primary care data: Clinical Practice Research Datalink

### Data source, sampling and COPD code lists

Given the difficulties associated with the use of HSfE 2010 data, we decided to use Clinical Practice Research Datalink (CPRD) data extracts. CPRD is an ongoing primary care database of longitudinal anonymised electronic health records (EHRs) from general practitioners, with coverage of over 11.3 million patients from 674 practices in the UK.[71] With 4.4 million active (alive, currently registered) patients meeting quality criteria, approximately 6.9% of the UK population are included and patients are broadly representative of the UK general population in terms of age, sex and ethnicity. The distribution of CPRD practices is shown in Figure 2 below.

Figure : distribution of 674 CPRD practices by region in England, and in Wales, Scotland and Northern Ireland



## Outcome definition: definite/probable COPD

We identified cases of COPD in three ways:

1. cases diagnosed by a doctor (usually the GP) and entered into CPRD
2. cases with linked Hospital Episode Statistics (HES) inpatient diagnosis of COPD, which has been validated for other diseases
3. cases which can be inferred from records of symptoms and prescriptions.

In CPRD, version 2 5-byte Read codes, which are hierarchical, are converted into non-hierarchical numeric codes (“medcodes”). We compiled a list of CPRD medcodes for doctor diagnosis of COPD, for the symptoms which make up the COPD classification and for the drugs used on COPD patients. In the 2014 paper by Quint et al,[46] efforts were made to select only definite COPD cases. For that reason, not all the Read codes included in the QOF COPD list were selected. The same medcodes were used here. As one of the objectives of the local COPD prevalence estimates is to compare them with QOF prevalence, using the Quint et al code list as an outcome might underestimate prevalence. The list of QOF codes is shown in Table 10.

Table : QOF Read codes and codes used by Quint et al (2014)

| QOF Read code | QOF Read term | Quint et al 2015 |
| --- | --- | --- |
| H32..00 | Emphysema | **√** |
| H3...00 | Chronic obstructive pulmonary disease | **√** |
| H3z..00 | Chronic obstructive airways disease NOS | **√** |
| H38..00 | Severe chronic obstructive pulmonary disease | **√** |
| H37..00 | Moderate chronic obstructive pulmonary disease | **√** |
| H36..00 | Mild chronic obstructive pulmonary disease | **√** |
| H322.00 | Centrilobular emphysema | **√** |
| H3y..00 | Other specified chronic obstructive airways disease | **√** |
| H312100 | Emphysematous bronchitis | **√** |
| H320z00 | Chronic bullous emphysema NOS | **√** |
| H320.00 | Chronic bullous emphysema | **√** |
| H32z.00 | Emphysema NOS | **√** |
| H3z..11 | Chronic obstructive pulmonary disease NOS | **√** |
| H312z00 | Obstructive chronic bronchitis NOS | **√** |
| H39..00 | Very severe chronic obstructive pulmonary disease | **√** |
| H31..00 | Chronic bronchitis |  |
| H312000 | Chronic asthmatic bronchitis |  |
| H312011 | Chronic wheezy bronchitis |  |
| H311.00 | Mucopurulent chronic bronchitis |  |
| H31z.00 | Chronic bronchitis NOS |  |
| H310000 | Chronic catarrhal bronchitis |  |
| H32yz00 | Other emphysema NOS |  |
| H313.00 | Mixed simple and mucopurulent chronic bronchitis |  |
| H310.00 | Simple chronic bronchitis |  |
| H312300 | Bronchiolitis obliterans |  |
| H312.00 | Obstructive chronic bronchitis |  |
| H311100 | Fetid chronic bronchitis |  |
| H311000 | Purulent chronic bronchitis |  |
| H32y.00 | Other emphysema |  |
| H31y100 | Chronic tracheobronchitis |  |
| H321.00 | Panlobular emphysema |  |
| H320000 | Segmental bullous emphysema |  |
| H32y111 | Acute interstitial emphysema |  |
| H320200 | Giant bullous emphysema |  |
| H310z00 | Simple chronic bronchitis NOS |  |
| H311z00 | Mucopurulent chronic bronchitis NOS |  |
| H32y200 | MacLeod's unilateral emphysema |  |
| H31y.00 | Other chronic bronchitis |  |
| H3y..11 | Other specified chronic obstructive pulmonary disease |  |
| H31yz00 | Other chronic bronchitis NOS |  |
| H320100 | Zonal bullous emphysema |  |
| H32y100 | Atrophic (senile) emphysema |  |
| H32y000 | Acute vesicular emphysema |  |
| H320300 | Bullous emphysema with collapse |  |
| H320311 | Tension pneumatocoele |  |
| H3A..00 | End stage chronic obstructive airways disease |  |
| H583200 | Eosinophilic bronchitis |  |

To determine the extent of undiagnosed (but diagnosable) COPD we then developed a diagnostic algorithm using the criteria shown in row 5 of Table 7: the positive predictive value (PPV) and proportion of patients diagnosed with chronic obstructive pulmonary disease (COPD) within each algorithm. For “diagnosis” via the algorithm, patients had two or more codes for sputum, breathlessness, or cough, plus two or more prescriptions for a possible COPD therapy (see 7.1 CPRD medcodes and drug codes), and a smoking history.

### CPRD risk factors

We used the literature review described in the Background to extract CPRD data on risk factors. There were two main reasons why some risk factors from the literature were not used in the final model. Firstly, the data was not available in CPRD. For example, data on educational level, occupational class and socioeconomic status is very poorly recorded. The occupational classification for which Read codes are available is from a 1986 Office for National Statistics classification so is outdated. Physical activity is also poorly recorded, although this is improving because of the dissemination of the GP Physical Activity Questionnaire (GPPAQ),[72] and the capture of GPPAQ data at the time of NHS Health Checks in particular. CPRD links most patients’ data to Index of Multiple Deprivation (IMD) data based on postcode. Secondly, to produce local estimates we use “joint distributions”- cross tabulations which distribute data on each risk factor across the data for all other risk factors- of local risk factor data to which we apply the CPRD prevalence estimates for the same distributions. Hence we can only use in the final regression model variables which are also available locally. This may cause model performance to deteriorate. We evaluated the extent of this by comparing Receiver Operating Characteristic (ROC) curves for the two models.

Risk factor data were extracted by a defined Read code lists. These are created by searching for relevant Read version 2 5-byte codes using either CPRD’s own code browser or using the “NHS browser” maintained by the Health & Social Care information Centre (HSCIC). We used the NHS browser to create code lists for smoking by searching relevant read terms or going down the hierarchy of relevant read codes. Social class was defined using the Index of Multiple Deprivation (IMD) deprivation score of the postcode of patients’ general practice. This linkage is only availalble in about 50% of CPRD practices and patients.

### CPRD descriptive analyses

We performed a number of descriptive analyses on the patient-level dataset including demographics, risk factor breakdowns and categories.

### CPRD regression modelling

We fitted uni-variate then multivariate logistic regression models for non-specific and radicular back pain as described in previous publications, to produce odds ratios (ORs) and regression coefficients.[2] A range of multivariate regression models were fitted in order to obtain the best performing. We included one additional variable at a time to observe the effects.

### Interactions

There is an interaction between the effects of two exposures if the effect of one exposure varies according to the level of the other exposure.[73] For example, there might be an interaction between the back pain risk factors of education level and social class. An alternative term for interaction is effect modification. In this example, we can think of this as educational level modifying the effect of social class. The most flexible approach to examine interactions is to use regression models, but when using Mantel-Haenszel methods to control for confounding an alternative is to use a χ2 test for effect modification, commonly called a test of heterogeneity. Interaction, effect modification and heterogeneity are three different ways of describing the same thing. Log likelihoods are compared in the two models excluding and including the interaction parameters to test the null hypothesis that there is no interaction between selected variables.

### Internal validation

We fitted a range of multivariate logistic regression models in order to obtain the best performing. We included one additional variable at a time to observe the effects. In order to obtain the most parsimonious models we then applied stepwise backward and forward variable selection using the *stepwise* command in Stata. Finally, we internally validated the models by generating receiver operating characteristic (ROC) curves, by using the ***predict*** regression post-estimation command to generate for each respondent the probability of having PAD using the derived odds ratios (ORs), and by using these probabilities to examine sensitivity and specificity.

All statistical analysis was carried out in Stata SE14 or MP14.

## Local prevalence estimates

Derived ORs (or rather, regression coefficients) are used to estimate prevalence in small population subgroups. Local population breakdowns for each risk factor are used, where these are available. ICL has a wide range of small population risk factor prevalence breakdowns, including age, sex, deprivation, smoking, ethnicity, cardiovascular diseases and other disease conditions. The local model uses locally available data.

The “local” model includes only those variables that are available at local population level i.e. age, sex, socioeconomic status, BMI, smoking status, depression and other disease conditions. The steps in applying the prevalence estimates are as follows and in the equations below:

• Use the regression coefficients to generate log odds (since they are from a logistic regression model) for each risk factor subcategory

• Generate a similar table of odds by exponentiation

• Generate a similar table of prevalence in each risk factor subcategory using the epidemiologic formula

• Produce a matching table of small population subcategories. If there are no corresponding local data with a sufficiently granular breakdown e.g. ethnicity by age by sex, this requires deciding how each risk factor should be attributed across other risk factor categories, with evenly as the default. For example, we used the national age/sex/ethnicity breakdown from the Census and age/smoking breakdowns from the HSfE to attribute this data at small population levels. The actual breakdown will be somewhat different and needs to be borne in mind as another source of potential error.

• Multiply the population cells by the corresponding prevalence to estimate the number of people in each cell with the disease

In mathematical notation:

Predicted log odds of prevalence = *b0* + *b1x1i* +  *b2x2 i* + *b3x3 i* +  *b4x4 I*

where *b0* = regression constant, *b1, b2,  b3, b4*= other regression coefficients

*x 1 i, x2 i, x3 i, x4 i* = value of risk factors for individual ***i***

(NB since all the variables are binary variables, x =1 if specified risk factor is present, x=0 if it is absent). Predicted log odds of prevalence for a community of n individuals is derived by averaging over the values for all individuals included in the community:

Predicted log odds of prevalence in community of n individuals:

= 1/*n* ∑i=1n (*b0* + *b1x1i* +  *b2x2 i* + *b3x3 i* +  *b4x4 i)*

= *b0* + *b1p1* +  *b2p2* + *b3p3* +  *b4pp4*

where p1 , p2, p3, p4=proportion of individuals in the community with characteristic x1 , x2 , x3 , x4 . (i.e. proportion with x.=1 rather than x.=0 as in the remainder).

The predicted prevalence for an individual is derived from their predictive log odds using:

prevalence = exp(log odds)/[1+exp(log odds)]

= *exp*(*b0* + *b1x1i* +  *b2x2 i* + *b3x3 i* +  *b4x4 i)/[1+* *exp*(*b0* + *b1x1i* +  *b2x2 i* + *b3x3 i* +  *b4x4 i)]*

Predicted prevalence in community of n individuals:

*= 1/n ∑i=1n[exp(b0 +b1x1i +b2x2 i +b3x3 i +b4x4 i)/[1+ exp(b0 +b1x1i +b2x2 i +b3x3 i +b4x4 i)]]*

Unfortunately, the equation above does not simplify to a linear combination of the predictor variables (in the way the mean log odds does). The average/overall prevalence is not the same as the prevalence for a person with “average” risk factors. So, for instance, it cannot be found by taking exp(log odds)/[1+ exp(log odds)] of the average log odds. There is no linear relationship with the regression coefficients, and with proportions of population with specified risk factors.

In order to find a synthetic estimate of prevalence, ideally we need to know the joint distributions of the included risk factors in the relevant population (the population on which are synthetic estimates are required). Ideally, we would know how many people in the population have each specific combination of risk factors. In practice, it might be good enough to know the distribution of some risk factors individually, rather than in combination. For instance, we might know what proportion of the population are smokers, and what proportion are ex-smokers, but not how many smokers we have by age and sex. In this situation, we have assumed that the same proportion of all ages and both genders are smokers and ex-smokers. Even if this is not exactly correct, then the synthetic estimate of prevalence may still be a reasonably accurate estimate (assuming that the smoking distribution does not vary too much by age, sex and other included risk factors). This is considered a good enough approach, and the best possible based on the information currently available in many cases.

In practice, we know the population distributions by age and sex, therefore we do not need to make the assumption that the proportion of males is the same for each age group. We use the more precise method of using the actual proportions of males in each age group. From the ELSA longitudinal survey we also know that older people/ older females in particular are generally less educated (on the basis of qualifications held). Therefore we apply the proportions with any educational qualifications according to age and sex group.

For other risk factors, we do not know whether these risk factors are more or less common in males than in females, nor according to age group, nor educational status i.e. we do not know their distributions in combination with any of the other risk factors included in the model. Therefore we make the assumption that the distribution of all other risk factors (apart from afore-mentioned age, sex and educational status), is equal across all other risk factors. This makes the calculations somewhat easier, even though this assumption might make for slightly less accurate estimates, the loss of accuracy is not thought to be great.

In order to find the estimated prevalence for each population, it is necessary to calculate the synthetic prevalence of risk factors for each possible combination of risk factor (as included in the chosen disease-specific logistic regression model). The estimated prevalence for a population is then the weighted average of the prevalence estimates for each combination of risk factors, according to the estimated number of people with each risk factor combination in the population (the population on which synthetic estimates are sought). These calculations can be carried out in Excel (using VBA code to link prevalence and risk factor spreadsheets with formulae in a workbook) or in Stata software to produce confidence intervals as well as the estimates.

We have developed two methods for producing small population estimates and associated CIs in Stata software. One uses a bootstrapping method to produce repeated samples (Method 1), the other (Method 2) uses inverse probability weights. Both methods produce CIs for the estimates, which are derived from the variance in the logistic model, not the local populations. It would have been useful to compare the results of both methods, but because of the short timeframe for this project we only used Method 2: Logistic regression and inverse probability weights.

### Method 1: bootstrapping procedure to produce repeated samples

The detailed methods of the Stata code we developed and used is included in Annex 1: synthetic estimation using Stata. In summary, within Stata, a new set of variables is created, one for each combination of these risk factors pertinent to the logistic regression model for the chosen disease. With our dataset set up in this way, we can now use Stata’s “predict” command to give us the predicted log odds. Then we find the weighted average of these, averaged across all possible combinations of risk factors, using the weights calculated as above (stored in variable named xyz). The weighted average can be found using the “collapse” command as follows, which results in one line of data per practice or MLSOA (using the population identifier as the by variable) in Stata.

We calculated in Stata CIs for prevalence estimates using a “bootstrap” procedure. There is uncertainty in these synthetic estimates of prevalence based on the imprecision not in the more usual sample of people from the population (since the estimates are not a sample but are externally applied), but in the estimated coefficients from the logistic regression equations. A bootstrap procedure can be used to construct confidence intervals on these synthetic estimates of prevalence, based on the imprecision in these logistic regression coefficients.

The philosophy underlying the bootstrap procedure is to consider that the people included in the data set used to derive the logistic regression equation represent the whole population of possible people. However, the whole population is effectively considered to contain thousands of copies of each of these people. Bootstrap samples are taken randomly from our initial populations (the subsets of the CPRD population that has complete data on appropriate risk factors). Logistic regression of the same risk factors can then be applied to this boot strap sample, i.e. we rerun the logistic regression that gave us our chosen predictive model. However, we get slightly different regression coefficients, because of the modified sample. Prevalence estimates are then derived for each combination of risk factors, based on these new regression equations.

This process is repeated 1,000 times, to find 1,000 different boot strap samples, by random sampling processes, and to then fit logistic regression equations on each. The prevalence estimates are calculated for each combination of risk factors, for each of these 1,000 boot strap samples. For each small population, a synthetic estimate is calculated for each boot strap sample, by appropriately weighting the prevalence estimates on each combination of risk factors (with the same weights as described above which reflect the anticipated prevalence of each combination of risk factors in the population). From these 1,000 synthetic estimates of prevalence of each population, a 95% confidence interval is calculated as the 2.5th to 97.5th centiles. Given that the estimates are distributed normally, these are taken to be mean +/- 1.96 SD (taking mean and SD of the 1,000 boot strap synthetic prevalence estimates for each specified region).

### Method 2: Logistic regression and inverse probability weights

Inverse probability weighting methods are used to standardise from a sampled population to a target population. They are usually defined as a function of a panel of one or more sampling-probability predictor variables. For each combination of the predictor variables, the sampling probability weight is the ratio of the frequency of that combination in the target population to the frequency of that combination in the sampled population. Inverse probability weighting is therefore a generalization of direct standardization. In Stata, it is implemented by using a *pweight* qualifier on an estimation command. This normally implies the use of a Huber variance formula to generate the confidence limits.

In a population case-control study, our sampled population is an exhaustive list of disease cases, plus a random sample of controls without the disease, with a known sampling fraction. The sampling probability weights are inversely proportional to the sampling fraction for each sub-population. For cases, the sampling probability weight is 1. And, for controls, the sampling probability weight is the reciprocal of the sampling fraction. (So, if the sampling fraction is 1/8, then controls are weighted upwards by a factor of 8.) These sampling-probability weights are used in logistic regression models. Predicted disease probabilities from these models will then be unbiased, if the model is correctly specified.

Similarly to Method 1 we estimated population parameters for logistic regression models. The risk factors in the model fell into two classes, namely always-present risk factors and sometimes-missing risk factors. The always-present risk factors were gender (Male or Female), age group (18-44, 45-64, 65-74 and 75+), ethnicity (White, Mixed, Black, Asian or Other, imputed to White if not known). The sometimes-missing risk factors were practice index of multiple deprivation (IMD) quintile (1, 2, 3, 4 or 5), smoking status (Non-smoker, Ex-smoker or Smoker), alcohol units per week category (None, (0,14], (14,42] or >42), and body mass index in kilos/square metre (BMI) category ((0, 18.5], (18.5,25], (25,30] or >30).

We fitted the logistic regression model, using Huber variances and sampling-probability weights. The parameters were a baseline odds for each of the 2x4=8 combinations of gender and age group, an odds ratio for each ethnicity except White, an odds ratio for each IMD quintile except the first, an odds ratio for each smoking status except Non-smoker, an odds ratio for each alcohol consumption category except Zero units, and an odds ratio for each BMI category except (18.5,25] kilos per square metre. The sampling-probability weights used were equal to the products of two sets of component sampling-probability weights. The first set of component weights standardised by case status from the case-control study sample to the denominator population from which the cases and controls were sampled, and were equal to 1 for RA cases (assumed to be sampled exhaustively from the cases in the CPRD denominator population), and equal in the controls to the reciprocal of the sampling fraction of the controls as a fraction of the non-cases in the CPRD denominator population (equal to 27.211693).

We also use inverse probability weights to correct for missing values as an easy-to-use alternative to multiple imputation. We then define the inverse probability weights using a completeness-propensity score. We have a panel of variables *V1…VK* that are always present (such as age and gender), and a panel of variables *U1…UJ* that are sometimes missing. Let C (for completeness) be the binary indicator variable indicating that all the variables *U1…UJ* are present. We then use a logistic regression model, regressing C with respect to the always-complete variables *V1…VK*. The completeness-propensity score is defined as the predicted completeness probability for each individual, under that regression model. The inverse-probability weight, for each individual with a complete set of data *U1…UJ*, is then the reciprocal of that individual’s completeness-propensity score. Therefore, individuals with a high probability of having complete data (like elderly females) are weighted downwards. And individuals with a low probability of completeness (like young males) are weighted upwards. These inverse-probability weights can then be used in further regression models, such as a logistic regression model to predict disease.

Therefore, the second set of component weights were computed to standardise the sample of cases and controls with all risk factors present to the total sample of cases and controls by gender, age group and ethnicity, and were derived as inverse probabilities of presence of the full set of risk factors (completeness) from a logistic regression model with completeness as the outcome, fitted to the cases and controls, using the first set of sampling-probability weights to standardise by case status, and whose parameters were a baseline odds for each of the 8 combinations of gender and age group and an odds ratio for each non-white ethnic category. The product weights therefore were computed to standardise the odds and odds ratios from the sample of cases and controls with all risk factors present (272,369 subjects out of a total of 101,870 cases and 440,293 sampled controls) to the total denominator population of subjects aged at or above 18 years, with or without RA, on their birthdays in 2015 (13,864,783 subjects). We also fitted logistic regression models of RA status with respect to the 8 combinations of gender and age only, using only the first set of sampling probability weights to standardise by RA status, in order to estimate odds (and thereby prevalence) of RA for each combination of gender and age group in the CPRD population at large.

Having estimated the regression model parameters, we used these for out-of-sample prediction of RA prevalence, using the *margprev* add-on Stata package [74 ,75]. These predicted prevalence estimates were for the sub-populations of patients for 7,692 practices, for 204 clinical care groups (CCGs), and for 6,755 MSOAs, for which information was available on the marginal frequencies of the seven risk factors in the model. We computed estimated prevalence assuming that, within each sub-population, the seven risk factors were mutually statistically independent, implying that we could give each possible combination of the seven risk factors a sampling-probability weight proportional to the product of the proportions of subjects with each of the appropriate risk-factor values. Therefore, for each subpopulation, we had 2x4x5x5x3x4x4=9600 combinations of risk factor values, with proportions of subjects calculated assuming statistical independence, and estimated the expected subpopulation prevalence of RA accordingly. The assumption of statistical independence of risk factors is probably not literally true, but might be expected to give prevalence estimates that are not vastly in error if the effects of the risk factors are not too non-additive. We have not internally or externally validated this method yet.

We have used method 2, logistic regression and inverse probability weights for these models because of the large number of variables in most of the models. This required us to produce Stata datasets of local risk factor data which have one observation for every permutation of all the risk factors for every practice, which generated very large files (up to 60 GB). We were able to process these using Stata/MP, the fastest and largest version of Stata. On dual-core chips, Stata/MP runs 40% faster overall and 72% faster on time-consuming estimation commands. It can handle a maximum number of 32,767 variables and 20 billion observations. Some of the datasets we used included over one billion observations. Processing was carried out on a multicore server. It would not have been possible to run the bootstrapping procedure to produce repeated samples which requires fitting a logistic model 1,000 times for each practice.

## Validation of local estimates

### Internal validation

In addition to the internal and external validation of the regression models, The local estimates can also be validated by aggregating them to the lowest geography available in the raw data and comparing them, a form of internal validation. These and external validations are shown in the Results. As noted above, we have over time increased the number of variables used in the local models as more local data has become available. However as more variables are added we need to take account of the joint effects of multiple risk factors, i.e. it assumes they operate independently. Estimation of the joint effects of multiple risk factors is complex for several reasons. In particular, some of the effects of more distal risk factors are mediated through intermediate factors. We have acknowledged this by creating specific joint distributions for variables where this is known e.g. age and educational level, as older age groups are less likely to have tertiary education.

### External validation

Because of the short timeframe for this project we have not had time to externally validate the local estimates using other similar datasets. However there are Quality & Outcomes Framework (QOF) disease registers[76] for all the models we produced here. We have experience in comparing QOF-registered prevalence and estimated prevalence right down to practice level using spatial analyses.[77] The local estimates can also be validated against the corresponding QOF register for each geography using Bland-Altman plots. This method uses graphical methods to investigate the assumptions of the method and also gives confidence intervals.[78] It aims to quantify the agreement between and clinical importance of two methods of clinical measurement using the differences between observations made using the two methods on the same subjects. The 95% limits of agreement, estimated by mean difference 1.96 standard deviation of the differences, provide an interval within which 95% of differences between measurements by the two methods are expected to lie. The second method is based on errors-in-variables regression in a classical (X,Y) plot and focuses on confidence intervals, whereby two methods are considered equivalent when providing similar measures notwithstanding the random measurement errors.[79] A recent update reconciles these two methodologies and shows their similarities and differences using both real data and simulations.[80]

# Results

## COPD definitions and prevalence

### Missing data

CPRD data source may not include all patients’ data in terms of all the demographic aspects, such as ethnicity and smoking. There is some missing risk factor data, and different methods were used to deal with it. Patients with missing IMD scores for their general practice location (1,837,537 patients or 51.3% of the whole analysis dataset) were dropped from further analysis. For ethnicity, missing data were considered as “White population”. Those without a code for ex or current smoking are classified as never smokers. Table 13 shows the baseline characteristics of patients (both COPD cases and non-COPD cases) that we included in the modelling. The characteristics of these five groups are relatively similar, despite the fact that there is a greater number of younger people in the control group. The Medcode/Readcode list of drugs used for COPD is shown in Table 24: product/drug codes relevant for the diagnosis of COPD in the Appendix: additional information, Section 7.1.

## CPRD COPD definitions, incidence & prevalence

### COPD definions and flowchart

Figure 3 shows a flowchart of the COPD diagnosis sources we used for the model. We obtained from CPRD a file conrtaining all HES diagnoses, either primary or secondary, for COPD. This was linked with our CPRD extract containing diagnostic and clinical codes as shown in Section 7.1 of the Appendix: additional information.

### Doctor diagnosed COPD cases

Of the 10,272,602 over 35 patients in the CPRD dataset, 169,900 patients had a doctor-diagnosis of COPD in their CPRD electronic health record, giving a crude prevalence of 1.65%. Use of this definition has been validated previously.[46] We then linked the CPRD dataset to the HES dataset, which contained 158,595 patients with a COPD diagnosis. Of these, only 54,384 also had a CPRD diagnosis. This left 104,211 patients identified only through HES, giving an overall total of 274,211 patients with a doctor- (GP or HES) COPD diagnoses, a crude prevalence of 2.67%. This is still well below the minimum prevalence of 4-5% from the various population surveys quoted in the Background.

There were 563,926 patients with a smoking history, two or more symptoms and two or more prescriptions for inhaled COPD therapy. Of these patients, only 56,134 already had a COPD diagnosis, leaving 507,792 patients for further investigation.

Figure : flowchart of COPD diagnosis sources

Extraction of records from CPRD database

(N=10,272,602)

Extract medcodes relevant to the diagnosis of COPD

Patients with smoking history and 2+ symptoms and 2+ prescriptions for inhaled COPD therapy

N= 563,926

Identify doctor diagnosed COPD cases (N=169,900)

Final CPRD doctor diagnosed COPD cases (N=169,900)

Excluding doctor (HES or CPRD) diagnosed COPD

N= 56,134

Linked HES data

(N=627,672)

Extracting ICD-10 codes relevant to the diagnosis of COPD

Identifying doctor diagnosed COPD cases (N=158,595)

Excluding COPD cases who have a CPRD COPD diagnosis (N=54,384)

Additional HES diagnosed COPD cases (N=104,211)

Algorthm-positive possible COPD cases (N=507,792)

Doctor diagnosed COPD cases (N=274,111)

### CPRD prevalence and incidence

Prevalence of COPD in the CPRD data was calculated for CPRD and HES doctor-diagnosed COPD with and without algorithm-diagnosed COPD (or “high risk of COPD”) using algorithm B from Quint et al.[46] The prevalence of COPD for the years 2004-2015 is shown in Table 11 for males and Table 12 for females, and in Figure 4. As noted before, there are considerable numbers of historical diagnoses for doctor-diagnosed COPD but these were obviously not used for algorithm-diagnosed COPD.

Table 11 and Table 12 show the prevalence and incidence of doctor diagnosed and algorithm diagnosed COPD in the years 2004-2015, broken down by age group and sex.

Table : Prevalence of doctor-diagnosed COPD per 100,000 patients in CPRD data 2000-2014: males only, by age group

| Year | 35-40 | 41-50 | 51-60 | 61-70 | 71-80 | 81+ |
| --- | --- | --- | --- | --- | --- | --- |
| 2004 | 17.3 | 134.5 | 864.2 | 3061.2 | 5732.5 | 6550.7 |
| 2005 | 20.9 | 177.5 | 998.6 | 3376.1 | 6324.7 | 7418.0 |
| 2006 | 28.7 | 200.1 | 1106.1 | 3593.3 | 6703.7 | 8312.3 |
| 2007 | 32.8 | 231.1 | 1167.5 | 3714.0 | 7023.8 | 8772.6 |
| 2008 | 32.1 | 256.2 | 1206.6 | 3818.9 | 7336.5 | 9092.7 |
| 2009 | 35.6 | 283.8 | 1243.2 | 3904.7 | 7527.1 | 9323.5 |
| 2010 | 37.0 | 318.0 | 1286.1 | 4048.0 | 7785.7 | 9748.9 |
| 2011 | 37.4 | 348.0 | 1376.0 | 4240.7 | 7988.0 | 9935.1 |
| 2012 | 41.9 | 355.3 | 1435.6 | 4376.7 | 8155.0 | 9962.1 |
| 2013 | 40.3 | 411.8 | 1491.0 | 4497.2 | 8283.7 | 10001.6 |
| 2014 | 42.3 | 428.5 | 1498.2 | 4458.6 | 8322.7 | 9909.8 |
| 2015 | 32.8 | 422.7 | 1486.8 | 4393.4 | 8299.5 | 9785.0 |

Table : Prevalence of doctor-diagnosed COPD per 100,000 patients in CPRD data 2000-2014: females only by age group

| Year | 35-40 | 41-50 | 51-60 | 61-70 | 71-80 | 81+ |
| --- | --- | --- | --- | --- | --- | --- |
| 2004 | 15.5 | 169.9 | 851.5 | 2259.2 | 3585.4 | 2920.0 |
| 2005 | 23.0 | 208.7 | 993.6 | 2581.1 | 4017.0 | 3488.9 |
| 2006 | 30.5 | 234.9 | 1108.3 | 2830.2 | 4357.6 | 3958.8 |
| 2007 | 33.5 | 266.2 | 1191.1 | 3014.0 | 4649.6 | 4389.2 |
| 2008 | 34.2 | 281.3 | 1261.8 | 3187.4 | 4914.7 | 4712.3 |
| 2009 | 33.2 | 313.1 | 1335.9 | 3297.1 | 5135.9 | 4950.8 |
| 2010 | 33.9 | 348.7 | 1416.1 | 3426.3 | 5377.0 | 5314.7 |
| 2011 | 33.6 | 370.9 | 1501.2 | 3592.4 | 5654.8 | 5638.1 |
| 2012 | 31.9 | 391.0 | 1569.2 | 3753.6 | 5834.9 | 5837.7 |
| 2013 | 29.7 | 429.7 | 1638.3 | 3864.4 | 6034.5 | 5960.6 |
| 2014 | 31.8 | 458.9 | 1656.2 | 3921.8 | 6135.8 | 6009.1 |
| 2015 | 33.6 | 461.1 | 1636.7 | 3978.3 | 6179.4 | 5880.4 |

Figure : prevalence of doctor-diagnosed COPD in the CPRD data: 2000-2014 by sex and age group



### Baseline descriptive characteristics of CPRD patients

Table 13 shows the baseline characteristics of patients (both CPRD/HES/algorithm-identified COPD cases and non-COPD cases) included in the regression modelling. The characteristics of these groups are relatively similar, despite the fact that there is a greater number of younger patients in the controls group because of the increasing prevalence with age.

Table : Baseline characteristics of patients included in the logistic regression models

|  | CPRD+HES diagnosis (N,%) | | CPRD+HES+Algorithm (N,%) | |
| --- | --- | --- | --- | --- |
|  | COPD | Non-COPD | COPD | Non-COPD |
| Age |  |  |  |  |
| <40 | 514 (0.71) | 1,755,953 (50.0) | 141,320 (24.4) | 1,615,147 (53.81) |
| 40-49 | 3,253 (4.5) | 514,970 (14.7) | 87,545 (15.1) | 430,678 (14.4) |
| 50-59 | 9,929 (13.8) | 467,938 (13.3) | 95,812 (16.5) | 382,055 (12.7) |
| 60-69 | 20,466 (28.5) | 372,715 (10.6) | 108,246 (18.7) | 284,935 (9.5) |
| 70-79 | 23,050 (32.0) | 243,000 (6.9) | 90,453 (15.6) | 175,597 (5.9) |
| 80+ | 14,737 (20.5) | 154,516 (4.4) | 56,365 (9.7) | 112,888 (3.8) |
| Sex |  |  |  |  |
| Male | 37,048 (51.5) | 1,734,515 (49.4) | 269,128 (46.4) | 1,502,435 (50.1) |
| Female | 34,901 (48.5) | 1,774,542 (50.6) | 310,605 (53.6) | 1,498,838 (49.9) |
| Smoking |  |  |  |  |
| Current | 34,630 (48.1) | 616,278 (17.6) | 315,657 (54.5) | 335,251 (11.2) |
| Ex | 27,094 (37.7) | 572,428 (16.3) | 235,859 (43.8) | 345,663 (11.5) |
| Never | 10,225 (14.2) | 2,320,386 (66.1) | 10,225 (1.8) | 2,320,386 (77.3) |
| Deprivation (practice postcode Index of Multiple Deprivation) | | | | |
| IMD quintile 1 (least deprived) | 44,040 (15.6) | 255,979 (17.5) | 44,040 (15.6) | 255,979 (17.5) |
| IMD quintile 2 | 64,961 (23.0) | 337,610 (23.1) | 64,961 (23.0) | 337,610 (23.1) |
| IMD quintile 3 | 45,776 (16.2) | 255,091 (17.5) | 45,776 (16.2) | 255,091 (17.5) |
| IMD quintile 4 | 55,024 (19.5) | 271,795 (18.6) | 55,024 (19.5) | 271,795 (18.6) |
| IMD quintile 5 (most deprived) | 72,556 (25.7) | 340,672 (23.3) | 72,556 (25.7) | 340,672 (23.3) |
| IMD missing | 1,837,537 (51.3%) | | 1,837,537 (51.3%) | |

## Regression modelling using CPRD data

### CPRD univariate logistic analysis

Table 14 shows the results of univariate logistic models for individual risk factors and the outcome.

Table 14: Univariate logistic model for individual risk factors

### Multivariate logistic analysis

We went through an extensive model fitting process to compare the performance of different models that included COPD patients identified by different methods. Table 15 below shows the logistic regression model results including patients with only CPRD doctor-diagnosed COPD. As we would expect from the literature, COPD is significantly higher in males, ORs rise very rapidly with age, are high for smokers and ex-smokers, and increase with increasing deprivation.

Table 15: M1- logistic regression model including patients with only CPRD doctor-diagnosed COPD

| Parameter | Odds Ratio | Lower 95% CI | Upper 95% CI | *p* value |
| --- | --- | --- | --- | --- |
| Sex |  |  |  |  |
| Male | 1 | 1 | 1 | . |
| Female | 0.956 | 0.932 | 0.981 | 0.000 |
| Age group |  |  |  |  |
| <40 | 1 | 1 | 1 | . |
| >40 & <50 | 16.717 | 6.877 | 40.642 | 0.000 |
| >50 & <60 | 54.289 | 22.505 | 130.963 | 0.000 |
| >60 & <70 | 141.475 | 58.754 | 340.661 | 0.000 |
| >70 & <80 | 202.261 | 83.973 | 487.175 | 0.000 |
| >80 | 124.298 | 51.440 | 300.352 | 0.000 |
| Smoking |  |  |  |  |
| Non-smoker | 1 | 1 | 1 | . |
| Current smoker | 25.734 | 10.321 | 64.160 | 0.000 |
| Ex-smoker | 16.790 | 6.499 | 43.378 | 0.000 |
| Interaction term age group x smoking |  |  |  |  |
| Age group <40 x non-smoker | 1 | 1 | 1 | . |
| Age group <40 x current smoker | 1 | 1 | 1 | . |
| Age group <40 x ex-smoker | 1 | 1 | 1 | . |
| Age group >40 & <50 x non-smoker | 1 | 1 | 1 | . |
| Age group >40 & <50 x current smoker | 0.370 | 0.146 | 0.936 | 0.036 |
| Age group >40 & <50 x ex-smoker | 0.264 | 0.101 | 0.695 | 0.007 |
| Age group >50 & <60 x non-smoker | 1 | 1 | 1 | . |
| Age group >50 & <60 x current smoker | 0.412 | 0.164 | 1.031 | 0.058 |
| Age group >50 & <60 x ex-smoker | 0.277 | 0.107 | 0.721 | 0.008 |
| Age group >60 & <70 x non-smoker | 1 | 1 | 1 | . |
| Age group >60 & <70 x current smoker | 0.425 | 0.170 | 1.064 | 0.068 |
| Age group >60 & <70 x ex-smoker | 0.328 | 0.126 | 0.849 | 0.022 |
| Age group >70 & <80 x non-smoker | 1 | 1 | 1 | . |
| Age group >70 & <80 x current smoker | 0.515 | 0.206 | 1.288 | 0.156 |
| Age group >70 & <80 x ex-smoker | 0.443 | 0.171 | 1.148 | 0.094 |
| Age group >80 x non-smoker | 1 | 1 | 1 | . |
| Age group >80 x current smoker | 0.862 | 0.343 | 2.167 | 0.753 |
| Age group >80 x ex-smoker | 0.866 | 0.333 | 2.251 | 0.768 |
| Deprivation |  |  |  |  |
| IMD quintile 1 (least deprived) | 1 | 1 | 1 | . |
| IMD quintile 2 | 1.244 | 1.189 | 1.302 | 0.000 |
| IMD quintile 3 | 1.446 | 1.379 | 1.517 | 0.000 |
| IMD quintile 4 | 1.576 | 1.506 | 1.650 | 0.000 |
| IMD quintile 5 (most deprived) | 1.861 | 1.783 | 1.943 | 0.000 |
| Constant | 0.000 | 0.000 | 0.000 | 0.000 |

Table 16 shows the logistic regression model including patients with only HES COPD diagnosis. It is fairly similar to the results for CPRD diagnoses, with some minor differences such as an insignificant difference between males and females.

Table 16: M2- logistic regression model including patients with only HES COPD diagnosis

| Parameter | Odds Ratio | Lower 95% CI | Upper 95% CI | *p* value |
| --- | --- | --- | --- | --- |
| Sex |  |  |  |  |
| Male | 1 | 1 | 1 | . |
| Female | 1.025 | 0.984 | 1.067 | 0.241 |
| Age group |  |  |  |  |
| <40 | 1 | 1 | 1 | . |
| >40 & <50 | 2.668 | 1.715 | 4.152 | 0.000 |
| >50 & <60 | 7.683 | 5.038 | 11.718 | 0.000 |
| >60 & <70 | 23.379 | 15.437 | 35.408 | 0.000 |
| >70 & <80 | 55.684 | 36.839 | 84.168 | 0.000 |
| >80 | 88.918 | 58.849 | 134.351 | 0.000 |
| Smoking |  |  |  |  |
| Non-smoker | 1 | 1 | 1 | . |
| Current smoker | 2.499 | 1.426 | 4.381 | 0.001 |
| Ex-smoker | 1.135 | 0.525 | 2.452 | 0.748 |
| Interaction term age group x smoking |  |  |  |  |
| Age group <40 x non-smoker | 1 | 1 | 1 | . |
| Age group <40 x current smoker | 1 | 1 | 1 | . |
| Age group <40 x ex-smoker | 1 | 1 | 1 | . |
| Age group >40 & <50 x non-smoker | 1 | 1 | 1 | . |
| Age group >40 & <50 x current smoker | 1.623 | 0.891 | 2.955 | 0.113 |
| Age group >40 & <50 x ex-smoker | 1.564 | 0.691 | 3.538 | 0.283 |
| Age group >50 & <60 x non-smoker | 1 | 1 | 1 | . |
| Age group >50 & <60 x current smoker | 1.849 | 1.039 | 3.291 | 0.037 |
| Age group >50 & <60 x ex-smoker | 1.727 | 0.786 | 3.792 | 0.174 |
| Age group >60 & <70 x non-smoker | 1 | 1 | 1 | . |
| Age group >60 & <70 x current smoker | 1.291 | 0.730 | 2.282 | 0.380 |
| Age group >60 & <70 x ex-smoker | 1.323 | 0.608 | 2.879 | 0.480 |
| Age group >70 & <80 x non-smoker | 1 | 1 | 1 | . |
| Age group >70 & <80 x current smoker | 0.981 | 0.555 | 1.734 | 0.948 |
| Age group >70 & <80 x ex-smoker | 1.069 | 0.492 | 2.320 | 0.867 |
| Age group >80 x non-smoker | 1 | 1 | 1 | . |
| Age group >80 x current smoker | 0.881 | 0.496 | 1.563 | 0.664 |
| Age group >80 x ex-smoker | 1.053 | 0.485 | 2.285 | 0.897 |
| Deprivation |  |  |  |  |
| IMD quintile 1 (least deprived) | 1 | 1 | 1 | . |
| IMD quintile 2 | 1.216 | 1.130 | 1.309 | 0.000 |
| IMD quintile 3 | 1.450 | 1.342 | 1.567 | 0.000 |
| IMD quintile 4 | 1.717 | 1.597 | 1.847 | 0.000 |
| IMD quintile 5 (most deprived) | 2.069 | 1.931 | 2.217 | 0.000 |
| Constant |  |  |  |  |

Table 17 shows the logistic regression model for patients with only algorithm/possible COPD diagnosis (smoking history and 2+ symptoms and 2+ prescriptions for inhaled COPD therapy), and excluding those with HES or CPRD COPD diagnoses. In contrast to the models for doctor-diagnosed COPD, the ORs we obtained were very dissimilar to the other models and to what we would expect from the literature. Females have a higher OR, prevalence decreases with age, as does ORs for more deprived populations. The algorithm appears to select a different and much younger population who nevertheless are smokers who meet the criteria. The PPV for this group from the 2014 paper by Quint et al was 45%, so a significant proportion of them should have similar ORs to those with diagnoses. However we did not have the time or resource to investigate this group in more detail, which would involve as a first step determing how many do have COPD e.g from spirometry data, and we decided not to include them in the final model.

Table 17: M3- logistic regression model including patients with only algorithm/possible COPD diagnosis (smoking history and 2+ symptoms and 2+ prescriptions for inhaled COPD therapy)

| Parameter | Odds Ratio | Lower 95% CI | Upper 95% CI | *p* value |
| --- | --- | --- | --- | --- |
| Sex |  |  |  |  |
| Male | 1 | 1 | 1 | . |
| Female | 1.229 | 1.198 | 1.261 | 0.000 |
| Age group |  |  |  |  |
| <40 | 1 | 1 | 1 | . |
| >40 & <50 | 0.267 | 0.191 | 0.373 | 0.000 |
| >50 & <60 | 0.091 | 0.066 | 0.126 | 0.000 |
| >60 & <70 | 0.035 | 0.026 | 0.049 | 0.000 |
| >70 & <80 | 0.020 | 0.015 | 0.028 | 0.000 |
| >80 | 0.017 | 0.012 | 0.023 | 0.000 |
| Smoking |  |  |  |  |
| Non-smoker | 1 | 1 | 1 | . |
| Current smoker | 0.583 | 0.397 | 0.856 | 0.006 |
| Ex-smoker | 1.000 | 1.000 | 1.000 | . |
| Interaction term age group x smoking |  |  |  |  |
| Age group <40 x non-smoker | 1 | 1 | 1 | . |
| Age group <40 x current smoker | 1 | 1 | 1 | . |
| Age group <40 x ex-smoker | 1 | 1 | 1 | . |
| Age group >40 & <50 x non-smoker | 1 | 1 | 1 | . |
| Age group >40 & <50 x current smoker | 0.730 | 0.488 | 1.091 | 0.125 |
| Age group >40 & <50 x ex-smoker | 1 | 1 | 1 | . |
| Age group >50 & <60 x non-smoker | 1 | 1 | 1 | . |
| Age group >50 & <60 x current smoker | 0.679 | 0.459 | 1.003 | 0.052 |
| Age group >50 & <60 x ex-smoker | 1.000 | 1.000 | 1.000 | . |
| Age group >60 & <70 x non-smoker | 1 | 1 | 1 | . |
| Age group >60 & <70 x current smoker | 0.749 | 0.508 | 1.103 | 0.143 |
| Age group >60 & <70 x ex-smoker | 1.000 | 1.000 | 1.000 | . |
| Age group >70 & <80 x non-smoker | 1 | 1 | 1 | . |
| Age group >70 & <80 x current smoker | 0.790 | 0.536 | 1.165 | 0.235 |
| Age group >70 & <80 x ex-smoker | 1 | 1 | 1 | . |
| Age group >80 x non-smoker | 1 | 1 | 1 | . |
| Age group >80 x current smoker | 0.911 | 0.616 | 1.348 | 0.643 |
| Age group >80 x ex-smoker | 1.000 | 1.000 | 1.000 | . |
| Deprivation |  |  |  |  |
| IMD quintile 1 (least deprived) | 1 | 1 | 1 | . |
| IMD quintile 2 | 0.828 | 0.791 | 0.866 | 0.000 |
| IMD quintile 3 | 0.711 | 0.677 | 0.745 | 0.000 |
| IMD quintile 4 | 0.655 | 0.626 | 0.685 | 0.000 |
| IMD quintile 5 (most deprived) | 0.574 | 0.550 | 0.599 | 0.000 |
| Constant | 238.960 | 173.374 | 329.356 | 0.000 |

Table 18 therefore shows the final complete logistic regression model including patients with CPRD doctor-diagnosed COPD and HES COPD diagnosis only. The modelling also demonstrated a significant interaction between age group and smoking status. All the variables included in the final national model were available at the local level (apart from the missing data already described), so this represents the local estimates as well.

Table 18: M4- final logistic regression model including patients with CPRD doctor-diagnosed COPD and HES COPD diagnosis only

| Parameter | Odds Ratio | Lower 95% CI | Upper 95% CI | *p* value |
| --- | --- | --- | --- | --- |
| Sex |  |  |  |  |
| Male | 1 | 1 | 1 | . |
| Female | 0.974 | 0.953 | 0.995 | 0.017 |
| Age group |  |  |  |  |
| <40 | 1 | 1 | 1 | . |
| >40 & <50 | 5.182 | 3.521 | 7.627 | 0.000 |
| >50 & <60 | 16.061 | 11.024 | 23.400 | 0.000 |
| >60 & <70 | 44.932 | 30.926 | 65.281 | 0.000 |
| >70 & <80 | 83.552 | 57.527 | 121.351 | 0.000 |
| >80 | 97.312 | 66.960 | 141.421 | 0.000 |
| Smoking |  |  |  |  |
| Non-smoker | 1 | 1 | 1 | . |
| Current smoker | 6.645 | 4.332 | 10.194 | 0.000 |
| Ex-smoker | 3.935 | 2.415 | 6.413 | 0.000 |
| Interaction term age group x smoking |  |  |  |  |
| Age group <40 x non-smoker | 1 | 1 | 1 | . |
| Age group <40 x current smoker | 1 | 1 | 1 | . |
| Age group <40 x ex-smoker | 1 | 1 | 1 | . |
| Age group >40 & <50 x non-smoker | 1 | 1 | 1 | . |
| Age group >40 & <50 x current smoker | 1.089 | 0.697 | 1.701 | 0.708 |
| Age group >40 & <50 x ex-smoker | 0.844 | 0.506 | 1.405 | 0.514 |
| Age group >50 & <60 x non-smoker | 1 | 1 | 1 | . |
| Age group >50 & <60 x current smoker | 1.260 | 0.816 | 1.947 | 0.297 |
| Age group >50 & <60 x ex-smoker | 0.918 | 0.559 | 1.508 | 0.737 |
| Age group >60 & <70 x non-smoker | 1 | 1 | 1 | . |
| Age group >60 & <70 x current smoker | 1.191 | 0.773 | 1.834 | 0.428 |
| Age group >60 & <70 x ex-smoker | 0.971 | 0.594 | 1.588 | 0.906 |
| Age group >70 & <80 x non-smoker | 1 | 1 | 1 | . |
| Age group >70 & <80 x current smoker | 1.168 | 0.758 | 1.799 | 0.482 |
| Age group >70 & <80 x ex-smoker | 1.031 | 0.631 | 1.685 | 0.902 |
| Age group >80 x non-smoker | 1 | 1 | 1 | . |
| Age group >80 x current smoker | 1.144 | 0.740 | 1.768 | 0.545 |
| Age group >80 x ex-smoker | 1.145 | 0.700 | 1.872 | 0.589 |
| Deprivation |  |  |  |  |
| IMD quintile 1 (least deprived) | 1 | 1 | 1 | . |
| IMD quintile 2 | 1.244 | 1.197 | 1.294 | 0.000 |
| IMD quintile 3 | 1.465 | 1.406 | 1.526 | 0.000 |
| IMD quintile 4 | 1.642 | 1.579 | 1.708 | 0.000 |
| IMD quintile 5 (most deprived) | 1.968 | 1.896 | 2.042 | 0.000 |
| Constant | 0.000 | 0.000 | 0.000 | 0.000 |

### ROC curves

We next examined the receiver operating characteristics (ROC) curves for the various models. The best ROC curve which predicts data perfectly will touch the top-left corner of the plot (area 1.0), and the larger the area under the ROC curve the better the prediction. An area of 0.5 signifies a prediction no better than chance. The results are summarised in Table 19, and in Figure 5 (we have only shown the actual ROC curve for the choden model M2 for illustrative purposes. Models M1-M3 all have very good and acceptable c statistics of around 90%. M2 was chosen for the local estimates as it maximises the number of cases without using algorithm diagnosed cases which are compromised by their risk factor ORs.

The c statistics are simply a method of assessing how well the model predicts caseness given the dataset used. Model M4 predicts algorithm-positivity acceptably, but we excluded doctor (HES or CPRD) diagnosed COPD (N= 56,134) before fitting the model. The model suggests that this population is made up of much younger people who are smokers and meet the prescribing and symptoms criteria but do not yet have COPD.

Table : receiver operating characteristics (ROC) curves/c statistics for the various CPRD models

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Model description | Model | Observations | ROC area | SE | 95% CI |
| Patients with only CPRD doctor-diagnosed COPD | M1 | 1,743,485 | 0.9180 | 0.0006 | 0.91762-0.91843 |
| Patients with CPRD doctor-diagnosed COPD and HES COPD diagnosis | M2 | 1,743,485 | 0.9071 | 0.0006 | 0.90671-0.90757 |
| Patients with HES-only doctor-diagnosed COPD | M3 | 1,743,485 | 0.8785 | 0.0013 | 0.87799-0.87896 |
| Patients only with algorithm-defined COPD cases | M4 | 282,353 | 0.7838 | 0.0011 | 0.78230-0.78534 |

Figure : ROC curve-M2



### Probability and sensitivity/specificity analysis

We can use the automatic stepwise forward model to predict the probability of individual being COPD case in the CPRD data set. No matter which cut-off point we choose, there will always be mis-classified people, with either non-COPD cases being classified as predicted COPD cases, or COPD cases being classified as predicted non-COPD cases. Therefore, we use sensitivity and specificity plots to help with this decision. The sensitivity/specificity versus probability cut-off plot shows us the corresponding sensitivity and specificity in each possible probability cut-off point (See Figure 6). Higher sensitivity would usually yield low specificity and vice versa, the rule of thumb is to choose a cut-off probability to maximize both. We would choose the cut-off probability where sensitivity and specificity lines cross as shown below, which would be a probability cut-off of .0303-.0324.

Figure : Sensitivity/specificity versus probability cut-off

| Cutpoint | Sensitivity | Specificity | Correctly classified | LR+ | LR- |
| --- | --- | --- | --- | --- | --- |
| .0252.. | 86.84% | 80.19% | 80.33% | 4.3835 | 0.1641 |
| .0259.. | 86.06% | 80.79% | 80.91% | 4.4806 | 0.1725 |
| .0271.. | 85.32% | 81.24% | 81.33% | 4.5485 | 0.1807 |
| .0277.. | 84.99% | 81.49% | 81.57% | 4.5918 | 0.1841 |
| .0279.. | 84.64% | 81.81% | 81.87% | 4.654 | 0.1877 |
| .0284.. | 84.24% | 82.11% | 82.16% | 4.71 | 0.1919 |
| .0295.. | 84.04% | 82.24% | 82.28% | 4.7321 | 0.194 |
| .0303.. | 83.46% | 82.78% | 82.79% | 4.8463 | 0.1998 |
| .0324.. | 82.96% | 83.08% | 83.08% | 4.9041 | 0.2051 |
| .0332.. | 82.46% | 83.38% | 83.36% | 4.9617 | 0.2104 |
| .0342.. | 81.90% | 83.72% | 83.68% | 5.0315 | 0.2162 |
| .0346.. | 81.25% | 84.16% | 84.09% | 5.1288 | 0.2227 |
| .0351.. | 80.76% | 84.50% | 84.42% | 5.2094 | 0.2277 |
| .0355.. | 80.45% | 84.65% | 84.56% | 5.2419 | 0.231 |

## Local estimates

Because of the short timeframe for the modelling, which was further truncated because of delays in obtaining the CPRD linkage data, local estimates were calculated using the previously-described inverse probability weights method only.

### Internal validation

A useful form of internal validation is to aggregate small population (in this case practice) prevalence estimates derived from the model to the lowest level available in the raw national dataset used to produce the model. The lowest level in CPRD data is Regional level, so we aggregated the practice level prevalence estimates to Regional level. The results are shown in Table 20. In comparing the prevalence it needs to be recognised that the estimates are based on real risk factor levels, whereas the CPRD prevalence is dependent on the CPRD practice populations. Although they have been shown to be similar to the general population in terms of age and sex structure, CPRD practices may not necessarily have the same levels of risk factors. For example, if CPRD practices tend to be in less deprived areas (as we think they probably are in some regions) they will under-estimate prevalence which has smoking and deprivation as risk factors. Reviewing Table 20, estimates and CPRD prevalence is generally similar with no consistent pattern. We know that smoking prevalence is higher in NE and NW England, and this is reflected in both their prevalence results.

There were no CPRD cases in East Midlands in our dataset. There are relatively few Vision/CPRD practices in this region, where EMIS systems dominate. We have examined the practice file, and East Midlands practices are there, but there were not many to begin with, and none of them currently have patients which are contributing at the time of our cross-section. All of their patients’ follow-up times had ended by the study cross-section, and we do not know if they are 1) alive or dead; or 2) have COPD or not, so they are not included. However as the modelled estimates are based on the whole national dataset, East Midlands’ estimates are as robust as any other region’s.

Table : Comparison at regional level of aggregated practice-level prevalence estimates and CPRD raw data

|  |  | List Size/ CPRD denominator | Estimated/CPRD cases | Estimated/CPRD prevalence | Practices |
| --- | --- | --- | --- | --- | --- |
| Blank | **Estimated** | 1,214,894 | 32,125.22 | 2.64% | 147 |
| **CPRD raw data** | N/A | 23,998 | 1.98% |  |
| East Midlands | **Estimated** | 4,670,890 | 117,056.40 | 2.51% | 579 |
| **CPRD raw data** | 0 | 0 | 0.00% |  |
| East of England | **Estimated** | 6,156,294 | 149,258.09 | 2.42% | 743 |
| **CPRD raw data** | 218,932 | 3,881 | 1.77% |  |
| London | **Estimated** | 8,965,337 | 151,249.25 | 1.69% | 1,340 |
| **CPRD raw data** | 413,489 | 7,063 | 1.71% |  |
| North East | **Estimated** | 2,192,911 | 63,755.82 | 2.91% | 313 |
| **CPRD raw data** | 30,438 | 1,088 | 3.57% |  |
| North West | **Estimated** | 7,370,326 | 194,590.53 | 2.64% | 1,159 |
| **CPRD raw data** | 341,173 | 9,992 | 2.93% |  |
| South East | **Estimated** | 8,357,166 | 190,798.24 | 2.28% | 958 |
| **CPRD raw data** | 433,381 | 8,411 | 1.94% |  |
| South West | **Estimated** | 5,449,948 | 151,386.95 | 2.78% | 670 |
| **CPRD raw data** | 257,670 | 5,589 | 2.17% |  |
| West Midlands | **Estimated** | 5,824,981 | 143,941.90 | 2.47% | 879 |
| **CPRD raw data** | 289,993 | 5,700 | 1.97% |  |
| Yorkshire & Humber | **Estimated** | 5,489,778 | 143,028.46 | 2.61% | 733 |
| **CPRD raw data** | 38,203 | 1,156 | 3.03% |  |
| England | **Estimated** | 55,692,525 | ########## | 2.40% | 7,521 |
| **CPRD raw data** | 2,504,341 | 50,700 | 2.02% |  |

### External validation of practice estimates against QOF prevalence

The funding for the project does not include an in-depth external validation. For example, this could be carried out by obtaining an extract from a similar dataset e.g. comparing the CPRD COPD prevalence models’ risk factors, odds ratios and ROC curves to HSfE 2010 data or a dataset from another GP research database. In addition, ideally such validations should be carried out by an impartial third party. However another useful external data source is the Quality & Outcomes Framework (QOF) GP-diagnosed COPD prevalence. This can obviously be compared with diagnosed COPD prevalence from the model. Using the aggregated estimated prevalence data from the internal validation we have also aggregated practice-level QOF prevalence to Regional level to allow visual comparisons to be made. Table 21 shows that NE and NW Regions have the highest aggregated QOF prevalence (2.86% and 2.35% respectively) and the highest estimated prevalence (2.91% and 2.64% respectively).

Table : comparison of aggregated QOF and regional prevalence rates

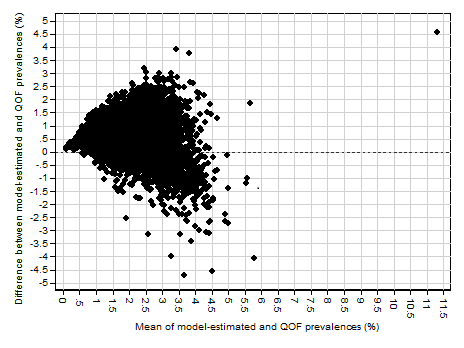
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Blank (new CCG) | | East Midlands | | East of England | | London | | North East | | North West | | South East | | South West | | West Midlands | | Yorkshire and The Humber | | England | |
|  | **Estd** | **QOF** | **Estd** | **QOF** | **Estd** | **QOF** | **Estd** | **QOF** | **Estd** | **QOF** | **Estd** | **QOF** | **Estd** | **QOF** | **Estd** | **QOF** | **Estd** | **QOF** | **Estd** | **QOF** | **Estd** | **QOF** |
| List Size | 1,214,894 | | 4,670,890 | | 6,156,294 | | 8,965,337 | | 2,192,911 | | 7,370,326 | | 8,357,166 | | 5,449,948 | | 5,824,981 | | 5,489,778 | | 55,692,525 | |
| Est/QOF register | 32,125.22 | 23,998 | 117,056.40 | 89,304 | 149,258.09 | 107,300 | 151,249.25 | 102,282 | 63,755.82 | 62,722 | 194,590.53 | 173,187 | 190,798.24 | 128,918 | 151,386.95 | 101,554 | 143,941.90 | 106,398 | 143,028.46 | 121,047 | 1,337,190.86 | 1,016,710 |
| Est/QOF prevlce | 2.64% | 1.98% | 2.51% | 1.91% | 2.42% | 1.74% | 1.69% | 1.14% | 2.91% | 2.86% | 2.64% | 2.35% | 2.28% | 1.54% | 2.78% | 1.86% | 2.47% | 1.83% | 2.61% | 2.20% | 2.40% | 1.83% |
| Practices | 147 | 138 | 579 | 578 | 743 | 743 | 1,340 | 1,340 | 313 | 313 | 1,159 | 1,159 | 958 | 958 | 670 | 670 | 879 | 879 | 733 | 733 | 7,521 | 7,511 |
| Mean | 2.754 | 2.087 | 2.513 | 1.915 | 2.438 | 1.785 | 1.736 | 1.161 | 2.921 | 2.994 | 2.648 | 2.441 | 2.325 | 1.589 | 2.852 | 1.922 | 2.460 | 1.864 | 2.626 | 2.287 | 2.421 | 1.886 |
| Std. Err. | 0.094 | 0.082 | 0.031 | 0.030 | 0.030 | 0.027 | 0.014 | 0.017 | 0.036 | 0.058 | 0.021 | 0.028 | 0.025 | 0.022 | 0.029 | 0.024 | 0.023 | 0.027 | 0.026 | 0.035 | 0.009 | 0.011 |
| Lower 95% CI | 2.568 | 1.926 | 2.453 | 1.856 | 2.380 | 1.732 | 1.709 | 1.128 | 2.850 | 2.879 | 2.608 | 2.386 | 2.277 | 1.547 | 2.794 | 1.874 | 2.416 | 1.810 | 2.574 | 2.219 | 2.403 | 1.866 |
| Upper 95% CI | 2.940 | 2.248 | 2.573 | 1.973 | 2.496 | 1.838 | 1.763 | 1.194 | 2.991 | 3.109 | 2.689 | 2.497 | 2.374 | 1.632 | 2.909 | 1.969 | 2.505 | 1.917 | 2.677 | 2.356 | 2.439 | 1.907 |

In addition we carried out a disagreement analysis between model-Estd and QOF prevalence (%) of diagnosed COPD in practices. We Estd three principal components of disagreement (discordance as measured by Kendall's tau-a, bias as measured by median difference, and calibration as measured by the Theil-Sen median slope). Using the COPD estimates, the Kendall's tau-a between model-Estd and QOF prevalence of COPD for 7507 practices was 0.498 (95% CIs 0.486-0.509), and p=0.000. Table 22 shows percentile differences between model-Estd and QOF prevalence of diagnosed COPD.

Table : percentile differences between model-Estd and QOF prevalence of COPD

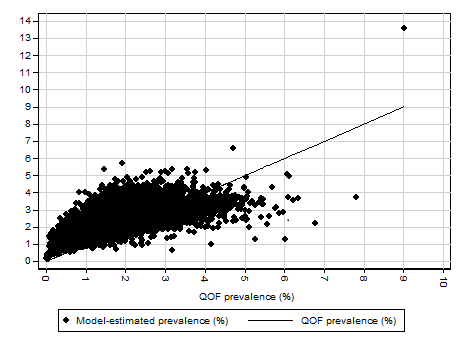
| Percent | Percentile | (95% CI) |
| --- | --- | --- |
| 0 | -4.7 | (-4.7,-4.7) |
| 25 | 0.2 | (0.1, 0.2) |
| 50 | 0.6 | (0.6, 0.6) |
| 75 | 1.0 | (1.0, 1.0) |
| 100 | 4.6 | (4.6, 4.6) |

Figure : Bland-Altman plot for model-Estd and QOF prevalence of xxx



The best way to display the data is to plot the difference between the measurements by the two methods for each subject against their mean. This plot for practice-level COPD prevalence (Figure 7) shows explicitly the extent of agreement. In contrast to the plots for some other models, e.g. CHD and stroke, the difference between the estimates and QOF is not great, at about 0.5% per practice, as might be expected if the only additional contribution of cases is from HES diagnoses, although in the majority of practices the Estd prevalence is higher. This is plausible if COPD is diagnosed in hospital or outpatients. **Error! Not a valid bookmark self-reference.** is a scatter plot of model-Estd and QOF prevalence of diagnosed COPD.

Figure : scatter plot of model-Estd and QOF prevalence of COPD



# Discussion

For the COPD model we chose to use CPRD as the data source because of the problems we had experienced previously using HSfE 2010 spirometry data when attempting to redevelop the 2007 COPD model. All methods of estimating local prevalence using risk factors are very data hungry because prevalence values have to be calculated for all permutations of risk factor categories. If too much data is missing from groups of cells, estimates become unstable. CPRD generally allows much larger samples of cases and controls. The disadvantage of CPRD data is that we know COPD is under-diagnosed in general practice, and also that spirometry recording in high risk e.g. over 35 smokers (as opposed to already diagnosed or very high risk patients where the GP suspects the disease) is very patchy. Few CCGs have run high risk screening programmes, although those that have often dramatically increase diagnoses as we have previously shown.[81 ,82]

The major problem with our estimates is our inability, in the time and resources available, to create a diagnostic algorithm which enabled us to reliably supplement the CPRD and HES diagnostic codes which form the final outcome used in the model. In combination with diagnostic codes (i.e. CPRD+HES+Algorithm COPD), the algorithm we used, which had the highest PPV of 45% as determined by Quint et al, identified from the baseline tables a prevalence of 579,741/3,001,300, or 16% of over 35s, which is obviously too high. Moreover, the ORs for the algorithm defined cases were quite different from those for the other groups, so we did not use this flow in producing the local estimates. As a result as-defined COPD prevalence in our CPRD dataset is only 2.4%, although this is markedly higher than the 1.83% national prevalence based on QOF COPD registers. Actual prevalence lies somewhere in between.

The actual prevalence of COPD is a moving target. Using the HSfE 2010 definition, data, COPD prevalence in English over 35s is about 12%- see our Table 6 using HSfE 2001 and 2010 data (2010 used the additional criterion of FEV1<80% predicted).[3] However many COPD experts believe that the PPV of the 2010 definition is only about 50%, implying over-diagnosis, and bronchodilator challenge was not used. Nevertheless, it seems likely that actual prevalence must be at least 6%, at least double what we have definitely established here.

The CPRD COPD prevalence model prevalence as it currently stands is therefore disappointing and certainly under-estimates actual prevalence, because we have failed to identify patients who are likely to have COPD but do not have a diagnosis from any source. However we did not have the time or resources to investigate further. It is possible that we could use 2010 HSfE data now that we have a better method of producing local estimates than was the case in 2012. In addition there is an obvious need to look within high risk groups such as our algorithm group for other supporting evidence e.g. spirometry data. We therefore recommend that these estimates should not be used except as an interim measure which now includes HES diagnoses, and suggest that PHE considers allocating additional funding to look further.

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# Appendix: additional information

## CPRD medcodes and drug codes

Table 23 shows the CPRD Medcodes relevant to the diagnosis of COPD from validated CPRD definitions.[46]

Table : Medcodes relevant to the diagnosis of COPD from validated CPRD definition[[2]](#footnote-2)

| Code type | Text | Medcodes |
| --- | --- | --- |
| Doctor diagnoses | emphysema | 794 |
| chronic obstructive airways disease | 998 |
| chronic obstructive pulmonary disease | 1001 |
| chronic bronchitis | 3243 |
| airways obstructn irreversible | 4084 |
| chronic obstructive airways disease nos | 5710 |
| chronic obstructive pulmonary disease monitoring | 9520 |
| severe chronic obstructive pulmonary disease | 9876 |
| moderate chronic obstructive pulmonary disease | 10802 |
| mild chronic obstructive pulmonary disease | 10863 |
| centrilobular emphysema | 10980 |
| admit copd emergency | 11019 |
| chronic obstructive pulmonary disease annual review | 11287 |
| emphysematous bronchitis | 14798 |
| chronic bronchitis nos | 15157 |
| other emphysema nos | 16410 |
| copd follow-up | 18476 |
| copd self-management plan given | 18501 |
| chronic obstructive pulmonary disease follow-up | 18621 |
| chronic obstructive pulmonary disease monitoring admin | 18792 |
| emergency copd admission since last appointment | 19003 |
| copd accident and emergency attendance since last visit | 19106 |
| chronic bullous emphysema nos | 23492 |
| chronic obstructive pulmonary disease monitoring by nurse | 26018 |
| chronic bullous emphysema | 26306 |
| chronic obstructive pulmonary disease monitoring 1st letter | 28755 |
| emphysema nos | 33450 |
| chronic obstructive pulmonary disease monitoring 2nd letter | 34202 |
| chronic obstructive pulmonary disease monitoring 3rd letter | 34215 |
| chronic obstructive pulmonary disease nos | 37247 |
| chronic obstructive pulmonary disease monitoring due | 37371 |
| other emphysema | 40788 |
| coad follow-up | 42624 |
| obstructive chronic bronchitis nos | 44525 |
| chronic obstructive pulmonary disease does not disturb sleep | 45771 |
| chronic obstructive pulmonary disease monitoring by doctor | 45998 |
| multiple copd emergency hospital admissions | 46036 |
| panlobular emphysema | 46578 |
| segmental bullous emphysema | 56860 |
| giant bullous emphysema | 60188 |
| [x]other specified chronic obstructive pulmonary disease | 65733 |
| [x]other emphysema | 66058 |
| other specified chronic obstructive pulmonary disease | 67040 |
| zonal bullous emphysema | 68662 |
| very severe chronic obstructive pulmonary disease | 93568 |
| copd - enhanced services administration | 97800 |
| copd structured smoking assessment declined - enh serv admin | 98283 |
| refer copd structured smoking assessment - enhanc serv admin | 98284 |
| copd patient unsuitable for pulmonary rehab - enh serv admin | 99948 |
| clinical chronic obstructive pulmonary disease questionnaire | 100877 |
| issue of chronic obstructive pulmonary disease rescue pack | 101042 |
| chronic obstructive pulmonary disease 3 monthly review | 102685 |
| chronic obstructive pulmonary disease 6 monthly review | 103007 |
| referred for copd structured smoking assessment | 103400 |
| copd structured smoking assessment declined | 103760 |
| copd patient unsuitable for pulmonary rehabilitation | 103864 |
| Cough | cough | 92 |
| chesty cough | 292 |
| bronchial cough | 1025 |
| [d]cough | 1160 |
| productive cough nos | 1234 |
| c/o - cough | 1273 |
| chronic cough | 1612 |
| night cough present | 3068 |
| persistent cough | 3628 |
| coughing up phlegm | 3645 |
| morning cough | 4070 |
| nocturnal cough / wheeze | 4836 |
| dry cough | 4931 |
| productive cough -clear sputum | 7706 |
| cough symptom nos | 7707 |
| productive cough-yellow sputum | 7708 |
| productive cough -green sputum | 7773 |
| smokers' cough | 16717 |
| difficulty in coughing up sputum | 22318 |
| evening cough | 29318 |
| unexplained cough | 43795 |
| cough aggravates symptom | 60903 |
| cough on exercise | 100333 |
| Breathlessness | [d]breathlessness | 735 |
| [d]shortness of breath | 741 |
| breathlessness | 1429 |
| [d]respiratory distress | 2563 |
| short of breath on exertion | 2575 |
| respiratory distress syndrome | 2737 |
| difficulty breathing | 2931 |
| [d]dyspnoea | 3092 |
| shortness of breath | 4822 |
| breathlessness symptom | 5175 |
| shortness of breath symptom | 5349 |
| dyspnoea - symptom | 5896 |
| breathless - moderate exertion | 6326 |
| paroxysmal nocturnal dyspnoea | 6434 |
| o/e - dyspnoea | 7000 |
| o/e - respiratory distress | 7534 |
| breathless - lying flat | 7683 |
| breathless - mild exertion | 7932 |
| [d]respiratory insufficiency | 9297 |
| nocturnal dyspnoea | 18116 |
| breathlessness nos | 21801 |
| short of breath dressing/undressing | 22094 |
| breathless - strenuous exertion | 24889 |
| breathless - at rest | 31143 |
| dyspnoea on exertion | 53771 |
| Unable to complete a sentence in one breath | 40813 |
| Sputum | chesty cough | 292 |
| bronchial cough | 1025 |
| productive cough nos | 1234 |
| [d]abnormal sputum | 1251 |
| Coughing up phlegm | 3645 |
| sputum sent for c/s | 3727 |
| productive cough -clear sputum | 7706 |
| productive cough-yellow sputum | 7708 |
| productive cough -green sputum | 7773 |
| sputum sample obtained | 8287 |
| [d]positive culture findings in sputum | 8760 |
| sputum - symptom | 9807 |
| acute purulent bronchitis | 11072 |
| sputum culture | 14271 |
| sputum microscopy | 14272 |
| sputum appearance | 14273 |
| sputum appears infected | 14804 |
| [d]sputum abnormal - colour | 15430 |
| sputum examination: abnormal | 16026 |
| sputum clearance | 18964 |
| [d]sputum abnormal - amount | 20086 |
| difficulty in coughing up sputum | 22318 |
| sputum microscopy nos | 23252 |
| [d]abnormal sputum nos | 23582 |
| sputum: mucopurulent | 24181 |
| yellow sputum | 30754 |
| sputum sent for examination | 30904 |
| [d]abnormal sputum - tenacious | 36515 |
| green sputum | 36880 |
| sputum evidence of infection | 43270 |
| [d]sputum abnormal - odour | 44214 |
| sputum: pus cells present | 49144 |
| sputum: organism on gram stain | 49694 |
| sputum: excessive - mucoid | 54177 |
| volume of sputum | 100484 |
| moderate sputum | 100524 |
| white sputum | 100629 |
| copious sputum | 100647 |
| brown sputum | 100931 |
| profuse sputum | 101782 |
| grey sputum | 103209 |

Table 24 shows the CPRD “product” or drug codes relevant to the diagnosis of COPD.

Table : product/drug codes relevant for the diagnosis of COPD

| Product name | prodcode |
| --- | --- |
| bricanyl 2.5 mg inj | 14482 |
| salbutamol 200microgram inhalation powder blisters with device | 50315 |
| bricanyl 500micrograms/dose turbohaler (necessity supplies ltd) | 52410 |
| fenoterol 200micrograms/dose inhaler | 5185 |
| pulmadil auto inhalation powder (3m health care ltd) | 10858 |
| airomir 100micrograms/dose inhaler (teva uk ltd) | 2655 |
| salbutamol respirator soln | 22467 |
| terbutaline 1.5mg/5ml oral solution sugar free | 7953 |
| bricanyl sa 7.5mg tablets (astrazeneca uk ltd) | 4541 |
| ventolin i/v 5 mg inj | 8429 |
| salbutamol 2mg/5ml oral solution sugar free (a a h pharmaceuticals ltd) | 28881 |
| terbutaline with guafenesin expectorant | 17875 |
| bronchodil 20mg tablet (viatris pharmaceuticals ltd) | 15075 |
| salbutamol 100micrograms/dose breath actuated inhaler cfc free | 1741 |
| salbutamol 2mg tablets (actavis uk ltd) | 34618 |
| salbutamol cfc/free b/a | 25218 |
| salbutamol 100microgram/inhalation inhalation powder (ivax pharmaceuticals uk ltd) | 28508 |
| terbutaline 250micrograms/dose inhaler | 1620 |
| salbutamol 100micrograms/dose inhaler (a a h pharmaceuticals ltd) | 31933 |
| ventolin easi-breathe 100microgram/actuation pressurised inhalation (allen & hanburys ltd) | 958 |
| salbutamol 2mg/5ml oral solution (lagap) | 21102 |
| salbuvent rondo | 10353 |
| bronchodil 10mg/5ml oral solution (viatris pharmaceuticals ltd) | 25820 |
| pirbuterol acetate inhaler | 16236 |
| ventolin cr 8mg tablet (allen & hanburys ltd) | 12042 |
| cobutolin inh | 19732 |
| ventolin 5mg nebules (glaxosmithkline uk ltd) | 1957 |
| exirel 7.5mg/5ml oral solution (3m health care ltd) | 25821 |
| salamol 100micrograms/dose inhaler cfc free (teva uk ltd) | 5170 |
| salbutamol 8mg modified-release tablets | 2869 |
| ventolin 100microgram/inhalation inhalation powder (glaxo wellcome uk ltd) | 31 |
| rimiterol inhaler | 8572 |
| pirbuterol 7.5mg/5ml oral solution | 25829 |
| salbulin 2mg/5ml oral solution (3m health care ltd) | 4055 |
| ventolin 200micrograms/dose accuhaler (mawdsley-brooks & company ltd) | 50503 |
| salbutamol 100microgram/inhalation inhalation powder (neo laboratories ltd) | 46551 |
| pulmadil inhalation powder (3m health care ltd) | 3758 |
| salbutamol 100microgram/inhalation spacehaler (celltech pharma europe ltd) | 3443 |
| salbutamol 100micrograms/actuation breath actuated inhaler | 30230 |
| salbutamol cyclocaps 200microgram inhalation powder (dupont pharmaceuticals ltd) | 38097 |
| cobutolin 2mg tablet (actavis uk ltd) | 26873 |
| ventolin rotahaler | 19649 |
| volmax 4mg modified-release tablets (glaxosmithkline uk ltd) | 1961 |
| ventmax sr 8mg capsules (chiesi ltd) | 22313 |
| bambec 20mg tablets (astrazeneca uk ltd) | 13575 |
| volmax 8mg modified-release tablets (glaxosmithkline uk ltd) | 1960 |
| ventolin rotahaler (glaxosmithkline uk ltd) | 4908 |
| exirel 10 mg tab | 26420 |
| airomir autohaler cfc free b/a | 26716 |
| salbutamol inhaler | 22512 |
| salbutamol 200microgram inhalation powder capsules | 882 |
| salbutamol 100micrograms/inhalation vortex inhaler | 14525 |
| asmasal 100microgram/inhalation spacehaler (celltech pharma europe ltd) | 9651 |
| salbutamol | 25073 |
| beclomethasone /salbutamol | 22225 |
| ventmax sr 4mg capsules (chiesi ltd) | 17696 |
| salamol 100micrograms/dose easi-breathe inhaler (de pharmaceuticals) | 60923 |
| salbuvent 5mg/ml respirator solution (pharmacia ltd) | 31082 |
| salbulin novolizer 100micrograms/dose inhalation powder (meda pharmaceuticals ltd) | 38136 |
| salbutamol 200micrograms/dose dry powder inhaler | 2978 |
| ventolin 200microgram rotacaps (glaxosmithkline uk ltd) | 2851 |
| bricanyl refill canister (astrazeneca uk ltd) | 2758 |
| salbutamol u.dose nebulising 2.5mg/2.5ml | 20781 |
| salbutamol 100micrograms/dose dry powder inhaler | 7017 |
| salbutamol 100microgram/inhalation inhalation powder (celltech pharma europe ltd) | 44713 |
| salamol 100microgram/actuation inhalation powder (ivax pharmaceuticals uk ltd) | 1093 |
| asmaven 100microgram inhalation powder (berk pharmaceuticals ltd) | 21859 |
| reproterol 500micrograms/dose inhaler | 15165 |
| salbutamol 200micrograms inahalation capsules | 30204 |
| ventodisks 400microgram/blister disc (allen & hanburys ltd) | 1950 |
| salbutamol 2mg/5ml oral solution sugar free | 282 |
| numotac 10mg tablet (3m health care ltd) | 32812 |
| salbulin cfc free | 31290 |
| salbulin 4mg tablet (3m health care ltd) | 3254 |
| salbutamol 4mg modified-release tablets | 3994 |
| pulvinal salbutamol 200micrograms/dose dry powder inhaler (chiesi ltd) | 13038 |
| salbuvent 100microgram/actuation inhalation powder (pharmacia ltd) | 40655 |
| salbutamol 100microgram/inhalation inhalation powder (c p pharmaceuticals ltd) | 34702 |
| easyhaler salbutamol sulfate 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd) | 16577 |
| terbutaline 500micrograms/dose dry powder inhaler | 1619 |
| bricanyl 5mg/2ml respules (astrazeneca uk ltd) | 43085 |
| ventodisks 200microgram with diskhaler (glaxosmithkline uk ltd) | 49368 |
| easyhaler salbutamol sulfate 100micrograms/dose dry powder inhaler (orion pharma (uk) ltd) | 13181 |
| fenoterol hydrobromide .5 % sol | 15441 |
| bricanyl respules (5mg/2ml) 2.5 mg/ml inh | 3764 |
| salbutamol 100micrograms/dose inhaler (generics (uk) ltd) | 33588 |
| salbutamol 400mcg/beclometh.100mcg r/cap inh | 3838 |
| salbutamol 4mg tablets (a a h pharmaceuticals ltd) | 32102 |
| salamol 100microgram/inhalation inhalation powder (sandoz ltd) | 13996 |
| terbutaline 1.5mg/5ml oral solution sugar free (a a h pharmaceuticals ltd) | 38419 |
| bricanyl 10mg/ml respirator solution (astrazeneca uk ltd) | 4222 |
| terbutaline 7.5mg modified-release tablets | 8522 |
| salbutamol cyclohaler type 5 insufflator inhalation powder (bristol-myers squibb pharmaceuticals ltd) | 27793 |
| steri-neb salamol 2.5 mg inh | 2149 |
| asmavent 100micrograms/dose inhaler cfc free (kent pharmaceuticals ltd) | 57249 |
| salbutamol .25 mg inj | 10958 |
| salbulin inhalation powder (3m health care ltd) | 862 |
| salbutamol 400microgram inhalation powder blisters | 52543 |
| ventolin 200micrograms/dose accuhaler (de pharmaceuticals) | 50956 |
| ventolin nebules | 19642 |
| salbutamol 400micrograms inahalation capsules | 34029 |
| pirbuterol 15 mg tab | 12463 |
| ventolin 200micrograms/dose accuhaler (glaxosmithkline uk ltd) | 42858 |
| ventodisks 200microgram (glaxosmithkline uk ltd) | 49370 |
| terbutaline 1.5mg/5ml oral solution (sandoz ltd) | 42867 |
| exirel 10mg capsule (3m health care ltd) | 23787 |
| salbutamol 100micrograms/dose inhaler cfc free (waymade healthcare plc) | 59409 |
| salbutamol 4mg tablets (actavis uk ltd) | 34938 |
| ventolin 2.5mg nebules (glaxosmithkline uk ltd) | 674 |
| salbutamol cyclohaler | 30212 |
| ventolin 400microgram rotacaps (glaxosmithkline uk ltd) | 1952 |
| bricanyl 250micrograms/dose spacer inhaler (astrazeneca uk ltd) | 7954 |
| bricanyl 250micrograms/dose inhaler (astrazeneca uk ltd) | 235 |
| salbutamol 400microgram inhalation powder capsules | 2850 |
| reproterol 10mg/5ml oral solution | 36677 |
| bambuterol 10mg tablets | 7192 |
| salbutamol 200micrograms disc | 3163 |
| salbutamol 100micrograms/dose inhaler cfc free (teva uk ltd) | 30118 |
| berotec 100microgram/actuation inhalation powder (boehringer ingelheim ltd) | 1794 |
| salbutamol 4mg tablets | 860 |
| exirel 15mg capsule (3m health care ltd) | 8012 |
| airomir 100micrograms/dose autohaler (teva uk ltd) | 5740 |
| monovent 1.5mg/5ml oral solution (lagap) | 17874 |
| exirel inhalation powder (3m health care ltd) | 12563 |
| ventolin evohaler 100 100microgram/inhalation pressurised inhalation (glaxo wellcome uk ltd) | 898 |
| salbutamol 100micrograms/dose inhaler cfc free (actavis uk ltd) | 33817 |
| salbulin 100micrograms/dose inhaler (3m health care ltd) | 4665 |
| salbutamol 2mg tablet (c p pharmaceuticals ltd) | 41549 |
| fenoterol 100microgram/actuation inhaler | 4842 |
| salamol easi-breathe 100microgram/actuation pressurised inhalation (ivax pharmaceuticals uk ltd) | 957 |
| ventolin 2mg tablet (allen & hanburys ltd) | 4171 |
| berotec 200micrograms/dose inhaler (boehringer ingelheim ltd) | 2020 |
| salbutamol rotahaler complete unit | 20675 |
| ventolin accuhaler 200 200microgram/actuation inhalation powder (glaxo wellcome uk ltd) | 4497 |
| salbutamol 100micrograms/dose inhaler cfc free (sandoz ltd) | 49591 |
| salbuvent 2mg/5ml oral solution (pharmacia ltd) | 1635 |
| ventolin s/r 8 mg spa | 8636 |
| ventolin 200micrograms/dose accuhaler (sigma pharmaceuticals plc) | 53297 |
| bambec 10mg tablets (astrazeneca uk ltd) | 14527 |
| maxivent 100microgram/inhalation inhalation powder (ashbourne pharmaceuticals ltd) | 7935 |
| salbutamol 100microgram/inhalation inhalation powder (berk pharmaceuticals ltd) | 34311 |
| terbutaline 250micrograms/dose inhaler with spacer | 7711 |
| salbutamol 2mg tablets (approved prescription services ltd) | 41548 |
| salamol 100microgram/inhalation inhalation powder (kent pharmaceuticals ltd) | 5889 |
| salbutamol 100micrograms/dose inhaler (kent pharmaceuticals ltd) | 33089 |
| ventodisks 400microgram with diskhaler (glaxosmithkline uk ltd) | 48809 |
| ventolin | 27573 |
| bricanyl 1.5mg/5ml syrup (astrazeneca uk ltd) | 3584 |
| exirel 15 mg tab | 8504 |
| salbutamol cyclocaps 400microgram inhalation powder (dupont pharmaceuticals ltd) | 38416 |
| ventolin respirator | 19653 |
| ventolin 100micrograms/dose evohaler (glaxosmithkline uk ltd) | 42830 |
| ventolin 200micrograms/dose accuhaler (lexon (uk) ltd) | 50557 |
| salbutamol 8mg modified-release capsules | 696 |
| salbulin 2mg tablet (3m health care ltd) | 18622 |
| bricanyl turbohaler 500 500microgram turbohaler (astrazeneca uk ltd) | 907 |
| ventolin | 26525 |
| salbulin novolizer 100micrograms/dose inhalation powder refill (meda pharmaceuticals ltd) | 38226 |
| spacehaler salbutamol 100microgram/inhalation spacehaler (celltech pharma europe ltd) | 22430 |
| monovent 1.5mg/5ml syrup (sandoz ltd) | 41832 |
| salbutamol 4mg modified-release capsules | 9384 |
| bronchodil 500microgram/dose inhalation powder (viatris pharmaceuticals ltd) | 12486 |
| ventolin 2.5mg nebules (mawdsley-brooks & company ltd) | 53019 |
| ventolin 5mg/ml respirator solution (glaxosmithkline uk ltd) | 510 |
| salbutamol 95micrograms/dose dry powder inhaler | 6462 |
| ventodisks 200microgram/blister disc (allen & hanburys ltd) | 1882 |
| bricanyl nebule 2.5 ml | 17901 |
| ventolin cr 4mg tablet (allen & hanburys ltd) | 10458 |
| salbutamol 100micrograms/dose inhaler cfc free (a a h pharmaceuticals ltd) | 34310 |
| reproterol 10mg/ml respirator solution | 22790 |
| ventodisks 400microgram (glaxosmithkline uk ltd) | 48742 |
| bricanyl tablet (astrazeneca uk ltd) | 26987 |
| airsalb 100micrograms/dose inhaler cfc free (sandoz ltd) | 58269 |
| terbutaline respules inh | 3763 |
| salbuvent inh inh | 3189 |
| ventolin 2mg/5ml syrup (glaxosmithkline uk ltd) | 856 |
| terbutaline 5mg tablets | 10825 |
| salbuvent 2mg tablet (pharmacia ltd) | 20838 |
| ventolin 100micrograms/dose evohaler (waymade healthcare plc) | 48519 |
| salbutamol 8mg tablet | 42497 |
| ventolin 100micrograms/dose evohaler (de pharmaceuticals) | 48490 |
| fenoterol hydrobromide complete unit inh | 8339 |
| salbutamol 100micrograms/dose dry powder inhalation cartridge | 38214 |
| pirbuterol 15mg capsule | 8252 |
| salbutamol 100micrograms/dose inhaler | 8 |
| ventolin s/r | 19726 |
| ventolin 4mg tablet (allen & hanburys ltd) | 987 |
| salbutamol 5mg/5ml solution for infusion ampoules | 18968 |
| salbuvent 4mg tablet (pharmacia ltd) | 29267 |
| ventolin 5mg/5ml solution for infusion ampoules (glaxosmithkline uk ltd) | 24645 |
| salbutamol 100micrograms/dose inhaler cfc free | 17 |
| bricanyl 5mg tablets (astrazeneca uk ltd) | 3534 |
| salbutamol 2mg tablets | 881 |
| bricanyl 500micrograms/dose turbohaler (astrazeneca uk ltd) | 42886 |
| salbutamol 2 mg/5ml syr | 2395 |
| asmasal 95micrograms/dose clickhaler (focus pharmaceuticals ltd) | 1087 |
| salbutamol 100micrograms/dose inhaler cfc free (phoenix healthcare distribution ltd) | 61591 |
| ventolin .25 mg inj | 7452 |
| terbutaline 250micrograms/actuation refill canister | 1628 |
| ventolin 100micrograms/dose evohaler (mawdsley-brooks & company ltd) | 48741 |
| pirbuterol 10mg capsule | 22661 |
| salbutamol 400 cyclocaps (teva uk ltd) | 32050 |
| bricanyl oral solution (astrazeneca uk ltd) | 15483 |
| salbutamol 5mg/50ml solution for infusion vials | 9805 |
| salbutamol 200microgram inhalation powder blisters | 49369 |
| salamol 100micrograms/dose inhaler cfc free (arrow generics ltd) | 48547 |
| salbutamol 2mg/5ml oral solution sugar free (sandoz ltd) | 41691 |
| salbutamol 400micrograms disc | 5753 |
| salbutamol 400microgram inhalation powder blisters with device | 52799 |
| salbutamol 100microgram/inhalation inhalation powder (kent pharmaceuticals ltd) | 34619 |
| ventolin rotacaps | 23688 |
| bambuterol 20mg tablets | 12144 |
| salapin 2mg/5ml syrup (pinewood healthcare) | 31845 |
| ventolin 200micrograms/dose accuhaler (dowelhurst ltd) | 57524 |
| duovent | 22550 |
| salamol 100micrograms/dose easi-breathe inhaler (teva uk ltd) | 5516 |
| salbutamol 100micrograms/dose dry powder inhalation cartridge with device | 38079 |
| salbutamol 200 cyclocaps (teva uk ltd) | 33373 |
| salbutamol 100micrograms/dose breath actuated inhaler | 1698 |
| sodium cromoglicate 1mg/dose / salbutamol 100micrograms/dose inhaler with spacer | 24380 |
| aerocrom inhaler (castlemead healthcare ltd) | 10360 |
| sodium cromoglicate 1mg/dose / salbutamol 100micrograms/dose inhaler | 8267 |
| aerocrom syncroner with spacer (castlemead healthcare ltd) | 18314 |
| ipratropium bromide with fenoterol hydrobromide 40micrograms + 100micrograms/actuation | 27505 |
| duovent inhaler (boehringer ingelheim ltd) | 2722 |
| duovent autohaler (boehringer ingelheim ltd) | 2862 |
| combivent inhaler (boehringer ingelheim ltd) | 556 |
| fenoterol 100micrograms/dose / ipratropium 40micrograms/dose inhaler | 3786 |
| ipratropium bromide with fenoterol hydrobromide 500micrograms + 1.25mg/4ml | 9270 |
| ipratropium bromide with salbutamol 20mcg + 100mcg | 2152 |
| ipratropium bromide with salbutamol 500micrograms + 2.5mg/2.5ml | 11046 |
| salbutamol 2.5mg with ipratropium bromide 500micrograms/2.5ml unit dose nebuilser solution | 12822 |
| ipratropium bromide with fenoterol hydrobromide 0micrograms + 100micrograms/actuation | 26616 |
| salbutamol 100micrograms/dose / ipratropium 20micrograms/dose inhaler | 12909 |
| fenoterol 100micrograms/dose / ipratropium bromide 40micrograms/dose breath actuated inhaler | 12808 |
| respontin 250micrograms/1ml nebules (glaxosmithkline uk ltd) | 23567 |
| atrovent | 19805 |
| respontin 500micrograms/2ml nebules (glaxosmithkline uk ltd) | 18140 |
| oxitropium bromide 100micrograms/dose inhaler | 2437 |
| ipratropium bromide 40micrograms/dose inhaler | 4268 |
| atrovent aerohaler 40microgram inhalation powder (boehringer ingelheim ltd) | 9681 |
| atrovent 20micrograms/dose inhaler (boehringer ingelheim ltd) | 534 |
| atrovent 20micrograms/dose inhaler cfc free (de pharmaceuticals) | 50810 |
| ipratropium bromide 250microgram/ml inhalation vapour (galen ltd) | 23961 |
| ipratropium bromide 20micrograms/dose breath actuated inhaler | 6081 |
| ipratropium bromide 40microgram inhalation powder capsules with device | 11779 |
| ipratropium bromide 20micrograms/dose inhaler | 1409 |
| ipratropium bromide 250microgram/ml | 37791 |
| atrovent 20micrograms/dose inhaler cfc free (boehringer ingelheim ltd) | 6512 |
| oxitropium bromide 100micrograms/dose breath actuated inhaler | 9658 |
| ipratropium bromide 20micrograms/dose inhaler cfc free | 6522 |
| atrovent aerocaps 40microgram inhalation powder (boehringer ingelheim ltd) | 2994 |
| atrovent 20micrograms/dose inhaler cfc free (lexon (uk) ltd) | 57557 |
| ipratropium bromide 40microgram inhalation powder capsules | 8333 |
| atrovent 20micrograms/dose autohaler (boehringer ingelheim ltd) | 1697 |
| ipratropium bromide (forte) | 25020 |
| atrovent 40microgram aerocaps with aerohaler (boehringer ingelheim ltd) | 43105 |
| oxivent 100micrograms/dose inhaler (boehringer ingelheim ltd) | 3039 |
| atrovent forte 40micrograms/dose inhaler (boehringer ingelheim ltd) | 3306 |
| atrovent 40microgram aerocaps (boehringer ingelheim ltd) | 43090 |
| ipratropium bromide 0.25mg/ml | 1410 |
| oxivent 100micrograms/dose autohaler (boehringer ingelheim ltd) | 3850 |
| atrovent forte | 20720 |
| ipratropium bromide 250micrograms/ml | 1411 |
| atrovent 20micrograms/dose inhaler cfc free (sigma pharmaceuticals plc) | 60920 |
| salbutamol 100micrograms/dose / beclometasone 50micrograms/dose inhaler | 11307 |
| ventide paediatric rotacaps (glaxosmithkline uk ltd) | 18484 |
| beclometasone 200micrograms with salbutamol 400micrograms inhalation capsules | 19376 |
| beclometasone 50micrograms with salbutamol 100micrograms/inhalation inhaler | 3556 |
| ventide inhaler (glaxosmithkline uk ltd) | 1801 |
| ventide rotacaps (glaxosmithkline uk ltd) | 16625 |
| salbutamol 200microgram / beclometasone 100microgram inhalation powder capsules | 18456 |
| beclometasone 100micrograms with salbutamol 200micrograms inhalation capsules | 19121 |
| salbutamol 400microgram / beclometasone 200microgram inhalation powder capsules | 14561 |
| indacaterol 300microgram inhalation powder capsules with device | 45610 |
| salmeterol 25micrograms/dose inhaler cfc free | 7270 |
| foradil 12microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd) | 10968 |
| serevent 25micrograms/dose inhaler (glaxosmithkline uk ltd) | 549 |
| formoterol 12micrograms/dose dry powder inhaler | 7133 |
| salmeterol 25micrograms/dose inhaler cfc free (a a h pharmaceuticals ltd) | 54742 |
| salmeterol 50micrograms/dose dry powder inhaler | 719 |
| vertine 25micrograms/dose inhaler cfc free (teva uk ltd) | 57694 |
| brelomax 2mg tablet (abbott laboratories ltd) | 26829 |
| tulobuterol 2mg | 19799 |
| oxis 12 turbohaler (waymade healthcare plc) | 56482 |
| atimos modulite 12micrograms/dose inhaler (chiesi ltd) | 25784 |
| neovent 25micrograms/dose inhaler cfc free (kent pharmaceuticals ltd) | 47638 |
| opilon 40mg tablet (concord pharmaceuticals ltd) | 10672 |
| serevent 25micrograms/dose evohaler (waymade healthcare plc) | 50051 |
| formoterol easyhaler 12micrograms/dose dry powder inhaler (orion pharma (uk) ltd) | 35725 |
| serevent 50micrograms/dose accuhaler (glaxosmithkline uk ltd) | 2224 |
| onbrez breezhaler 150microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd) | 43893 |
| formoterol 12microgram inhalation powder capsules with device | 6526 |
| indacaterol 150microgram inhalation powder capsules with device | 43738 |
| serevent 50microgram disks (glaxosmithkline uk ltd) | 35825 |
| opilon 40mg tablets (archimedes pharma uk ltd) | 43764 |
| serevent 50micrograms/dose accuhaler (de pharmaceuticals) | 56478 |
| tulobuterol 1mg/5ml sugar free syrup | 42103 |
| serevent 50micrograms/dose accuhaler (waymade healthcare plc) | 57544 |
| salmeterol 50micrograms disc | 3297 |
| oxis 6 turbohaler (lexon (uk) ltd) | 57558 |
| formoterol 6micrograms/dose dry powder inhaler | 9711 |
| salmeterol 50microgram inhalation powder blisters with device | 35542 |
| salmeterol 25micrograms/dose inhaler | 465 |
| onbrez breezhaler 300microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd) | 44064 |
| serevent 50microgram disks with diskhaler (glaxosmithkline uk ltd) | 35165 |
| formoterol 12micrograms/dose inhaler cfc free | 14306 |
| oxis 12 turbohaler (astrazeneca uk ltd) | 1974 |
| serevent 25micrograms/dose evohaler (glaxosmithkline uk ltd) | 7268 |
| moxisylyte 40mg tablets | 8365 |
| salmeterol 50microgram inhalation powder blisters | 35503 |
| oxis 6 turbohaler (astrazeneca uk ltd) | 1975 |
| respacal 2mg tablet (ucb pharma ltd) | 22663 |
| serevent diskhaler 50microgram inhalation powder (glaxo wellcome uk ltd) | 910 |
| fluticasone furoate 92micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler | 59439 |
| becotide susp for nebulisation | 19736 |
| seretide 500 accuhaler (mawdsley-brooks & company ltd) | 51861 |
| becotide rotahaler insufflator inhalation powder (allen and hanburys ltd) | 9356 |
| fluticasone 125micrograms/dose / formoterol 5micrograms/dose inhaler cfc free | 51209 |
| fostair 100micrograms/dose / 6micrograms/dose inhaler (chiesi ltd) | 37432 |
| seretide 500 accuhaler (de pharmaceuticals) | 51593 |
| relvar ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd) | 59327 |
| fostair nexthaler 100micrograms/dose / 6micrograms/dose dry powder inhaler (chiesi ltd) | 61644 |
| flutiform 50micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd) | 50689 |
| becotide 50 | 27525 |
| becotide 400microgram rotacaps (glaxosmithkline uk ltd) | 3075 |
| fluticasone 50micrograms/dose / formoterol 5micrograms/dose inhaler cfc free | 51270 |
| seretide 250 evohaler (waymade healthcare plc) | 49000 |
| budesonide 400micrograms/dose / formoterol 12micrograms/dose dry powder inhaler | 6746 |
| becotide rotahaler (glaxosmithkline uk ltd) | 50701 |
| fluticasone 250micrograms/dose / formoterol 10micrograms/dose inhaler cfc free | 49868 |
| beclometasone 100micrograms/dose / formoterol 6micrograms/dose inhaler cfc free | 37470 |
| seretide 250 evohaler (stephar (u.k.) ltd) | 50886 |
| becotide 200 inhaler (glaxosmithkline uk ltd) | 1258 |
| becotide rotacaps | 24219 |
| seretide 100 accuhaler (waymade healthcare plc) | 53283 |
| fluticasone 50micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free | 12994 |
| symbicort 400/12 turbohaler (de pharmaceuticals) | 53237 |
| seretide 125 evohaler (lexon (uk) ltd) | 51151 |
| symbicort 200/6 turbohaler (sigma pharmaceuticals plc) | 53491 |
| seretide 500 accuhaler (lexon (uk) ltd) | 55677 |
| fluticasone 250micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free | 11618 |
| seretide 250 accuhaler (de pharmaceuticals) | 53230 |
| salmeterol 50micrograms with fluticasone 100micrograms dry powder inhaler | 6938 |
| becotide 100 inhaler (glaxosmithkline uk ltd) | 99 |
| salmeterol 25micrograms with fluticasone 125micrograms cfc free inhaler | 6569 |
| flutiform 250micrograms/dose / 10micrograms/dose inhaler (napp pharmaceuticals ltd) | 48666 |
| seretide 250 accuhaler (waymade healthcare plc) | 61280 |
| duoresp spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (teva uk ltd) | 61782 |
| salmeterol 25micrograms with fluticasone 250micrograms cfc free inhaler | 5864 |
| salmeterol 50micrograms with fluticasone 500micrograms cfc free inhaler | 5558 |
| seretide 250 evohaler (glaxosmithkline uk ltd) | 5172 |
| seretide 125 evohaler (glaxosmithkline uk ltd) | 5161 |
| fluticasone propionate 100micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler | 13273 |
| relvar ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd) | 59573 |
| becotide rotahaler type 4 insufflator inhalation powder (allen and hanburys ltd) | 3437 |
| becotide 200microgram rotacaps (glaxosmithkline uk ltd) | 1537 |
| becotide 100 | 20707 |
| salmeterol 50micrograms with fluticasone 250micrograms cfc free inhaler | 5942 |
| duoresp spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler (teva uk ltd) | 61666 |
| seretide 250 evohaler (necessity supplies ltd) | 51909 |
| seretide 500 accuhaler (waymade healthcare plc) | 51394 |
| becotide 100microgram rotacaps (glaxosmithkline uk ltd) | 3947 |
| becotide easi-breathe 100microgram/actuation pressurised inhalation (allen & hanburys ltd) | 896 |
| symbicort 200/6 turbohaler (mawdsley-brooks & company ltd) | 51759 |
| symbicort 100/6 turbohaler (mawdsley-brooks & company ltd) | 50945 |
| seretide 100 accuhaler (de pharmaceuticals) | 62126 |
| seretide 250 evohaler (de pharmaceuticals) | 48739 |
| budesonide 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler | 10218 |
| symbicort 200/6 turbohaler (astrazeneca uk ltd) | 6325 |
| seretide 100 accuhaler (glaxosmithkline uk ltd) | 665 |
| seretide 50 evohaler (glaxosmithkline uk ltd) | 5143 |
| fluticasone 125micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free | 11588 |
| becotide 50 inhaler (glaxosmithkline uk ltd) | 1406 |
| symbicort 400/12 turbohaler (astrazeneca uk ltd) | 6780 |
| seretide 500 accuhaler (glaxosmithkline uk ltd) | 3666 |
| seretide 250 accuhaler (sigma pharmaceuticals plc) | 50560 |
| symbicort 200/6 turbohaler (de pharmaceuticals) | 51570 |
| becotide easi-breathe 50microgram/actuation pressurised inhalation (allen & hanburys ltd) | 1727 |
| fluticasone furoate 184micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler | 59899 |
| symbicort 100/6 turbohaler (sigma pharmaceuticals plc) | 49114 |
| beclometasone 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler | 62030 |
| flutiform 125micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd) | 50036 |
| budesonide 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler | 6796 |
| seretide 125 evohaler (de pharmaceuticals) | 51027 |
| symbicort 400/12 turbohaler (mawdsley-brooks & company ltd) | 50739 |
| symbicort 100/6 turbohaler (astrazeneca uk ltd) | 7013 |
| seretide 250 accuhaler (glaxosmithkline uk ltd) | 638 |
| salmeterol 25micrograms with fluticasone 50micrograms cfc free inhaler | 6616 |
| fluticasone propionate 250micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler | 13040 |
| fluticasone propionate 500micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler | 11410 |
| anoro ellipta 55micrograms/dose / 22micrograms/dose dry powder inhaler (glaxosmithkline uk ltd) | 61176 |
| umeclidinium bromide 65micrograms/dose / vilanterol 22micrograms/dose dry powder inhaler | 61490 |
| qvar 100 autohaler (sigma pharmaceuticals plc) | 54399 |
| budesonide 50micrograms/dose inhaler | 959 |
| fluticasone 250microgram/actuation pressurised inhalation | 2951 |
| qvar 100micrograms/dose easi-breathe inhaler (de pharmaceuticals) | 50129 |
| becodisks 100microgram disc (allen & hanburys ltd) | 2229 |
| flixotide 100microgram disc (allen & hanburys ltd) | 3989 |
| flixotide 0.5mg/2ml nebules (glaxosmithkline uk ltd) | 5551 |
| beclometasone 200micrograms/dose inhaler (a a h pharmaceuticals ltd) | 34794 |
| beclometasone 400 cyclocaps (teva uk ltd) | 41269 |
| beclometasone 250micrograms/dose inhaler (generics (uk) ltd) | 29325 |
| aerobec 250microgram/actuation pressurised inhalation (meda pharmaceuticals ltd) | 4499 |
| becloforte 250micrograms/dose inhaler (dowelhurst ltd) | 57589 |
| beclometasone 50microgram/actuation inhalation powder (actavis uk ltd) | 32874 |
| aerobec 50 autohaler (meda pharmaceuticals ltd) | 2159 |
| asmabec 250microgram/actuation spacehaler (celltech pharma europe ltd) | 14590 |
| beclazone 50 easi-breathe inhaler (teva uk ltd) | 1725 |
| pulmicort 400 turbohaler (astrazeneca uk ltd) | 908 |
| beclometasone 400microgram inhalation powder blisters | 35288 |
| clenil modulite 50micrograms/dose inhaler (mawdsley-brooks & company ltd) | 49367 |
| beclometasone 400microgram inhalation powder blisters with device | 35107 |
| flixotide 125microgram/actuation inhalation powder (allen & hanburys ltd) | 1676 |
| fluticasone 250micrograms/dose evohaler (sigma pharmaceuticals plc) | 49772 |
| budenofalk 9mg gastro-resistant granules sachets (dr. falk pharma uk ltd) | 48088 |
| beclometasone 250micrograms/dose inhaler (a a h pharmaceuticals ltd) | 33258 |
| pulvinal beclometasone dipropionate 200micrograms/dose dry powder inhaler (chiesi ltd) | 13037 |
| bdp 100microgram/actuation spacehaler (celltech pharma europe ltd) | 19031 |
| clenil modulite 50micrograms/dose inhaler (chiesi ltd) | 16158 |
| pulmicort refil 200 mcg inh | 2124 |
| beclometasone 100microgram inhalation powder capsules | 4759 |
| flixotide diskhaler-community pack 250 mcg | 3753 |
| pulmicort 200micrograms/dose inhaler (astrazeneca uk ltd) | 49711 |
| beclometasone 100micrograms/dose inhaler cfc free | 15326 |
| qvar 100 inhaler (teva uk ltd) | 2335 |
| flixotide accuhaler 50 50microgram/inhalation inhalation powder (allen & hanburys ltd) | 5580 |
| qvar 100 inhaler (sigma pharmaceuticals plc) | 51681 |
| budesonide 100micrograms/actuation inhaler | 8433 |
| asmabec 50 clickhaler (focus pharmaceuticals ltd) | 9577 |
| fluticasone 25micrograms/dose inhaler | 2723 |
| pulmicort l.s. refil | 23675 |
| fluticasone propionate 100microgram inhalation powder blisters with device | 35638 |
| beclometasone 250micrograms/actuation vortex inhaler | 9571 |
| qvar 100 inhaler (waymade healthcare plc) | 51234 |
| entocort cr 3mg capsules (waymade healthcare plc) | 60946 |
| fluticasone 50micrograms/dose inhaler cfc free | 5223 |
| flixotide 50micrograms/dose evohaler (lexon (uk) ltd) | 53057 |
| clenil modulite 100micrograms/dose inhaler (chiesi ltd) | 13290 |
| flixotide 100micrograms/dose accuhaler (glaxosmithkline uk ltd) | 42928 |
| pulvinal beclometasone dipropionate 400micrograms/dose dry powder inhaler (chiesi ltd) | 14736 |
| qvar 100 autohaler (lexon (uk) ltd) | 52806 |
| flixotide 250micrograms/dose accuhaler (stephar (u.k.) ltd) | 57525 |
| beclometasone 100microgram/actuation inhalation powder (neo laboratories ltd) | 33849 |
| pulmicort 0.5mg respules (necessity supplies ltd) | 52732 |
| flixotide 250microgram disks (glaxosmithkline uk ltd) | 35611 |
| becloforte vm 250microgram/actuation vm pack (allen & hanburys ltd) | 8111 |
| budesonide 200micrograms/dose inhaler cfc free | 39879 |
| beclometasone 250micrograms/dose inhaler | 1242 |
| pulmicort complete | 26665 |
| fluticasone propionate 50microgram inhalation powder blisters | 37447 |
| flixotide 125micrograms/dose evohaler (glaxosmithkline uk ltd) | 5718 |
| beclometasone 400microgram inhalation powder capsules | 7653 |
| beclometasone 100microgram/actuation inhalation powder (actavis uk ltd) | 28640 |
| beclometasone 100micrograms disc | 4365 |
| beclometasone 50micrograms/dose inhaler (teva uk ltd) | 34739 |
| flixotide 50microgram disc (allen & hanburys ltd) | 8635 |
| flixotide 50micrograms/dose accuhaler (de pharmaceuticals) | 57579 |
| qvar 100 autohaler (teva uk ltd) | 4413 |
| beclometasone 5mg gastro-resistant modified-release tablets | 37203 |
| fluticasone 125microgram/actuation pressurised inhalation | 4132 |
| beclometasone 50micrograms/dose inhaler | 3018 |
| beclometasone 200microgram inhalation powder capsules | 9233 |
| beclometasone 50micrograms/dose breath actuated inhaler | 2160 |
| beclometasone 400microgram disc | 2148 |
| beclometasone 50micrograms/dose inhaler (a a h pharmaceuticals ltd) | 34919 |
| budesonide 200micrograms/dose dry powder inhaler | 2092 |
| beclometasone 250micrograms/dose inhaler cfc free | 21005 |
| beclometasone 50micrograms/actuation extrafine particle cfc free inhaler | 10090 |
| beclazone 250 inhaler (teva uk ltd) | 1551 |
| clipper 5mg gastro-resistant modified-release tablets (chiesi ltd) | 39067 |
| qvar 50 inhaler (mawdsley-brooks & company ltd) | 51415 |
| becodisks 100microgram with diskhaler (glaxosmithkline uk ltd) | 35106 |
| becodisks 400microgram (glaxosmithkline uk ltd) | 35299 |
| qvar 50 inhaler (de pharmaceuticals) | 54207 |
| filair 100 inhaler (meda pharmaceuticals ltd) | 3927 |
| easyhaler budesonide 100micrograms/dose dry powder inhaler (orion pharma (uk) ltd) | 17670 |
| becodisks 200microgram disc (allen & hanburys ltd) | 883 |
| flixotide diskhaler-community pack 50 mcg | 8450 |
| flixotide 25micrograms/dose inhaler (glaxosmithkline uk ltd) | 3289 |
| qvar 100 autohaler (stephar (u.k.) ltd) | 53480 |
| budesonide 100micrograms/dose inhaler cfc free | 39102 |
| becloforte | 20763 |
| flixotide 500microgram disks (glaxosmithkline uk ltd) | 35374 |
| aerobec forte 250 autohaler (meda pharmaceuticals ltd) | 39200 |
| beclazone 50microgram/actuation inhalation powder (actavis uk ltd) | 9599 |
| beclometasone 250micrograms/dose dry powder inhaler | 5804 |
| beclazone easi-breathe (roi) 100microgram/actuation pressurised inhalation (ivax pharmaceuticals ireland) | 47943 |
| flixotide 250micrograms/dose evohaler (glaxosmithkline uk ltd) | 5683 |
| clenil modulite 100micrograms/dose inhaler (mawdsley-brooks & company ltd) | 48340 |
| beclazone 200 inhaler (teva uk ltd) | 1885 |
| flixotide accuhaler 250 250microgram/inhalation inhalation powder (allen & hanburys ltd) | 911 |
| budesonide 3mg gastro-resistant capsules | 6095 |
| beclometasone 250microgram/actuation pressurised inhalation (approved prescription services ltd) | 28073 |
| fluticasone 100microgram disc | 4131 |
| flixotide 500micrograms/dose accuhaler (glaxosmithkline uk ltd) | 43074 |
| fluticasone propionate 250microgram inhalation powder blisters | 35905 |
| pulmicort | 27583 |
| easyhaler beclometasone 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd) | 17654 |
| pulmicort ls 50microgram refill canister (astrazeneca uk ltd) | 4545 |
| flixotide 250microgram/actuation inhalation powder (allen & hanburys ltd) | 1412 |
| becloforte 400microgram disks with diskhaler (glaxosmithkline uk ltd) | 3363 |
| fluticasone propionate 500microgram inhalation powder blisters | 36462 |
| becodisks 200microgram (mawdsley-brooks & company ltd) | 56471 |
| qvar 50micrograms/dose easi-breathe inhaler (teva uk ltd) | 14294 |
| budesonide 200micrograms/actuation refill canister | 3570 |
| fluticasone propionate 50micrograms/dose dry powder inhaler | 9164 |
| easyhaler budesonide 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd) | 27188 |
| pulmicort 100micrograms/dose inhaler cfc free (astrazeneca uk ltd) | 39099 |
| flixotide accuhaler 100 100microgram/inhalation inhalation powder (allen & hanburys ltd) | 4926 |
| budesonide 400micrograms/dose dry powder inhaler | 1642 |
| beclometasone 250microgram/actuation inhalation powder (neo laboratories ltd) | 34859 |
| budesonide 200micrograms/actuation breath actuated powder inhaler | 16054 |
| pulmicort 100 turbohaler (astrazeneca uk ltd) | 960 |
| qvar 100 autohaler (de pharmaceuticals) | 51480 |
| fluticasone 500microgram disc | 7891 |
| becodisks 400microgram (waymade healthcare plc) | 56462 |
| fluticasone 250microgram disc | 7638 |
| beclometasone 100 micrograms/actuation vortex inhaler | 15706 |
| fluticasone prop disk refill | 27915 |
| beclometasone 200micrograms disc | 2893 |
| fluticasone propionate 100micrograms/dose dry powder inhaler | 5885 |
| budesonide 3mg gastro-resistant modified-release capsules | 3898 |
| qvar 50 inhaler (teva uk ltd) | 3546 |
| beclometasone 250micrograms/dose inhaler (teva uk ltd) | 30210 |
| becloforte easi-breathe 250microgram/actuation pressurised inhalation (allen & hanburys ltd) | 1552 |
| fluticasone 250micrograms/dose inhaler cfc free | 5822 |
| becodisks 200microgram with diskhaler (glaxosmithkline uk ltd) | 35430 |
| flixotide 250micrograms/dose accuhaler (glaxosmithkline uk ltd) | 42994 |
| flixotide 50microgram disks with diskhaler (glaxosmithkline uk ltd) | 36290 |
| spacehaler bdp 100microgram/actuation spacehaler (celltech pharma europe ltd) | 24898 |
| fluticasone propionate 500microgram inhalation powder blisters with device | 35700 |
| pulmicort complete 50 mcg inh | 3188 |
| budesonide 100micrograms/dose dry powder inhaler | 7788 |
| beclometasone 200microgram inhalation powder blisters with device | 35293 |
| pulmicort refil 50 mg inh | 8251 |
| beclometasone 200micrograms/dose inhaler | 1259 |
| budenofalk 3mg gastro-resistant capsules (dr. falk pharma uk ltd) | 16525 |
| pulmicort ls 50micrograms/dose inhaler (astrazeneca uk ltd) | 1680 |
| mometasone 400micrograms/dose dry powder inhaler | 10254 |
| pulmicort refill | 20812 |
| bdp 250microgram/actuation spacehaler (celltech pharma europe ltd) | 14524 |
| beclazone 50 inhaler (teva uk ltd) | 2992 |
| fluticasone 50microgram disc | 7602 |
| flixotide 2mg/2ml nebules (glaxosmithkline uk ltd) | 16305 |
| pulvinal beclometasone dipropionate 100micrograms/dose dry powder inhaler (chiesi ltd) | 14757 |
| budesonide 200micrograms/dose inhaler | 909 |
| pulmicort 0.5mg respules (astrazeneca uk ltd) | 1959 |
| aerobec 100 autohaler (meda pharmaceuticals ltd) | 1861 |
| mometasone 200micrograms/dose dry powder inhaler | 16018 |
| budelin novolizer 200micrograms/dose inhalation powder (meda pharmaceuticals ltd) | 35631 |
| pulmicort 200 turbohaler (dowelhurst ltd) | 60937 |
| pulmicort 0.5mg respules (waymade healthcare plc) | 50037 |
| asmabec 50microgram/actuation spacehaler (celltech pharma europe ltd) | 19389 |
| fluticasone propionate 500micrograms/dose dry powder inhaler | 2282 |
| qvar 100micrograms/dose easi-breathe inhaler (teva uk ltd) | 18848 |
| flixotide accuhaler 500 500microgram/inhalation inhalation powder (allen & hanburys ltd) | 2440 |
| novolizer budesonide 200microgram/actuation pressurised inhalation (meda pharmaceuticals ltd) | 23741 |
| flixotide diskhaler-community pack 100 mcg | 3988 |
| budelin novolizer 200micrograms/dose inhalation powder refill (meda pharmaceuticals ltd) | 35724 |
| entocort cr 3mg capsules (astrazeneca uk ltd) | 1380 |
| budenofalk 9mg gastro-resistant granules sachets (dr. falk pharma uk ltd) | 56144 |
| flixotide 50micrograms/dose accuhaler (sigma pharmaceuticals plc) | 56475 |
| pulmicort 200micrograms/dose inhaler cfc free (astrazeneca uk ltd) | 40057 |
| becloforte 250micrograms/dose inhaler (glaxosmithkline uk ltd) | 1236 |
| beclometasone 400micrograms/dose dry powder inhaler | 11497 |
| becodisks 100microgram (glaxosmithkline uk ltd) | 35408 |
| beclometasone 250microgram/actuation inhalation powder (actavis uk ltd) | 34315 |
| pulmicort 200 turbohaler (astrazeneca uk ltd) | 956 |
| bdp 50microgram/actuation spacehaler (celltech pharma europe ltd) | 18394 |
| beclometasone 200micrograms/dose inhaler cfc free | 14321 |
| beclometasone 50micrograms/dose breath actuated inhaler cfc free | 11732 |
| filair forte 250micrograms/dose inhaler (meda pharmaceuticals ltd) | 3993 |
| flixotide 100microgram disks with diskhaler (glaxosmithkline uk ltd) | 35225 |
| beclometasone 200micrograms/dose dry powder inhaler | 5521 |
| asmabec 100 clickhaler (focus pharmaceuticals ltd) | 4601 |
| clenil modulite 250micrograms/dose inhaler (chiesi ltd) | 16148 |
| becloforte 400microgram disks (glaxosmithkline uk ltd) | 2892 |
| becodisks 200microgram (glaxosmithkline uk ltd) | 35071 |
| budesonide 200micrograms/dose dry powder inhalation cartridge with device | 35510 |
| asmabec 250 clickhaler (focus pharmaceuticals ltd) | 14567 |
| pulmicort 200 turbohaler (waymade healthcare plc) | 56498 |
| betamethasone valerate | 24660 |
| budesonide 9mg gastro-resistant granules sachets | 51997 |
| beclometasone 100micrograms/dose breath actuated inhaler | 1734 |
| flixotide 100microgram disks (glaxosmithkline uk ltd) | 36090 |
| fluticasone 125micrograms/dose inhaler cfc free | 5975 |
| beclometasone 250micrograms/actuation inhaler and compact spacer | 19401 |
| beclazone 100 easi-breathe inhaler (teva uk ltd) | 895 |
| flixotide 250micrograms/dose evohaler (waymade healthcare plc) | 51815 |
| fluticasone propionate 50microgram inhalation powder blisters with device | 36021 |
| beclometasons 50 micrograms/actuation vortex inhaler | 11198 |
| qvar 100 inhaler (de pharmaceuticals) | 50287 |
| beclometasone 50microgram/actuation inhalation powder (neo laboratories ltd) | 34428 |
| beclometasone 100micrograms/dose inhaler (teva uk ltd) | 26063 |
| budesonide 200micrograms/dose dry powder inhalation cartridge | 35602 |
| beclometasone 50microgram/actuation pressurised inhalation (approved prescription services ltd) | 30238 |
| budesonide 400micrograms/actuation inhaler | 14700 |
| beclometasone 100micrograms/dose inhaler | 38 |
| beclazone 100microgram/actuation inhalation powder (actavis uk ltd) | 13815 |
| budesonide 50micrograms/actuation refill canister | 947 |
| budesonide 400microgram inhalation powder capsules | 10321 |
| flixotide 500microgram disc (allen & hanburys ltd) | 1426 |
| beclometasone 100micrograms/actuation extrafine particle cfc free inhaler | 3150 |
| beclometasone 200microgram inhalation powder blisters | 35113 |
| flixotide 250microgram disc (allen & hanburys ltd) | 1424 |
| beclazone 250microgram/actuation inhalation powder (actavis uk ltd) | 4803 |
| qvar 50micrograms/dose easi-breathe inhaler (sigma pharmaceuticals plc) | 56493 |
| clenil modulite 250micrograms/dose inhaler (waymade healthcare plc) | 61664 |
| fluticasone propionate 100microgram inhalation powder blisters | 35772 |
| becloforte integra 250microgram/actuation inhaler with compact spacer (glaxo laboratories ltd) | 3119 |
| beclometasone 100micrograms/dose dry powder inhaler | 5522 |
| beclometasone 100micrograms/dose inhaler (a a h pharmaceuticals ltd) | 25204 |
| betamethasone valerate 100micrograms/actuation inhaler | 7724 |
| filair 50 inhaler (meda pharmaceuticals ltd) | 3743 |
| pulmicort 1mg respules (astrazeneca uk ltd) | 1956 |
| flixotide 500micrograms/dose accuhaler (waymade healthcare plc) | 56499 |
| pulmicort 200microgram refill canister (astrazeneca uk ltd) | 2125 |
| fluticasone propionate 250microgram inhalation powder blisters with device | 36401 |
| fluticasone 50microgram/actuation pressurised inhalation | 4688 |
| bextasol inhalation powder (allen & hanburys ltd) | 3065 |
| becodisks 400microgram with diskhaler (glaxosmithkline uk ltd) | 35118 |
| flixotide 50microgram/actuation inhalation powder (allen & hanburys ltd) | 1518 |
| flixotide 50micrograms/dose evohaler (glaxosmithkline uk ltd) | 5309 |
| budesonide 9mg gastro-resistant granules sachets | 47225 |
| easyhaler budesonide 400micrograms/dose dry powder inhaler (orion pharma (uk) ltd) | 30649 |
| beclometasone 100microgram inhalation powder blisters with device | 35580 |
| beclometasone 400micrograms/actuation inhaler | 41412 |
| spacehaler bdp 250microgram/actuation spacehaler (celltech pharma europe ltd) | 20825 |
| flixotide 250microgram disks with diskhaler (glaxosmithkline uk ltd) | 35461 |
| flixotide 50micrograms/dose accuhaler (glaxosmithkline uk ltd) | 42985 |
| beclometasone 100micrograms/dose breath actuated inhaler cfc free | 9921 |
| flixotide 125micrograms/dose evohaler (de pharmaceuticals) | 56474 |
| flixotide 50microgram disks (glaxosmithkline uk ltd) | 35986 |
| betnelan 500microgram tablets (focus pharmaceuticals ltd) | 11149 |
| beclazone 250 easi-breathe inhaler (teva uk ltd) | 1243 |
| beclometasone 50micrograms/dose inhaler (generics (uk) ltd) | 31774 |
| flixotide 100micrograms/dose accuhaler (waymade healthcare plc) | 56477 |
| beclometasone 250micrograms/dose breath actuated inhaler | 2600 |
| clenil modulite 200micrograms/dose inhaler (chiesi ltd) | 16151 |
| beclazone 100 inhaler (teva uk ltd) | 1100 |
| becodisks 400microgram disc (allen & hanburys ltd) | 1951 |
| fluticasone propionate 250micrograms/dose dry powder inhaler | 7948 |
| beclometasone 100micrograms/dose inhaler (generics (uk) ltd) | 21482 |
| asmabec 100microgram/actuation spacehaler (celltech pharma europe ltd) | 9477 |
| beclometasone 100microgram/actuation pressurised inhalation (approved prescription services ltd) | 27679 |
| beclometasone 100microgram inhalation powder blisters | 35652 |
| beclometasone 200 cyclocaps (teva uk ltd) | 46157 |
| flixotide 250micrograms/dose accuhaler (waymade healthcare plc) | 56484 |
| pulmicort complete 200 mcg inh | 3442 |
| spacehaler bdp 50microgram/actuation spacehaler (celltech pharma europe ltd) | 28761 |
| beclometasone 50micrograms/dose dry powder inhaler | 5992 |
| pulmicort 200microgram inhaler (astrazeneca uk ltd) | 454 |
| qvar 50 autohaler (teva uk ltd) | 3220 |
| budesonide 200microgram inhalation powder capsules | 18537 |
| flixotide 125micrograms/dose evohaler (dowelhurst ltd) | 57555 |
| qvar 100micrograms/dose easi-breathe inhaler (sigma pharmaceuticals plc) | 48709 |
| beclometasone 50micrograms/dose inhaler cfc free | 16584 |
| flixotide 500microgram disks with diskhaler (glaxosmithkline uk ltd) | 35392 |
| tiotropium bromide 18microgram inhalation powder capsules with device | 35014 |
| robinul 1mg tablet (idis world medicines) | 6474 |
| spiriva 18microgram inhalation powder capsules with handihaler (de pharmaceuticals) | 50577 |
| tiotropium bromide 18microgram inhalation powder capsules | 35011 |
| aclidinium bromide 375micrograms/dose dry powder inhaler | 49227 |
| spiriva 18microgram inhalation powder capsules with handihaler (waymade healthcare plc) | 50103 |
| robinul 2mg tablet (wyeth pharmaceuticals) | 7908 |
| spiriva 18microgram inhalation powder capsules with handihaler (sigma pharmaceuticals plc) | 59638 |
| spiriva 18microgram inhalation powder capsules (mawdsley-brooks & company ltd) | 51967 |
| seebri breezhaler 44microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd) | 53982 |
| spiriva 18 microgram capsule (boehringer ingelheim ltd) | 6050 |
| glycopyrronium bromide 2mg tablets | 7597 |
| eklira 322micrograms/dose genuair (almirall ltd) | 49228 |
| glycopyrronium bromide 200micrograms/5ml oral suspension | 59173 |
| tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device cfc free | 36864 |
| glycopyrronium bromide 500micrograms/5ml oral solution | 55911 |
| spiriva 18microgram inhalation powder capsules with handihaler (boehringer ingelheim ltd) | 34995 |
| spiriva 18microgram inhalation powder capsules (boehringer ingelheim ltd) | 35000 |
| glycopyrronium bromide 1mg/5ml oral solution | 29138 |
| glycopyrronium bromide 1mg/5ml oral suspension | 47269 |
| glycopyrronium bromide 600micrograms/5ml oral suspension | 54151 |
| glycopyrronium bromide 500micrograms/5ml oral suspension | 55795 |
| glycopyrronium bromide 2mg/5ml oral solution | 38377 |
| glycopyrronium bromide 1mg tablets | 7218 |
| spiriva respimat 2.5micrograms/dose solution for inhalation cartridge with device (boehringer ingelheim ltd) | 36869 |
| umeclidinium bromide 65micrograms/dose dry powder inhaler | 62109 |
| spiriva 18microgram inhalation powder capsules (sigma pharmaceuticals plc) | 50292 |
| glycopyrronium bromide 5mg/5ml oral suspension | 55794 |
| glycopyrronium bromide 5mg/5ml oral solution | 50047 |
| glycopyrronium bromide 200micrograms/5ml oral solution | 56262 |
| incruse ellipta 55micrograms/dose dry powder inhaler (glaxosmithkline uk ltd) | 61879 |
| glycopyrronium bromide 55microgram inhalation powder capsules with device | 53761 |
| tiotropium 18 microgram capsule | 746 |
| glycopyrronium bromide 2mg/5ml oral suspension | 38538 |
| glycopyrronium bromide 5mg/5ml oral solution | 46214 |
| spiriva respimat 2.5micrograms/dose solution for inhalation cartridge with device (waymade healthcare plc) | 61582 |

1. values in brackets indicate age-gender specific prevalence rates (%) of COPD [↑](#footnote-ref-1)
2. Codes are classified as (1) doctor diagnoses, ( [↑](#footnote-ref-2)