Better Targeting of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease

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Abstract

Introduction: Inhaled corticosteroids (ICS) have long been a treatment option for Chronic Obstructive Pulmonary Disease (COPD). However, questions over their efficacy have persisted and recent changes to guidance have stated that further research is needed to predict the patient factors that indicate ICS responsiveness. The aim of this thesis was to investigate the effect of variables, including smoking status, asthma co-diagnosis and blood eosinophil counts, on the outcomes of COPD with ICS use.

Method: Three methodologies were used to investigate the aims of this thesis. *Systematic review:* To examine the literature on the effect of smoking on outcomes with ICS use in COPD an electronic database search was conducted. Fully published randomised controlled trials, in the English language that stratified the participants by smoking status were included. The primary outcome measures were changes in lung function and yearly exacerbation rates.

Random effects panel data model: The Clinical Practice Research Datalink with linkage to Hospital Episode Statistics and Office of National Statistics data were used. The cohort was identified based on a previously validated method by Quint *et al* (2014). The impact of patient variables on the outcomes of lung function, yearly exacerbations and deaths with COPD after three, five and ten years were investigated.

Prospective cohort study: Patients in the cohort above were categorised by yearly ICS usage. Patients prescribed ICS were matched to those not using ICS based on propensity score. The outcomes measured were lung function, yearly exacerbations

and deaths after three, five and ten years. Sub-group analysis was performed on the variables of smoking status, asthma co-diagnosis and blood eosinophil levels.

Results: *Systematic review:* Eight studies were identified. Heavier or current smokers did not gain the same benefit from ICS use on lung function and exacerbation rates as lighter or ex-smokers do, however effect size may not be clinically important.

Random effects panel data model: An asthma co-diagnosis in people with COPD resulted in a lower probability of death, better lung function and less hospital-treated exacerbations compared to no asthma co-diagnosis. Smoking resulted in reduced lung function and an increased probability of death compared to non-smokers. However, there was no overall effect on yearly exacerbations.

Prospective cohort study: ICS use was associated with a greater decline in lung function and increased exacerbation rates but lower probability of death versus no-ICS use. In the sub-group analysis, smoking was associated with an additional 58ml decline in lung function at year five, an increase of 0.074 yearly exacerbations and 6.8% increased probability of mortality with ICS use than for non-smokers. An asthma co-diagnosis conferred decreased probability of mortality of up to 8.2% at year five for ICS users compared to those with no asthma co-diagnosis. ICS use in the high eosinophil group decreased the probability of mortality by 10% at year five compared to non-use.

Conclusion: ICS are of some benefit in treating COPD in terms of lung function and exacerbation rates. If they are to be used, targeting them to people with a co-diagnosis of asthma, with high blood eosinophils or are not current smokers will produce the most benefit in terms of decreased probability of death.

Publications

SONNEX K, ALLEEMUDDER H, KNAGGS R. 2020. Impact of smoking status on the efficacy of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review. *BMJ Open*. Apr 15;10(4):e037509

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List of abbreviations

ACO	Asthma-COPD overlap syndrome
BD	Budesonide Dipropionate
CAT	COPD assessment tool
CMV	Continuous Measure of Medication Gaps
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
DDD	Daily defined dosage
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced expiratory volume in one second (measured in litres or as a percentage of the patients maximum predicted volume)
FP	Fluticasone propionate
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Obstructive Lung Disease
HDAC2	Histone Deacetylase 2
ICD-9 ICD-10	International Classification of Diseases 9^{th} or 10^{th} revision
ICS	Inhaled corticosteroid
IMD	Index of Multiple Deprivation
LABA	Long acting beta agonist
LAMA	Long acting muscarinic antagonist
LTA	Leukotriene receptor antagonist
MAR	Missing at random
MCAR	Missing completely at random
mMRC	British Medical Research Council dyspnoea scale
MNAR	Missing not at random
NICE	National Institute for clinical and healthcare excellence
NN	Nearest neighbour matching
OCS	Oral corticosteroid
ONS	Office for National Statistics

PPV	Positive prediction value
QOF	Quality Outcome Framework
RR	Rate ratio
SABA	Short acting beta agonist
SAMA	Short acing muscarinic antagonist
YE	Yearly exacerbations

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1. Introduction

1.1 Introduction to COPD

Chronic Obstructive Pulmonary Disease (COPD) is a global health problem; it is currently the third leading cause of death worldwide and causes 6% of total deaths globally (WHO, 2020). In the UK, data has shown that 0.9-1.2 million people are currently diagnosed with COPD, while up to two million more may live with the disease but are currently undiagnosed (Commission, 2006, Snell et al., 2016). Morbidity and mortality from the disease has resulted in substantial economic and social burden.

Several global and national organisations have been set up to tackle this growing problem and provide evidence-based diagnosis, treatment and prevention. Internationally, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has produced guidance and nationally the National Institute for Clinical Excellence (NICE) has adopted these and refined them for use in the UK. GOLD defines COPD as:

"a common preventable and treatable disease…characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients." (Halpin et al., 2021)

World-wide, there is substantial variation in the reported prevalence of COPD mostly due to methodological variation and under-diagnosis of the disease. However, most

data suggest that the prevalence of diagnosed COPD is 5-10% of the adult population (Halbert et al., 2006, Mannino and Buist, 2007).

1.1.1 Pathophysiology

Airflow limitation in COPD occurs as a result of narrowing of the small airways and destruction of the lung parenchyma. This is due to exposure to noxious particles and/or abnormal lung development causing chronic inflammation or lung injury (Halpin et al., 2021). There is a well-established inflammatory cascade occurring in COPD that differs from other obstructive airways diseases, such as asthma (Compton et al., 2013) . This inflammatory cascade is discussed in greater depth later in this chapter.

Risk factors

Tobacco smoking has long been linked to a higher prevalence of COPD in higher income countries; however other outdoor and indoor air pollutants such as burning of wood and biomass fuels are also major risk factors for COPD. It is estimated that approximately 80% of all COPD diagnoses in higher income countries are in current- or ex-smokers (Schneider et al., 2010, Lamprecht et al., 2011). Active cigarette smoking is associated with accelerated decline in lung function and a higher mortality rate (Anthonisen et al., 2002).

Although smoking is a well-studied risk factor for COPD, fewer than 50% of heavy smokers develop COPD in their lifetime (Lundback et al., 2003), suggesting that the disease results from a complex interaction of the person's genes and other factors such as age, sex and lung development. Genetically, a deficiency of alpha-1-antitrypsin protein is known to lead a person to be more susceptible to developing COPD (Brode

et al., 2012). Aging is associated with loss of lung function and increased life-time exposure to noxious particles (Parkes et al., 2008), which may be related to increased risk of COPD. Now COPD prevalence is almost equal in men and women, possibly reflecting changes in smoking habits.

1.1.2 Diagnosis

GOLD characterises COPD by airflow limitation that is not fully reversible. There are many symptoms that indicate a diagnosis of COPD should be considered (Table 1-1); however, spirometry is required for a clinical diagnosis. Airflow limitation is defined by spirometry after inhalation of a bronchodilator; a ratio of the forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) of <0.7 (Halpin et al., 2021).

The severity of COPD can partially be determined by the severity of airflow limitation, by using the percentage of predicted FEV_1 achieved post-bronchodilator, as per GOLD guidance (Halpin et al., 2021) (Table 1-2). The predicted FEV_1 is calculated based on population statistics and the height, sex and age of the individual concerned. This is then used in combination with other factors such as the frequency of exacerbations, modified British Medical Research Council (mMRC) dyspnoea scale and COPD assessment tool (CAT) of health status impairment to guide management of the disease.

Symptom/risk factor	Diagnostic criteria
Exposure to smoke	Current or ex-smoker; occupational exposure to smoke or dust Smoke from home cooking or heating fuels
Dyspnoea	Persistent, progressively worsening; worse on exertion
Wheezing and chest tightness	Variable over the course of a day and from day to day
Cough	Intermittent cough progressing to chronic; recurrent wheeze
Sputum production	Regular sputum production
Recurrent lower respiratory tract infections	-
Family history	Low birthweight, genetic factors, childhood respiratory infections

Table 1-1 Symptoms and risk factors indicative of a COPD diagnosis
Adapted from GOLD guidance (Halpin et al., 2021)

GOLD score	Severity	% predicted FEV_1
1	Mild	>80%
2	Moderate	50-79%
3	Severe	30-49%
4	Very severe	<30%

Table 1-2 Severity of airflow limitation in COPD
As determined by spirometry. Adapted from GOLD guidance (Halpin et al., 2021)

Similarities and differences to asthma

COPD can commonly be misdiagnosed as asthma due to the significant overlap in the presenting symptoms. There are many important diagnostic differences between asthma and COPD (Table 1-3). Many of the drugs used to treat COPD and asthma are the same; however, there are important differences in treatment protocols due to the difference in underlying cause of the diseases. It is therefore important that the initial diagnosis is correct, so that the best evidence-based treatment can be given. Increasingly it is becoming more apparent that there are some people with COPD that have an underlying cause to their inflammation that is more like asthma than the typical COPD (Cao et al., 2012), which may alter treatment protocols. This will be discussed in more detail later in this chapter.

	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptoms under 35 years	Uncommon	Common
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Night-time waking with wheeze or breathlessness	Uncommon	Common
Day to day variability of symptoms	Uncommon	Common

Table 1-3 Differences in signs and symptoms between asthma and COPD

1.1.3 Prognosis

Morbidity due to COPD is significant, with many people requiring doctor visits and hospitalisations. Morbidity due to exacerbations of the disease and deterioration in the quality of life are most common, however COPD is often associated with other diseases such as diabetes and cardiovascular disease, related to smoking (Sin et al., 2006).

1.2 Current therapies in COPD

1.2.1 Management of COPD

The overall aim of treatment is to prevent or reduce disease progression; reduce symptoms, reduce exacerbation rates, reduce mortality and improve health status. This is done by a combination of pharmaceutical interventions and other therapies such as smoking cessation, pulmonary rehabilitation, vaccinations, lifestyle changes and oxygen therapy.

Exacerbations of the disease leading to hospitalisation are responsible for significant reductions in the quality of life and prognosis. Exacerbations are associated with an increase in airway inflammation and decline in lung function (Kerkhof et al., 2020) (Whittaker et al., 2020). Although COPD is traditionally viewed as a neutrophilic inflammatory response, eosinophilic inflammation also plays a role. Blood eosinophilia has been associated with increased mortality (Hospers et al., 1999), whilst increased numbers of eosinophils have been found in induced sputum during exacerbations. Furthermore, oral corticosteroid treatment which is known to reduce eosinophil

counts but not neutrophil counts is considered to be an effective treatment for COPD exacerbations (Siva et al., 2007).

1.2.2 Drug therapies

The mainstay of pharmaceutical treatment is the use of inhaled therapies. However, none of the medications available have been shown to significantly reduce the decline in lung function, most reduce exacerbation rates and improve health status and symptoms. Currently, the only therapy shown to reduce the decline in lung function is smoking cessation (Anthonisen et al., 2002). Inhaled therapies include the short acting beta agonists (SABA), long acting beta agonists (LABA), short acting muscarinic antagonists (SAMA), long acting muscarinic antagonists (LAMA), inhaled corticosteroids (ICS) and combination products. There are also a few oral therapies available, such as mucolytics and theophylline. Other than ICS treatment, the other inhaled therapies offer symptomatic relief by bronchodilation.

Both NICE and GOLD set out similar treatment guidelines for people with COPD; based on the severity of their disease (as measured by percentage of predicted FEV_1) and the rate of exacerbations per year (Figure 1-1). The important point to note from this treatment protocol is where the use of ICS fall; ICS are only recommended for people with asthmatic features of COPD, or more frequent exacerbations. It can also be used add on therapy for a three-month trial when other treatments have failed. This is in marked contrast to asthma treatment protocols, where ICS are used from a much earlier stage and are used alone (with LABAs introduced at a later stage).

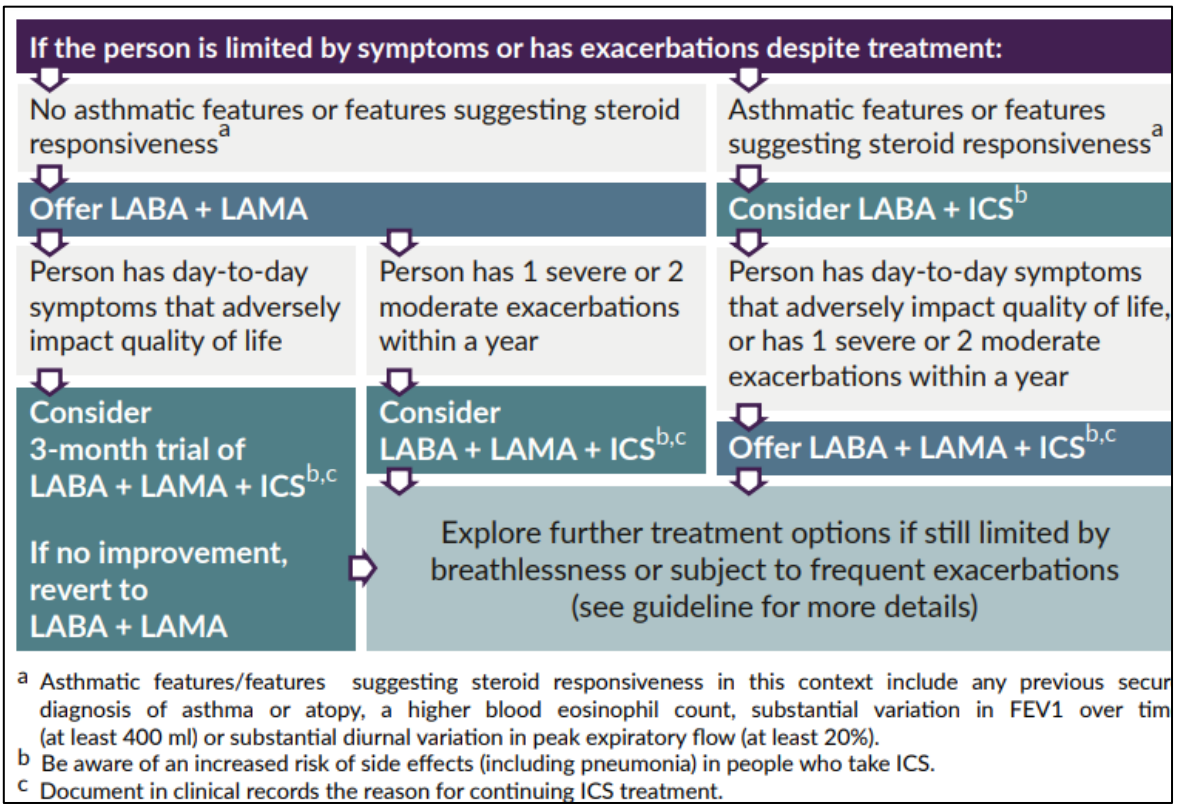

Figure 1-1 NICE COPD inhaled therapy guidance
Taken from NICE COPD guidance 2020. This guidance is used if there is a confirmed diagnosis of COPD and a short acting bronchodilator has been unsucessful in managing symptoms or preventing exacerbations (NICE, 2020b)

1.2.3 Limitations of Current Drug therapy

The national guidance on the previous page was newly published in 2020 and is a marked contrast to previous guidance in terms of ICS use. The previous guidance suggested the ICS were suitable for all patients with 'severe' or 'very severe' airflow limitation (i.e. an FEV_1 <50% predicted), which resulted in high numbers of people using ICS.

There is currently a lack of a cohesive approach to ICS prescribing in COPD because many questions regarding their use are unanswered due to change in guidance and the rapidly increasing evidence base. Despite this guidance, there may still be people with COPD that would benefit from an ICS that are not currently receiving them. In fact, the NICE guidance identifies ICS responsiveness as a key area where more research is needed (NICE, 2020b).

Current research is looking to tackle the question of specifically which people with COPD are gaining benefit from them and there is much research looking at sputum eosinophilia and mechanisms of corticosteroid resistance as markers of steroid responsiveness during exacerbations and stable disease.

1.3 Inflammation in COPD

Underlying chronic inflammation in COPD is a leading cause of persistent airflow limitation due to lung parenchymal destruction and small airway fibrosis. The inflammation seen in COPD is a modified response to the normal inflammatory process due to noxious particles such as cigarette smoke (Compton et al., 2013). Exposure to tobacco smoke leads to an inflammatory cascade involving inflammatory cells including increased numbers of macrophages, neutrophils and lymphocytes. In some patients there may also be increases in eosinophils. Inflammatory mediators such as pro-inflammatory cytokines and chemotactic factors are also known to be present.

COPD exacerbations are usually triggered by bacterial or viral infections. During the exacerbation, these inflammatory cell numbers may be increased, but the relationship is complex, however acute exacerbations are an important cause of mortality and morbidity in patients with COPD (Sapey and Stockley, 2006).

Asthma and COPD have previously been considered different diseases due to their clinical phenotypes and observation of inflammatory cells and thus different treatment protocols have been observed. However, recently the evidence has suggested that there are similarities in the inflammatory cells seen (Cao et al., 2012), and that it may be more appropriate to consider asthma and COPD together but stratified according to factors such as the presence or absence of eosinophilia or smoking and treated appropriately. There are potential drug therapies for each of the main causes of inflammation in COPD, however efficacy of these varies substantially.

1.3.1 Neutrophil-mediated airway inflammation

Neutrophil-mediated airway inflammation is considered the main cause of lung inflammation and subsequent airflow limitation in COPD because of its association with cigarette smoking (Halpin et al., 2021). Cigarette smoking causes increased numbers of macrophages and T-lymphocytes, particularly CD8 cells, which in turn cause neutrophil influx into the airway lumen; this is summarised in Figure 1-2. Thus, smoking-cessation is known to slow the decline of lung function (Fletcher and Peto, 1977). Treatment with low-dose macrolide antibiotics, such as erythromycin, have shown some efficacy in decreasing airway neutrophilia (Parnham et al., 2005). However, as there is no established drug therapy to prevent the underlying cause of inflammation for most people with COPD, smoking cessation and bronchodilator therapy to ease symptoms is the mainstay currently. Interestingly, ICS have been shown to inhibit neutrophil apoptosis and increase neutrophil survival (Zhang et al., 2001), thereby potentially worsening inflammation in people with neutrophilic-type inflammation.

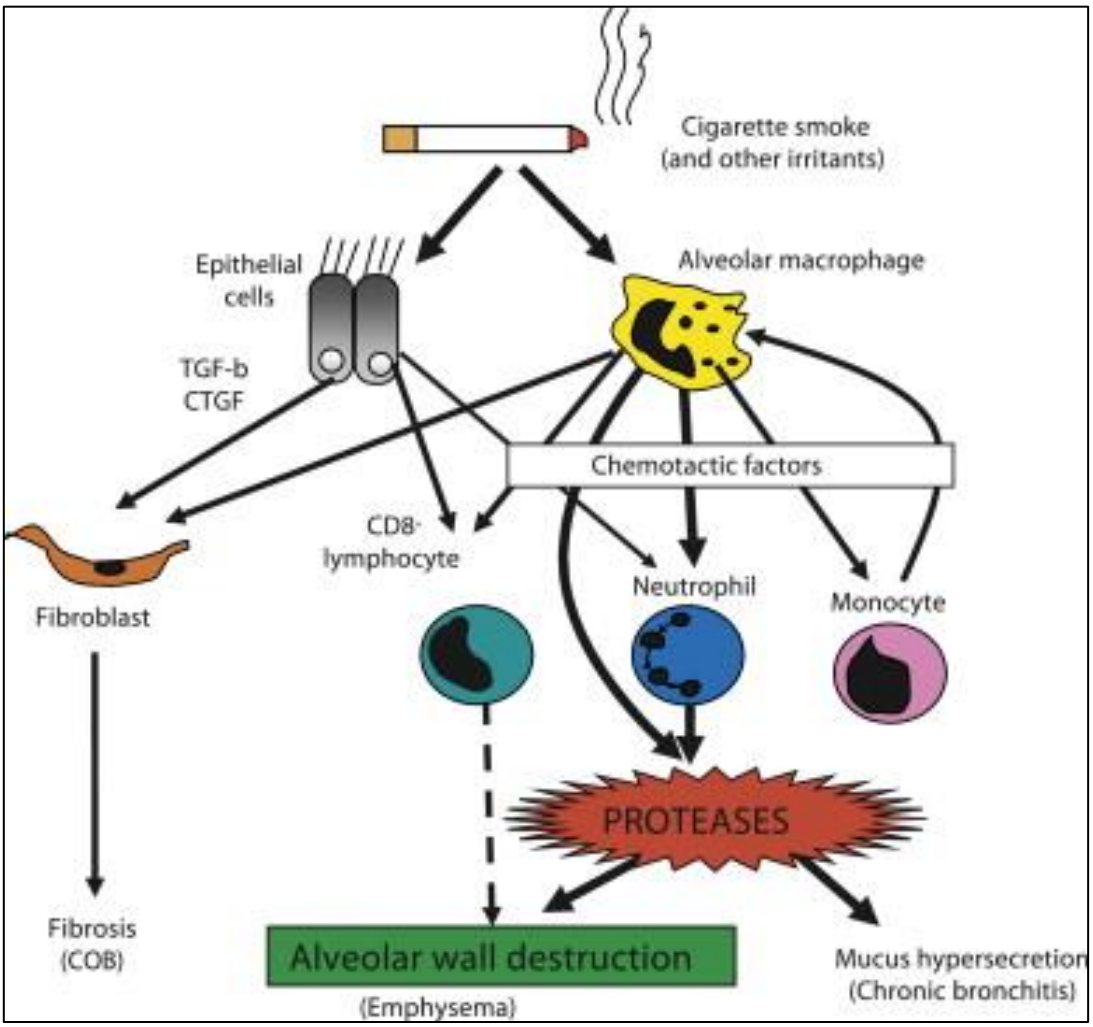

Figure 1-2 Inflammation response in COPD
Adapted from The Novartis view on emerging drugs and novel targets for the treatment of chronic obstructive pulmonary disease (Compton et al., 2013)

1.3.2 Eosinophil mediated airway inflammation

The presence of eosinophilic inflammation in some people with COPD is of interest as ICS treatment is known to be effective in asthmatic patients (who are known to have mostly eosinophil-mediated inflammation). Approximately one third of patients with COPD have sputum eosinophilia, although the threshold used varies between studies (Cao et al., 2012, Leigh et al., 2006). It is of interest to study people with eosinophil mediated-inflammation versus neutrophil-mediated inflammation in order to determine the most effective treatment protocols.

Eosinophil-mediated inflammation occurs upon exposure to an allergen; mast cells are activated leading to bronchoconstriction and proinflammatory mediators cause eosinophils to become activated and migrate to sites of inflammation (George and Brightling, 2016). Once in the lungs, proinflammatory mediators, including cytokines and chemokines are released by and contribute to sustained inflammation and tissue damage.

Evidence suggests that eosinophilic airway inflammation is important in the pathogenesis of severe COPD exacerbations and that eosinophil counts are greater during exacerbations than during stable disease (Saha and Brightling, 2006, Bafadhel et al., 2011). There is also evidence that there is a relationship between eosinophilic inflammation and lung function decline. This relationship and the role of ICS in prevention will be investigated further in chapter two.

Allergic phenotype

Individuals with COPD classified as having an 'allergic phenotype' are at increased risk of COPD exacerbations and increased respiratory symptoms in comparison to COPD patients without an allergic phenotype. A classification of allergic phenotype is based on a diagnosis of hayfever or allergic upper airway symptoms, or a positive test result for IgE levels to at least one common allergen (Jamieson et al., 2013). The prevalence of this phenotype is 25-30% of people with COPD. As underlying airway eosinophilia is common and a known cause of hayfever and allergic airway symptoms, it is postulated that this is the cause. It has also previously been shown that repeated allergen exposure is associated with more severe disease and a more rapid decline in lung function (Wang et al., 2009).

1.3.3 Other inflammatory cells and mediators

Inflammation in COPD is complex and there are many inflammatory cell and mediators involved. Below the additional inflammatory cells with established drug therapy are highlighted.

Leukotrienes

Closely related to eosinophil-mediated inflammation are leukotrienes. Leukotriene receptor antagonists (LTAs), such as montelukast and zafirlukast are commonly used oral anti-inflammatory agents used in asthma (GINA, 2020). They have been shown to enhance the anti-inflammatory effect of ICS or act as steroid sparing agents in people with resistant forms of asthma (Barnes, 2000). They have also been shown to reduce sputum eosinophil levels in asthmatic patients. LTAs have so far remained largely un-investigated for their potential benefit in COPD patients (particularly those with the eosinophilic phenotype). As these agents have very few adverse effects and are generally well tolerated, this is a potential area of further investigation.

Leukotrienes are generated from mast cells and eosinophils, causing bronchial smooth muscle contraction, mucous production and recruitment of eosinophils. There is a leukotriene sub-type identified in humans, LTB4, that has not been linked with asthma, but may play a role in chronic bronchitis or emphysema. LTB4 is a potent pro-inflammatory mediator and an attractant for neutrophils (Usery et al., 2008).

Zileuton, a 5-lipoxygenase enzyme blocker, which blocks LTB4, is available in the US and is currently used as maintenance treatment in asthmatic patients. There may be greater potential for this medication to have a beneficial impact on COPD treatment

strategies. It is not currently available in the UK and the two LTAs available, montelukast and zafirlukast, do not block LTB4 (Scott and Peters-Golden, 2013).

Phosphodiesterase-4

The Phosphodiesterase-4 (PDE4) isoenzyme is implicated in most inflammatory cells responsible for the pathogenesis of COPD. Its inhibition alters the production and/or release of proinflammatory mediators (Spina, 2003). PDE4 is also present in airway smooth muscle. Theophylline is a non-selective PDE inhibitor which is often used in COPD, although it is used as an oral bronchodilator as an add-on to inhaled therapy. Roflumilast is a specific PDE4-inhibitor, however, is currently not widely used.

1.4 Inhaled corticosteroid use in COPD

1.4.1 Introduction

Of all potential drug therapies to target inflammation in COPD, ICS are the only currently established treatment. ICS exert their anti-inflammatory effect in a complex way, in asthma they are known to reduce the numbers of inflammatory cells, including eosinophils, T-lymphocytes and mast cells (Barnes, 2010).

ICS have historically been widely used to treat COPD, as per national and international guidance. However, this guidance for the use of ICS in COPD has undergone review and changes in recent years (NICE, 2020b, Halpin et al., 2021). Previous iterations of the guidance suggested that ICS (in combination with a LABA) should be used for more 'severe' COPD. Severity of COPD was defined by a combination of lung function and symptoms; forced expiratory volume in one second (FEV_1) of <50% predicted and symptoms such as frequent exacerbations were used.

In recent years the guidance has changed in line with the wealth of literature suggesting that basing ICS use of severity of COPD was not substantially beneficial to patients in terms of reducing decline in lung function and reducing exacerbations. The most recent evidence is that ICS are only recommended to be used alongside LAMA and LABA inhalers, often known as 'triple therapy' (NICE, 2020b). Several trials have reported significant reductions in exacerbation and mortality comparing triple therapy with dual bronchodilator therapy (Lipson et al., 2018, Rabe et al., 2020, Papi et al., 2018).

As more research has been done into the use of ICS in COPD, it has become clear that there may be some features that patients have that may indicate that treatment with ICS will be successful. Both the NICE (2020) and GOLD (2021) guidance indicate that ICS should be used where there are indicators of responsiveness; including asthmatic features and high eosinophil counts. As shown in Figure 1-1 and Figure 1-3.

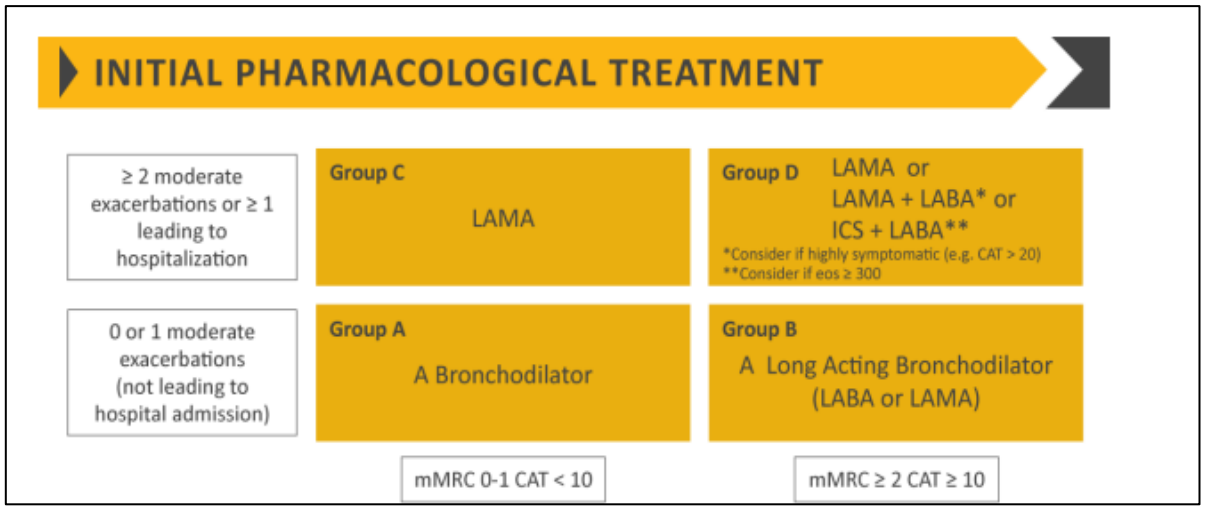

Figure 1-3 GOLD guidance for treatment of stable COPD
Taken from Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. The 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease. (Halpin et al., 2021)

This guidance is supported by several Cochrane systematic reviews of the literature (which will be discussed later) and the underlying pathophysiology of COPD (Horita et al., 2017, Oba et al., 2018, Kew and Seniukovich, 2014); which indicates a neutrophilic cause of inflammation due to smoking for the majority of patients. ICS are known to affect eosinophil levels in the blood and sputum; these are the most common cause of the underlying inflammation and pathophysiology in asthma and therefore it has been repeatedly shown that ICS are effective treatments in all severities of asthma.

As the guidelines for treatment of COPD with ICS have only recently changed, there are still many people using ICS as per the previous guidance; around 60% of people with COPD are currently prescribed some form of ICS, although there has been a downward trend in their prescribing in the last few years (Bloom et al., 2019). Due to the adverse effect profile of ICS, it is worth noting that many of the COPD population may be receiving the adverse effects with little or no benefit from the medication. This problem is compounded by lack of medication review; guidance suggests that people with COPD that meet the criteria for ICS use be trialled on them and then reviewed and the medication stopped if no benefit is seen, however this is rarely done in practice. In addition, it is possible that the popularity of ICS in COPD has been due to their successful use in asthma, leading to prescriber confusion.

As discussed previously this chapter, there are various causes of the underlying inflammation seen in COPD. For most patients this inflammation manifests itself as neutrophilia. An eosinophilic inflammatory phenotype has only recently been established in COPD and may explain why ICS have some benefit in the wider COPD population despite lack of theoretical mechanism of action. This section aims to establish the evidence base for the use of ICS in COPD, as recommended by current guidance.

1.4.2 Cochrane reviews of ICS effectiveness

There are two primary Cochrane systematic reviews that contributed to the NICE (2020) guidance and support the GOLD (2021) guidance. The first, Oba et al. (2018), compared dual inhaled therapy (i.e. LABA/ICS or LABA/LAMA) to mono-bronchodilator

therapy (i.e. LAMA or LABA). The second, Horita et al. (2017) compared two dual inhaled therapies to each other; LABA/ICS versus LABA/LAMA.

Oba et al 2018

The efficacy and safety of four different groups of inhalers (LABA/LAMA combination, LABA/ICS combination, LAMA, and LABA) in people with moderate to severe COPD was reviewed. Randomised controlled trials (RCTs) that recruited people aged 35 years or older with a diagnosis of COPD and a baseline FEV_1 of less than 80% of predicted were included. All studies were of at least 12 weeks' duration. A network meta-analysis (NMA) was performed. Primary outcomes were COPD exacerbations (moderate to severe and severe), and secondary outcomes included quality-of-life scores and lung function.

A total of 101,311 participants from 99 studies were included. The NMAs suggested that the LABA/LAMA combination was the highest ranked treatment group to reduce COPD exacerbations followed by LAMA in the population.

LABA/LAMA combination decreased moderate to severe exacerbations in comparison to LABA/ICS combination, LAMA, and LABA (network hazard ratios (HRs) 0.86 (95% credible interval (CrI) 0.76 to 0.99), 0.87 (95% CrI 0.78 to 0.99), and 0.70 (95% CrI 0.61 to 0.8) respectively). The LABA/LAMA combination reduced severe exacerbations compared to LABA/ICS combination and LABA (network HR 0.78 (95% CrI 0.64 to 0.93) and 0.64 (95% CrI 0.51 to 0.81), respectively).

There was a general trend towards a greater improvement in symptom and quality-of-life scores with the combination therapies compared to monotherapies, and the combination therapies were generally ranked higher than monotherapies.

Horita et al 2018

The benefits and harms of LAMA/LABA versus LABA/ICS for treatment of people with stable COPD were reviewed. Randomised controlled trials, parallel-group trials, and cross-over trials comparing of at least one-month duration were included.

There were 11 studies comprising 9839 participants in the analysis. Most studies included people with moderate to severe COPD, without recent exacerbations. One pharmaceutical sponsored trial that included only people with recent exacerbations was the largest study and accounted for 37% of participants. Five studies recruited GOLD category B participants, one study recruited category D participants, two studies recruited category A/B participants, and three studies recruited participants regardless of category (GOLD categories can be found in Figure 1-3). Follow-up ranged from 6 to 52 weeks.

Compared to the LABA/ICS arm, the results for the pooled primary outcomes for the LAMA/LABA arm were as follows: exacerbations, odds ratio (OR) 0.82 (95% CI 0.70 to 0.96, P = 0.01); serious adverse events OR 0.91 (95% CI 0.79 to 1.05, P = 0.18); and trough FEV_1 change from the baseline, 0.08 L (95% CI 0.06 to 0.09, P < 0.0001).

In summary, both Oba *et al* and Horita *et al* have shown that LABA/LAMA dual therapy is superior to LABA/ICS in terms of reducing exacerbations and may show better outcomes in terms of quality of life and lung function. Furthermore, a guideline on

withdrawing ICS demonstrates a lack of evidence that this increases exacerbations, worsens symptoms or causes a decline in lung function. However, those with blood eosinophils ≥300cells/microL or frequent exacerbations should not be withdrawn from ICS therapy (Chalmers et al., 2020)

1.4.3 Adverse effects of inhaled corticosteroid

The adverse effect profile of both inhaled and oral corticosteroids is well documented and they are known to cause a high frequency of these adverse effects. Some of the most common and most severe include; adrenal suppression, increased susceptibility to infections (particularly pneumonia with ICS use), psychiatric reactions (such as insomnia and psychosis), osteoporosis, muscle wasting, peptic ulceration and oral candidiasis (BNF, 2023). Many of these adverse effects are dose dependent due to systemic absorption at higher doses. The evidence base and treatment guidelines for COPD recommend using the highest possible doses of ICS as treatment when ICS are indicated; this translates as doses of 800mcg/day beclomethasone, or equivalent (NICE, 2020b).

The two Cochrane reviews discussed above also included analysis of adverse effects with ICS/LABA versus bronchodilator therapy. The results showed the ICS groups had a higher incidence of adverse effects (Horita et al., 2017, Oba et al., 2018). Horita *et al* found that compared to the LABA/ICS arm, the results for the pooled secondary outcomes for the LAMA/LABA arm were as follows: pneumonia, OR 0.57 (95% CI 0.42 to 0.79, P = 0.0006); all-cause death, OR 1.01 (95% CI 0.61 to 1.67, P = 0.88). There were significant overlaps in the rank statistics in the other safety outcomes including

mortality, total, COPD, and cardiac serious adverse events, and dropouts due to adverse events.

A further Cochrane systematic review into inhaled steroids and the risk of pneumonia for chronic obstructive pulmonary disease was also conducted (Kew and Seniukovich, 2014). Parallel group randomised controlled trials of at least 12 weeks' duration were included. Studies were included if they compared the ICS budesonide or fluticasone versus placebo, or either ICS in combination with a LABA versus the same LABA as monotherapy for people with COPD. A total of 43 studies met the inclusion criteria: fluticasone (26 studies; n = 21,247) and budesonide (17 studies; n = 10,150). Fluticasone increased non-fatal serious adverse pneumonia events (requiring hospital admission) (OR 1.78, 95% CI 1.50 to 2.12), and no evidence suggested that this outcome was reduced by delivering it in combination with salmeterol or vilanterol, or that different doses, trial duration or baseline severity significantly affected the estimate. Budesonide also increased non-fatal serious adverse pneumonia events compared with placebo, but the effect was less precise and was based on shorter trials (OR 1.62, 95% CI 1.00 to 2.62). Some of the variation in the budesonide data could be explained by a significant difference between the two commonly used doses: 640 mcg was associated with a larger effect than 320 mcg relative to placebo.

Furthermore, it is thought that treatment with fluticasone propionate is associated with a higher risk of pneumonia than treatment with budesonide (Halpin et al., 2011, Singh and Loke, 2010, Lapi et al., 2013, Janson et al., 2013). It is postulated that this is due to the highly-lipophilic nature of fluticasone propionate versus moderate-lipophilic

nature of budesonide; resulting in fluticasone staying around in the lung tissue for much longer (Janson et al., 2017).

1.4.4 Beyond Cochrane and NICE

From the evidence, ICS (in dual therapy with LABA) is not as effective as bronchodilator therapy such as LAMA/LABA in terms of exacerbation rates and lung function. Additionally, ICS have a much higher incidence of adverse effects, particularly pneumonia.

In theory ICS should not be beneficial to most people with COPD due to their mechanism of action being on eosinophil-mediated inflammation and not, as per most people with COPD, neutrophil-mediated inflammation. As it has been recently established that around a third of people with COPD have underlying eosinophil-mediated inflammation (similar to asthma), it may be that the small beneficial effect seen in older trials is due to these patients, which was not studied at the time. The NICE (2020) guidance recognises this lack of data and notes some areas where further research is needed. NICE states:

"*Key recommendations for research:*

Inhaled corticosteroid responsiveness: What features predict inhaled corticosteroid responsiveness most accurately in people with COPD?

Why this is important: Bronchodilators and/or steroids are the main pharmacological treatments used to manage COPD. People with asthma or asthmatic features that may make them steroid responsive may need a different combination of drugs to other groups of people with COPD for the most effective treatment of their symptoms.

Identifying these people would help ensure that they receive appropriate treatment."

(NICE, 2020b)

Furthermore, there may even be a direct interaction of cigarette smoking on glucocorticoid receptors, causing ICS to be less effective at treating COPD (Ito et al., 2001). This mechanism, known as 'steroid resistance' is discussed further in the next chapter.

1.5 Summary

Inflammation, due to smoking and/or possible allergic components, is the underlying cause of airflow limitation COPD. The only anti-inflammatory medications widely used in COPD currently are ICS. ICS have been extensively studied in comparison to bronchodilator therapies, given to people with COPD based on the severity of their disease. This has found only moderate efficacy, with bronchodilator inhaled therapy repeatedly being shown to be superior. There are questions over efficacy of ICS for all patients as it may only be effective for those with eosinophil-mediated inflammation. By reducing inflammation there is the possibility to reduce exacerbations and improve symptoms such as breathlessness cause by airflow limitation. As around a third of people with COPD may have eosinophil-mediated COPD and some people have a co-diagnosis of asthma, which has also been shown to be responsive to ICS, these are potential areas for further investigation. Furthermore, there is evidence that smoking can cause ICS to be less effective at treating COPD by causing steroid resistance.

Further investigation of these factors: eosinophilia, asthma co-diagnosis and smoking status, that may impact upon the outcomes of using ICS in COPD will be undertaken in the next chapter.

2. Literature review

In the previous chapter, ICS were discussed as an important therapy in the treatment of COPD, however questions remained regarding the specific situations in which they are most effective. The impact of smoking causing 'steroid resistance', the role of eosinophils as the key inflammatory mediators in some people with COPD and those people with either an allergic phenotype or asthma co-diagnosis were identified as possible predictors of ICS efficacy in COPD. The literature review in this chapter is a narrative review of these three key areas in terms of their impact on ICS efficacy in COPD.

The review was conducted by an electronic database search in PubMed, Ovid Medline, Ovid Embase and the Cochrane Library. Three structured search strategies were used including free text and MeSH terms related to COPD, inhaled corticosteroids, lung function, exacerbations, mortality and one of: asthma, smoking or eosinophils was used to retrieve literature for this review. The reference lists of the retrieved papers were also searched to identify further relevant studies. Fully published randomised controlled trials (RCTs), systematic reviews or meta-analyses, and cohort studies were retrieved. Any search result where only the abstract was available or not published in the English language were excluded.

2.1 The Effect of Eosinophilic Inflammation on Efficacy of ICS in COPD

2.1.1 Introduction

As discussed in chapter one, current NICE and GOLD guidance on ICS use in stable COPD states that the decision to start ICS therapy should be based on indication that the patient may respond to a steroid, i.e. if they have asthma-like features or eosinophilia. However, these features are poorly defined and are highlighted by the NICE guidance as needing further investigation.

It should also be noted, as also discussed in chapter one, that acute exacerbations of COPD are often driven by eosinophilia. However, patients who are not eosinophilic will often have different causes of the exacerbation (such as neutrophil-mediated) and therefore ICS or oral corticosteroids will be of limited benefit. Corticosteroids are even known to increase neutrophil numbers so may be detrimental to patients not suffering an eosinophil-mediated exacerbation.

The presence of eosinophilia during exacerbations of COPD and treatment with oral corticosteroids has been established as per national guidance (NICE, 2020b). whereas the role of eosinophilic inflammation and ICS use in stable disease has been more controversial as the underlying cause of inflammation in COPD has long been assumed to be mostly neutrophilic (as discussed in chapter one). These patients are sometimes known as having eosinophilic bronchitis or eosinophilic phenotype COPD and are often considered to be more similar (in terms of treatment strategies) to asthmatic patients. This has created great interest in the use of ICS targeted specifically to the eosinophilic COPD patients instead of based on severity of disease. It has been established that a

substantial proportion of COPD sufferers, up to a third, have sputum eosinophilia of >2% of the total white cell count (WCC) (Cao et al., 2012, Leigh et al., 2006). Additionally, corticosteroids are known to have an extensive adverse effect profile and a number needed to harm of five (Walters et al., 2009). Therefore given the currently known mechanism of action of ICS on eosinophils, it is of interest to investigate the use of eosinophil levels (regardless of COPD disease severity) as a biomarker, in order to determine if ICS will be efficacious at reducing eosinophil counts and thereby reducing exacerbation rates and improving lung function.

2.1.2 Eosinophils as a biomarker to target COPD therapy

Until recent years, much of the research into use of eosinophils as a biomarker has focussed on *sputum* eosinophil counts. For example, Balzano et al. (1999) found a correlation between sputum eosinophils and percentage predicted FEV_1 (r=-0.55; p=0.01), indicating that higher sputum eosinophils are associated with more severe COPD in terms of spirometry in stable disease. In sputum, studies have used a threshold of 1-3% for defining eosinophilia in COPD (Leigh et al., 2006, Bafadhel et al., 2011, Basanta et al., 2012). Using sputum eosinophil levels has been considered problematic as it is not a widely available test in the community and therefore other eosinophil biomarkers have been explored.

One such marker of eosinophilic inflammation is fractional exhaled nitric oxide (FeNO). The American Thoracic Society guidance suggests that measurements of >50ppb indicate eosinophilic inflammation and responsiveness to corticosteroids is likely, whereas at <25ppb it is unlikely (Dweik et al., 2011). Whereas the NICE guidance for

asthma diagnosis in the UK recommends a level of >40ppb being indicative of an asthma diagnosis (NICE, 2020a). Currently FeNO is only recommended as a diagnostic tool in asthma and not COPD in the UK. There is a significant overlap between the FeNO levels seen in asthma and COPD (Tilemann et al., 2011); this may be due to eosinophilic COPD patients giving high FeNO results. One limitation of FeNO testing is the lack of availability for general practitioners to perform the test. Another limitation was found by Hogman et al. (2019); FeNO is associated with eosinophil inflammation and the use of ICS in ex-smokers with COPD, but not in smokers. This suggests that the value of FeNO as an inflammatory biomarker is limited in smokers.

Due to issues with using sputum eosinophil levels and FeNO testing, blood eosinophil levels are of current interest to researchers as an important biomarker instead. Blood eosinophil measurements are widely available as it is reported with a simple full blood count test.

Other researchers have shown an interest in using blood eosinophil counts as a biomarker to predict ICS response. Brusselle et al. (2018) concluded that in patients with a history of COPD exacerbations, a higher blood eosinophil count predicts an increased risk of future exacerbations and is associated with improved response to treatment with inhaled corticosteroids. However, Vogelmeier et al. (2019) found that there was a high variability in blood eosinophil counts over a two year period, but there was a small proportion of people with COPD who had two or more exacerbations per year and high eosinophil count.

One issue with using blood eosinophil counts as a biomarker is the variability in what is considered eosinophilia versus a normal eosinophil count. Eosinophil numbers differ

during stable disease, exacerbations, and following treatment (George and Brightling, 2016) and the threshold used varies between studies. Studies have mostly used a threshold of 2% of total leukocytes (Bafadhel et al., 2011, Bafadhel et al., 2012, Pavord et al., 2016). Tashkin and Wechsler (2018) summarised the eosinophil thresholds in a number of trials and also demonstrated that absolute cell counts are also used. For example, ≥300 cells/microL correlated with increasing exacerbations (Watz et al., 2016, Siddiqui et al., 2015, Brightling et al., 2014). A recent meta-analysis confirmed the validity of using absolute blood eosinophil counts of ≥100 to ≥340 cells/microL in COPD in reduction of risk of moderate or severe exacerbations when using ICS (Oshagbemi et al., 2019b).

2.1.3 Eosinophilic inflammation and disease progression

Exacerbations have been linked with decreased lung function (Kerkhof et al., 2020, Whittaker et al., 2020) and as discussed previously, eosinophils increase in number during exacerbations and are linked to more severe exacerbations (Bafadhel et al., 2011). Furthermore, Liesker et al. (2011) found that eosinophil counts could be used to predict if ICS could be safely withdrawn without causing an exacerbation in COPD patients. During long term ICS use, 68 COPD patients were recruited and ICS stopped and the patients monitored until they had an exacerbation. It was found, using multi-variate analysis, that higher sputum eosinophilia was predictive of earlier exacerbation; HR=1.34 (p=0.02). Neutrophils were also measured; however, these did not impact on the risk of exacerbating when ICS were withdrawn which is consistent with the known mechanism of action of ICS. As discussed previously, Chalmers et al. (2020) recommended that ICS not be withdrawn if blood eosinophil counts were ≥300

cells/microL, These studies highlight the possibility that eosinophilic patients need ICS for disease control; whereas non-eosinophilic patients do better when they are withdrawn.

2.1.4 Effect of ICS targeted to eosinophilic patients with COPD

ICS have been found to have a mixed effect on eosinophil counts in COPD, with some studies finding that ICS use had no effect, or even increased blood or sputum eosinophil counts (Gan et al., 2005 Lapperre et al., 2009, Bourbeau et al., 2007). This may be because often eosinophil counts were secondary end points to other inflammatory markers and the presence of eosinophils in low numbers means that the studies were not powered to detect changes. It would have been expected that eosinophil counts would fall upon treatment with ICS, potentially leading to better patient outcomes.

There has been a recent surge in research into the effect that ICS have on COPD patient outcomes in people with either sputum, or blood eosinophilia, regardless of the effect on eosinophil counts themselves. As a result, a Delphi consensus prioritised 12 outcomes for evaluating eosinophil-guided treatment (Suehs et al., 2020). Two of these were identified as primary outcomes: death from any cause and the time required to meet predefined discharge criteria. The 10 secondary priority outcomes included survival, time with no sign of improvement, episodes of hospitalisation, exacerbation, pneumonia, mechanical or non-invasive ventilation and oxygen use, as well as comorbidities during the initial hospitalisation.

With regards to the effect of targeting ICS to people with sputum or blood eosinophilia in COPD in order to improve outcomes from COPD, the literature from RCTs and other

trials have been summarised in Table 2-1. The literature from observational studies is summarised in Table 2-2. This literature review focuses on death from any cause, exacerbations and lung function. No meta-analysis of the results has been undertaken as many of the studies use patients from healthcare databases and there is likely to be an overlap in the cases. However, one systematic review and meta-analysis on the effect on exacerbations rates is included in these results, which covers 11 RCTs and five observational studies; Harries et al. (2020). The other studies included in the tables below cover other end points such as lung function and mortality. Some of the studies included in the systematic review by Harries *et al* are included separately due to their reporting of end points other than exacerbations.

Study	Study design	Participants	Intervention	Eosinophil threshold	Outcomes measured	Result	Patient outcomes
Kitaguchi 2012	Non-randomised non-placebo controlled trial	63 participants, stable COPD of unknown severity; with either sputum eosinophilia/asthma or without	FP 400mcg/day for 2-3 months given to: COPD with asthma COPD without asthma	No threshold, sputum eosinophils measured in eash group: COPD with asthma = 12.3% ± 3.3 COPD without asthma = 2.0 ± 0.5	Lung function	**Lung function** Increase in FEV_1 in eosinophilic group (372 vs 120ml, p<0.01)	Greater increase in FEV1 in the eosinophilic group after ICS use
Brightling 2005	Randomised, double blind, crossover placebo-controlled trial	60 participants, stable COPD	Mometasone and placebo for 6 weeks each with 4 week washout between	No threshold, sputum eosinophils measured and patients assigned to tertiles	Lung function	**Lung function** No overall change in FEV1. However, in the most eosinophilic tertile FEV1 increase of 110ml (95% CI: 30 to 190)	Significant change in FEV1 in eosinophilic tertile
Leigh 2006	Single-blind, sequential placebo-controlled trial	40 participants, moderate to severe stable COPD, ≥40 years, ≥20 pack year smoking history	Placebo for 4 weeks followed by BD 1.6g daily for 4 weeks	Sputum eosinophils ≥3%	Lung function	**Lung function** BD increased FEV_1 (100ml vs 0ml, p<0.05)	Significant FEV1 improvement in eosinophilic group
Barnes 2016*	Randomised, placebo-controlled trial	751 participants, ≥40 years, moderate to severe COPD	FP 500mcg twice daily or placebo for 3 years	Blood eosinophils ≥2%	Lung function	**Lung function:** Eosinophils <2%: FEV_1 decline with FP versus placebo (-2.9 mL/year; p=0.688).	Decline in lung function was reduced when ICS was given to eosinophilic patients

						Eosinophils ≥2% the rate of decline decreased by 33.9 mL/year (p=0.003) **Mortality** Similar for FP and placebo groups with ≥2% eosinophils (7% and 7% respectively) **Pneumonia** Similar for FP and placebo groups with ≥2% eosinophils (4.7% and 4.8% respectively)	No difference in mortality and pneumonia
Harries 2020	Systematic review of 11 RCTs	25,881 participants with COPD	Use of ICS at any dose versus any non-ICS inhaler or placebo	Blood eosinophils ≥2% ≥150 cells/microL ≥300 cells/microL	Moderate or severe exacerbations	**Exacerbations:**20% fewer at ≥2% blood eosinophil threshold (RR, 0.80; 95% CI, 0.74–0.85), 35% at ≥150 cells/µL blood eosinophil threshold (RR, 0.65; 0.52–0.79), and 39% at ≥300 cells/µL blood eosinophil threshold (RR, 0.61; 0.44–0.78).	Fewer exacerbations across the range of eosinophil thresholds

Table 2-1 Summary of trials reporting outcomes of ICS in patients stratified by eosinophilia

FP = Fluticasone propionate, BD = Budesonide dipropionate,

*Exacerbation results reported in Harries et al. (2020) systematic review

Study	Study design	Participants	Intervention	Blood eosinophil threshold	Outcomes measured	Result	Patient outcomes
Harries 2020	Systematic review of 5 observational studies	109,704 participants with unknown severity COPD, ≥40 years	Use of ICS at any dose versus any non-ICS inhaler or placebo	≥4% ≥300 cells/microL	Moderate or severe exacerbations	No association in 4/5 studies. **Exacerbations:** **Suissa et al. (2018)** 21% fewer exacerbations when blood eosinophils ≥4% (RR, 0.79; 95% CI, 0.70–0.88) 24% fewer exacerbations when blood eosinophils ≥300 cells/microL (RR, 0.76; 95% CI, 0.67–0.85)	A lack of association between ICS and moderate/severe exacerbations in 4/5 studies
Kerkhof 2020	Prospective observational study using CPRD and OPCRD datasets	12,178 mild to moderate COPD, >=35 years, with a smoking history, from two electronic medical record databases	ICS use versus non-ICE use	<50 cell/microL 50-349 cells/microL ≥350 cells/microL	Lung function decline after exacerbations	**Lung function (FEV_1):** -19.4mL/year (95% CI 12.0 to 26.7, p<0.0001) with no ICS use -4.3mL/year (95% CI 1.9 to 6.7, p<0.0001) with ICS	Exacerbations are associated with more rapid loss of lung function when eosinophils ≥350 cell/microL not treated with ICS
Whittaker 2019	Prospective observational study using CPRD and HES	26,675 COPD patients aged 35 years or older, who were current or ex-smokers with >=2 FEV1 measurements >=6 months apart	ICS use versus non-ICS use, stratified by eosinophil count	higher stratum eosinophils >=150 cell/micro L	Lung function	**Lung function (FEV_1):** High eosinophil & ICS: -13.7 ml/year (95% CI -16.8 to -10.5) High eosinophil & no ICS: -20.8 (95% CI -29.8 to -11.9, p=0.016)	The rate of FEV_1 change was not significantly different when stratified by eosinophil level

				lower stratum eosinophils <150 cells/micro L		Low eosinophil & ICS: -10.2 (95% CI -19.0 to -1.3) Low eosinophil & no ICS: -21.7 (95%CI-32.7 to-10.8, p=0.043)	
Song 2017*	Prospective observational study using Korean hospital data	1,132 participants with COPD, FEV/FVC <0.7, ≥40 years, smoked ≥10 years	Any inhaled medication (LAMA, LABA and/or ICS). Patients stratified by eosinophil count into quartlies	>200 cell/microL >600 cells/microL	Lung function (FEV_1)	**Lung function:** >200 cells/microL: no impact on lung function >600 cell/microL: reduction in FEV_1 250.0ml±661.4 p=0.044	No effect on lung function
Oshagbemi 2018*	Retrospective observational study using CPRD	32,693 new diagnosis COPD of unknown severity, ≥40 years	Healthcare database analysis. Any patient on ICS stratified by eosinophil count	low (<2.0%) moderate (≥2.0 to 3.9%) high (4.0% to 5.9%) very high (≥6.0%)	Hospitalisations with COPD and all-cause mortality	**Mortality**: 12-24% reduction in moderate to very high eosinophil counts **Hospitalisations:** No difference	Only reduction in mortality seen.
Oshagbemi 2019*	Retrospective observational study using CPRD from 2005 to 2014	48,157 new diagnosis COPD with unknown severity, ≥40 years, moderate to severe exacerbation 6 weeks prior to index date	Healthcare database analysis. Any patient on ICS stratified by eosinophil count	≥340 cells/microL ≥4%	All-cause mortality	**Mortality:** No increase in mortality when ICS withdrawn	No increase in mortality when ICS withdrawn

Table 2-2 Summary of observational studies reporting outcomes of ICS in patients stratified by eosinophilia

*Exacerbation results reported in Harries et al. (2020) systematic review

Overall effect of targeting ICS to eosinophilic patients

The observational studies tend to show no effect in targeting ICS treatment to people with higher eosinophil counts on exacerbations, lung function or mortality. Whereas the RCTs do show that targeting ICS to more eosinophilic patients results in improvements in lung function and reduced exacerbation rates. This may demonstrate that real-world patients used in the observational studies have other factors that are not controlled for that influence outcomes. Alternatively, it could be because eosinophils were not specifically measured in the observational studies and their inclusion in the patients' records is incidental. Furthermore, each study used a different measure of eosinophilia making results more difficult to compare.

Effect on mortality

Two observational studies and one RCT post-hoc analysis included mortality as an end point and mixed results were seen. One observational study demonstrated a 12-24% reduction in mortality when ICS were targeted to patients with eosinophils over 2% (Oshagbemi et al., 2018). The higher reduction in mortality was only seen when eosinophils were very high, over 6%. The other observational study showed that mortality did not increase when ICS were withdrawn from patients with high eosinophil counts (Oshagbemi et al., 2019a). Barnes et al (2016) also demonstrated no difference in mortality between ICS and placebo in the ≥2% eosinophil group. Mixed effects on mortality have also been seen in previous studies that did not stratify patients by eosinophil count (Calverley et al., 2007, Vestbo et al., 2016, Wedzicha et al., 2008), so the result here is not unexpected.

Effect on exacerbations

The effect on exacerbations of targeting ICS to patients with eosinophilia was investigated extensively in both randomised controlled trials and observational studies; a meta-analysis and systematic review has summarised these (Harries et al., 2020). The meta-analysis of RCT results showed 20% fewer exacerbations at ≥2% blood eosinophil and 39% fewer at ≥300 cells/µL. However overall, the observational studies did not demonstrate any difference in exacerbation rates except one study by Suissa et al. (2018), which had a similar reduction in exacerbations to the meta-analysis. The reasons for the differences between the two study types may be due to differences in patient demographics or bronchodilator medication used. For example, all RCTs recruited patients with moderate to very severe airflow limitation, whereas the airflow limitation was unknown in three of the five observational studies (Suissa et al., 2018, Oshagbemi et al., 2018, Oshagbemi et al., 2019a) and mild or moderate in the remaining two (Song et al., 2017, Suissa et al., 2019). Additionally, bronchodilator use with LABA and LAMAs was not restricted in the observational studies, whereas the RCTs mostly excluded patients using these (except in ICS/LABA combinations).

The observational study that investigated withdrawal of ICS on exacerbation rates (Oshagbemi et al., 2019a) was consistent with other studies, such as WISDOM, that did not stratify patients by eosinophil count, which found no effect on exacerbation rates (Vestbo et al., 2017, Magnussen et al., 2014).

Effect on Lung Function

Although not included in the Delphi consensus statement, lung function changes as a result of targeting ICS to eosinophilic patients has been well studied. The four clinical

trials all concluded that there were beneficial effects on FEV_1 when ICS were targeted to more eosinophilic patients (Kitaguchi et al., 2012, Leigh et al., 2006, Brightling et al., 2005, Barnes et al., 2016). The size of the effect ranged from 34ml to 250ml, however each study used a different threshold of eosinophilia and different methodology. The observational studies found mixed results; two found no significant effect on lung function when ICS use was stratified by eosinophil count (Whittaker et al., 2019b, Song et al., 2017) but the last found exacerbations were associated with more rapid loss of lung function when eosinophils ≥350 cell/microL were not treated with ICS (Kerkhof et al., 2020).

As with exacerbations, the difference in results seen between the clinical trials and observational studies may be due to differences in patient demographics and concurrent medication use. Also, there were very low patient numbers in the clinical trial studies in comparison to the observational studies (and even in comparison to the meta-analysis on exacerbation rates).

Previous key studies, that did not stratify patients by eosinophilia, such as ISOLDE and TORCH (Burge et al., 2000, Calverley et al., 2007, Pauwels et al., 1999) did not find that use of ICS was associated with improvements in lung function.

Other end-points

Hospitalisations were only investigated in one observational study, despite it being part of the Delphi consensus (Oshagbemi et al., 2018). This study found no reduced risk of hospitalisation in ICS users stratified by blood eosinophil counts. The authors of this study postulated that the reason no effect was seen was because disease severity

was a confounding factor that was not controlled for and that ICS-users were more likely to be hospitalised than never-users.

Pneumonia was included in one study (Barnes et al., 2016), which found there was a similar incidence of pneumonia in the ≥2% eosinophil group between those treated with ICS and placebo.

In terms of eosinophil counts, Leigh et al. (2006) found that in participants without sputum eosinophilia the addition of budesonide did not reduce eosinophils and Brightling et al. (2005) found mometasone did not reduce eosinophil counts; these reflects the finding found previously by Gan et al. (2005).

No relationship between salbutamol reversibility and sputum eosinophilia was seen in Leigh et al. (2006); indicating that there may be no link between asthma and eosinophilia seen in COPD patients. In contrast, Kitaguchi et al. (2012) found that COPD patients with a co-diagnosis of asthma responded better to ICS than those without. This could possible suggest that it is in fact the asthma that is being treated by the ICS and hence causing the increase in FEV_1. However, most of the other trials and observational studies excluded patients with an asthma diagnosis but there may have been participants with undiagnosed asthma included in the analyses. Although an asthma co-diagnosis was excluded from these studies in order to clearly see the effect of eosinophils, asthma-COPD overlap syndrome is now recognised as being prevalent amongst people with COPD this complex relationship needs further investigation.

Limitations

The differences seen between the outcomes reported in RCT studies and those in the observational studies was postulated by Harries et al. (2020) to be because of differences in patient demographics and bronchodilator use. There are further limitations of the observational studies published to date in the way ICS use was defined and the durations of the studies. For example, in terms of follow up duration three of the studies were relatively short for an observational design: Suissa *et al* followed up for one year, Whittaker *et al* for 4.2 years and Kerkhof *et al* for three years. In terms of defining ICS use Whittaker *et al* defined it as presence of at least one ICS-containing medication in the year prior to the index date (versus no ICS) and Oshagbemi *et al* defined it as 'current' use (an ICS-containing prescription within three months prior to the start) versus 'never' use. Neither of these definitions seem satisfactory to identify patients who are consistently using ICS throughout the studies; ICS are prescribed at a variety of different strengths and consistent use of high doses over long periods would be expected to produce different outcomes than use for as little as one month. Exposure to ICS varies widely between patients, which has not been accounted for in these studies.

2.1.5 Conclusion

The effects of ICS on eosinophil counts have been inconclusive in a number of papers, most probably due to their low numbers in sputum resulting in under-powering of the studies (as eosinophils were not the focus of any of the trials discussed); thus leading to the inability to detect a small change in their numbers. In addition, the blood eosinophilia threshold is not well defined and different levels have been used in each study; the most commonly used thresholds seem to be ≥2% and ≥3% of total leukocytes or ≥150 cells/microL and ≥ 300 cells/microL.

A Delphi consensus prioritised 12 outcomes for evaluating eosinophil-guided treatment, however most studies have only included two of these as their end point: mortality and exacerbations. A clear effect on reduction of exacerbations was seen when ICS were targeted to eosinophilic patients in RCTs, however the outcome on mortality was mixed. Other prioritised outcomes, such as pneumonia and hospitalisations have been included in one study each only, with no significant outcome. Changes in lung function have been well studied, despite it not being included as a priority outcome and previous data showing ICS have little effect on it. Overall the result here showed that targeting ICS to more eosinophilic patients had beneficial effects on lung function. These studies should be considered with care; there were several very small studies and only one larger study, which was a post-hoc analysis.

There is some evidence that withdrawing ICS from non-eosinophilic patients is safe and does not result in increased exacerbations or increased mortality. This is reassuring, but further research is needed.

An asthma co-diagnosis was excluded in most of the studies investigating the impact of eosinophil counts. As asthma-COPD overlap syndrome is increasingly being recognised, this complex relationship of diseases and eosinophils needs to be investigated.

Nearly all the positive outcomes seen were from RCTs, when observational studies using real-world patients were used, most studies showed no impact on exacerbations, lung function or mortality when ICS were targeted to eosinophilic patients. However, methodological flaws in the definition of ICS use and study durations in the observational studies suggest potential areas for further research.

2.2 The effect of asthma co-diagnosis on the efficacy of ICS in COPD

2.2.1 Introduction

Up to 40% of patients with COPD have a co-diagnosis of asthma (Soriano et al., 2003, Gibson and Simpson, 2009, Hosseini et al., 2019); in fact it is estimated that 2% of the general population may have asthma-COPD overlap. Some will be due to the difficulty distinguishing between these two lung diseases (as discussed in chapter one) and some will have asthma-COPD overlap (ACO). The Global Initiative for Asthma (GINA) defines ACO as persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD, and indicate that ACO includes different clinical phenotypes and there are likely to be several different underlying mechanisms (Halpin et al., 2021, GINA, 2020). This suggests that there may be some overlap in the underlying causes, and perhaps inflammatory mediators, that cause both conditions. Similarly, this suggests that there is the potential to treat these overlap patients with pharmacological agents used in asthma, that target the underlying cause. NICE (2020b) guidance has indicated that ICS may be more beneficial to people with COPD who have asthma-like features, however the guidance also highlights that further research is needed. Indeed, further research is needed as most drug trials have historically, for either COPD or asthma treatment, specifically excluded people with the other disease. Additionally, asthma treatment trials have often excluded smokers (due to the difficulty in separating them from people with COPD). A meta-analysis indicated that outcomes for people with ACO were worse than either individual disease alone. (Alshabanat et al., 2015)

A recently published consensus included six criteria for diagnosis of ACO. Three major criteria: persistent airflow limitation, tobacco smoking and previous asthma or reversibility >400 mL FEV_1, and three minor: history of atopy or rhinitis, at least two positive bronchodilator tests and ≥300 blood eosinophils per microlitre (Sin et al., 2016).

ACO diagnosis is imprecise as it is uncertain as to how many features of both asthma and COPD a patient must have to make a diagnosis. For example, a smoking asthmatic may have ACO due to airflow limitation, but other features may differ from a person with COPD and no asthmatic features, such as presence of wheeze and allergic rhinitis. Conversely there are smokers who develop chronic airflow limitation on a background of eosinophilic inflammation without a previous diagnosis of asthma. Furthermore, it is thought that the ACO phenotype is associated with increased disease severity, in terms of more hospitalisations and exacerbations (Menezes et al., 2014). There is some on-going research to produce more specific diagnostic criteria, such as biomarkers including exhaled nitric oxide or serum IgE, however current guidance to diagnose ACO relies on the diagnostic criteria for asthma and COPD and comparing the number of features of each a patient displays (GINA, 2020).

2.2.2 ACO and eosinophilia or atopic phenotypes

Eosinophilia

The most accessible marker of asthmatic-type inflammation is increased concentrations of blood eosinophils. It has been established that blood and sputum eosinophil counts are significantly higher in patients with ACO compared with COPD (Kitaguchi et al., 2012). Cao et al. (2012) compared serum and sputum inflammatory

markers and clinical characteristics between asthma and COPD patients. There were 37 asthma and 29 COPD patients compared to 39 healthy subjects. Inflammatory cytokines were measured and analysed according to smoking status and eosinophilia of the airways. The expression of cytokines was more significantly different between eosinophilic and non-eosinophilic participants than between asthmatic and COPD patient. There was little difference between smoking and non-smoking subgroups. At present asthmatic patients are treated as per asthma protocols and COPD patients as per COPD protocols. However, the results of this study indicate that it may be more appropriate to consider the cytokine cause of the inflammation (and potentially treat this) rather than the diagnosis of the disease. In this study the diagnosis of asthma was based on GINA guidelines and COPD on post-bronchodilator FEV_1/FVC ratio. This study considered over 2% to be eosinophilia, however in most literature a higher percentage such as 3 or 4% is used.

ACO and atopic phenotype

Atopic phenotypes in people with COPD have also been looked at; patients with COPD and no diagnosis of asthma but with an allergic phenotype (as defined by self-reported doctor diagnosed hayfever or allergic upper respiratory symptoms or detectable specific IgE) have been identified and compared to COPD controls (Jamieson et al., 2013). Two separate cohorts were analysed (from the NHANES III and CODE studies). It was found that those with the allergic phenotype were at an increased risk of COPD exacerbation in both NHANES III and CODE respectively (NHANES III OR=1.7, p=0.04; CODE OR=3.79, p=0.02). The prevalence of the allergic phenotype in the COPD population in this study was 25-30%. It should be noted that it is possible that some of

the allergic phenotype patients had underlying undiagnosed asthma as these were not screened out; this could be considered an advantage of this study as it used real-life patients who may well have co-morbidities that are undiagnosed. There was no difference in severity of COPD between the allergic phenotype and control group. No treatments were given to these patients, but it is easy to see that along with other work that has identified specific chemokines and cytokines that cause this kind of inflammation, current drug therapy such as oral and inhaled corticosteroids could be better targeted to phenotype of disease rather than severity.

It is becoming apparent that a co-diagnosis of asthma is not necessarily an indicator for outcomes of COPD, however this may be a proxy for the factors that do affect it, such as eosinophilia and allergic phenotype. However, as discussed previously, eosinophilia is not necessarily easy to pinpoint due to the lack of agreement on the level for diagnosis and allergic phenotype is also a nebulous term. An asthma diagnosis is much more accessible to doctors in community practice to guide treatment than eosinophil counts or IgE levels.

2.2.3 ACO and smoking

Smoking history is one of the key indicators to support a COPD diagnosis over an asthma diagnosis; however, up to 30% of asthmatics are smokers and in fact smoking-asthmatics are often considered to have ACO. It was previously discussed that those with COPD who are smokers may respond less favourable to ICS than those who are non-smokers. Similarly it is thought that people with asthma who are heavy smokers are often have ‘difficult’ asthma; i.e. non-responsive to the usual anti-inflammatory treatments (Tomlinson et al., 2005).

2.2.4 Treatment of people with ACO or atopic phenotype

The mainstay of treatment for people with asthma is the use of ICS and it is therefore of interest to investigate the impact of ICS on outcomes for those with COPD thought to have the ACO phenotype. It has already been established earlier in this chapter the effect that smoking and eosinophilia have on treatment outcomes in COPD; these are both related to a diagnosis of ACO. However, as there are other markers of ACO, as mentioned above such as reversibility, it is of use to investigate the outcomes of ICS targeted to people identified as having ACO and not just smokers or eosinophilia. After an extensive literature search, very little research on the efficacy of ICS in ACO could be found. This may be in part due to the difficulty in defining ACO, and as mentioned before the exclusion of patients with asthma from COPD trials. Below is a summary of the relevant literature.

One study found that use of either LAMA or ICS/LABA inhaled medication was associated with a lower risk of exacerbations (Su et al., 2018). This large Taiwan-based study (251,398 patients with ACO and 514,522 patients with COPD alone) followed up patients after a mean period of 9.85 years. LAMA, or ICS/LABA combinations were lower risk for exacerbations (LAMA, HR 0.51, 95% CI 0.49-0.54; ICS/LABA combinations, HR 0.61, 95% CI 0.60-0.62; all P <.0001) than were those for LABAs or ICS in patients with ACO.

In a smaller study, patients with stable COPD enrolled in the Korean COPD subgroup study cohort were assessed for asthma overlap (Jo et al., 2020). Among 1067 patients with COPD, 138 (12.9%) were classified as having ACO by the Global Initiative for Asthma (GINA)/Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.

The ACO exacerbation rate was higher than that for COPD alone (incidence rate ratio [IRR] = 1.65; P <0.01). The only factor associated with a decrease in ACO exacerbation after ICS use was a blood eosinophil count of ≥300 cells/microL (IRR = 0.52, P = 0.03). This study suggests that ICS treatment can decrease the risk of exacerbation in patients with ACO, and that a blood eosinophil count of ≥300 cells/microL can predict the response to ICS treatment.

In a final small study of 152 patients with COPD, 45 (29.6%) fulfilled the criteria for an ACO diagnosis (Lee et al., 2016). After a 3-month treatment with ICS/LABA, the increase in FEV_1 was significantly greater in ACO patients than in those with COPD alone (240.2±33.5 vs 124.6±19.8 mL, *P*=0.002).

2.2.5 Conclusion

ACO has several features that indicate its diagnosis and treatment, including smoking, blood or sputum eosinophilia, airway reversibility and atopy. However, most commonly this comes down to asthmatics who smoke and COPD patients with eosinophilia. The use of ICS in people with COPD who are or are not smokers and those with sputum or blood eosinophilia have been discussed in depth elsewhere in this chapter. However, although these are the most accessible markers of ACO, they are not the only determinants of ACO. When people with COPD, who are also thought to have any of the features of ACO are considered, and given more asthma-like treatment, i.e. ICS, there may be some beneficial effect in terms of improved lung function and reduced exacerbations. However, there is very little published research in this area. Patients with COPD should no longer be considered in isolation, many patients may have some or many features of ACO and this may predict how effective treatments,

such as ICS will be. Further research is needed on the effect of ICS in people with COPD also thought to have ACO or a co-diagnosis of asthma.

2.3 Effect of smoking on ICS efficacy

2.3.1 Effect of smoking in COPD

It is well established that smoking has a detrimental effect on the lungs; causing an increased risk of lung cancer and a faster decline in lung function with age (Figure 2-1). In COPD the effect of decreased lung function causes a greater severity of symptoms such as breathlessness and lower quality of life, as measured by the St Georges Respiratory Questionnaire (SGRQ) score (Mohammed A. Zamzam, 2012). Although smoking cessation reduces the decline in lung function, and if done at an early enough age can maintain a person's lung function such that they do not suffer noticeable symptoms, many people with COPD do not stop.

Figure 2-1 Effect of smoking on lung function
Image taken from Effect of smoking on quit rate of telling patients their lung age (Parkes et al., 2008)

2.3.2 Steroid resistance

As previously discussed, inhaled corticosteroids have been shown to be of limited benefit to people with COPD in comparison to other inhaled therapies, and NICE guidance has identified that there may be patient features that predict response (or lack thereof) to ICS. There has been interest in investigating the role that cigarette smoking plays in causing steroid resistance and this lack of response.

Several mechanisms of steroid resistance in COPD have been postulated; of which reduction of histone deactylase has been most widely investigated. It is postulated that elements of steroid resistance in COPD are due to cigarette smoking and it has been shown that asthmatic patients who smoke require higher doses of ICS for control of their disease (Thomson and Spears, 2005). Oxidants in cigarette smoke are thought to inactivate histone deactylase-2 (HDAC2) via nitration of the HDAC2 by peroxynitrite species. HDAC2 is responsible for supressing inflammatory gene expression in lung macrophages and corticosteroids use this to switch off activated inflammatory genes (Ito et al., 2000, Ito et al., 2001) as per Figure 2-2. It is worth noting that this steroid resistance persists even after smoking cessation (Gamble et al., 2007). It has also been shown that asthmatic patients who smoke require higher doses of ICS for control of their disease (Thomson and Spears, 2005).

It has already been discussed that corticosteroids are not known to be effective on inflammation caused by neutrophils; this is postulated to be due to over-expression of glucocorticoid receptor (GR)-beta on neutrophils which inhibit the action of the functional GR-alpha (Hamid et al., 1999, Sousa et al., 2000).

It is not yet clear if smoking cessation reduces steroid resistance, however there are many other benefits that smoking cessation brings on disease control in COPD; including reduced disease progression and reduced exacerbation rates. One small study found that there may even be a small element of steroid resistance caused by direct interaction of environmental tobacco smoke and aerosolised corticosteroid particles; which may alter drug deposition in the lungs and a subsequent decline in steroid efficacy (Invernizzi et al., 2009).

Whilst there remains cellular observation of the resistance to ICS in smokers, as yet the clinical significance on patient outcomes, such as lung function and exacerbation rates, is still to be fully investigate; no systematic review or meta-analysis has been published yet.

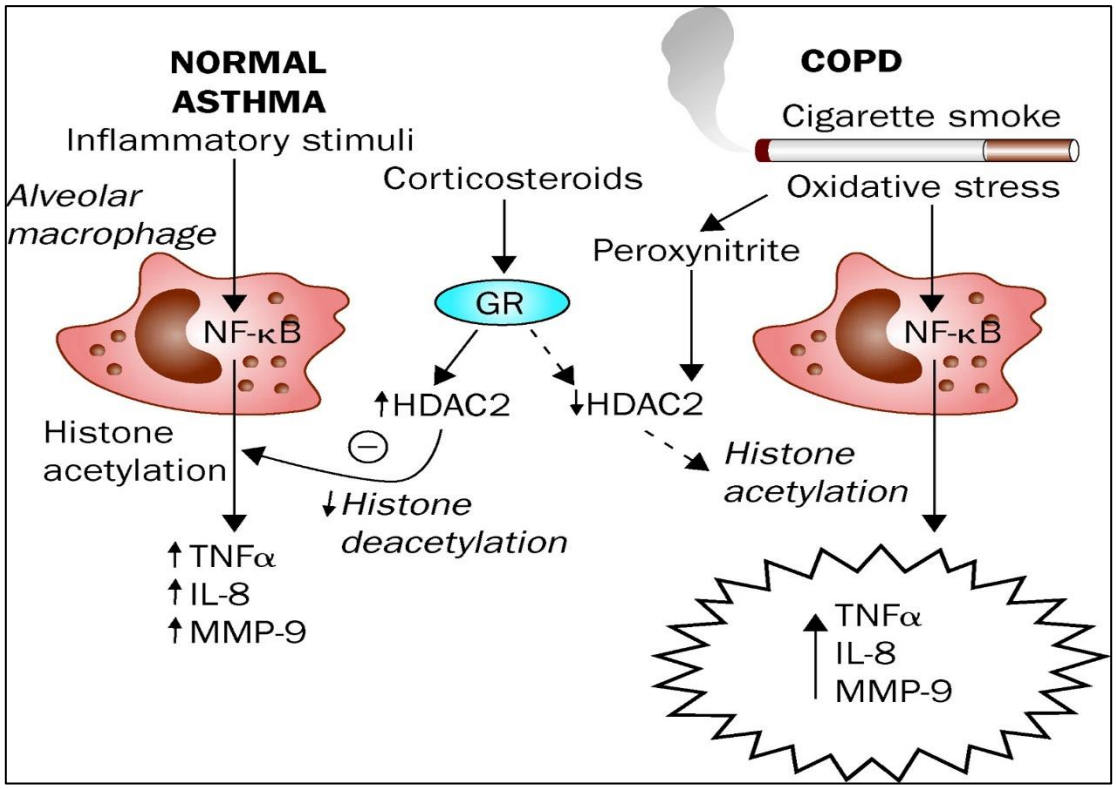

Figure 2-2 Possible mechanism of action of steroid resistance due to cigarette smoking
Image from: (Barnes et al., 2004)

2.4 Other factors influencing ICS efficacy

Although three key factors have been identified in this chapter for their potential impact on ICS outcomes in COPD, there may be many more. For example, socio-economic status is often a predictor of smoking status and may therefore have an indirect effect on ICS outcomes. Additionally, other medications and disease-states may impact outcomes such as hospitalisations and deaths.

2.4.1 Other medications

There are several current and novel treatments that are being investigated for their action on steroid resistance caused by smoking or to treat the causes of inflammation in COPD. Corticosteroid resistance is a problem that cannot be fully overcome by increased doses of ICS, and in any case, increased doses are associated with moderate to severe adverse effects including pneumonia and adrenal suppression. Many new targets to reverse corticosteroid resistance have been postulated and drug development and clinical trials are underway. These include HDAC2 activators and inhibitors of phosphodiesterase-4. Of these, the phosphodiesterase-4 inhibitor roflumilast is the best well known; however its current status and place in treatment strategies in the UK is uncertain. It has only recently been recommended for use in severe COPD where symptoms continue to worsen despite other treatments (NICE, 2017b). Until recently reports of adverse effects including suicidal ideation have hindered its use. Current therapies such as theophylline, anti-oxidants and macrolide antibiotics are also being investigated for new uses in tackling steroid resistance.

Theophylline

Theophlline has been shown to be beneficial on several of the pathways thought to contribute to steroid resistance in COPD. One such mechanism is through inhibition of phosphoinositide-3-kinase-delta, which was up-regulated in COPD patients and is thought to be involved in induction and activation of inflammatory cells (To et al., 2010). Theophylline has also been shown to induce a 6-fold increase in HDAC2 activity in alveolar macrophages (Cosio et al., 2004). Theophylline is already used in COPD for its bronchodilator effect; however, it is use is sparse and usually reserved as add on therapy when all other treatment strategies have proved ineffective. There is potential here to investigate its use at a much earlier stage of COPD severity for its steroid sparing effect and to reverse steroid resistance.

Anti-oxidants

As oxidative stress has been shown to reduce HDAC2 activity and further cause steroid resistant inflammation in COPD, it is unsurprising that anti-oxidant therapy has been trialled. However, poor bioavailability and stability have caused most to fail (Kirkham and Rahman, 2006).

N-acetylcysteine (NAC) is a mucolytic with anti-oxidant and anti-inflammatory properties. NAC acts as a reactive oxygen species scavenger and a precursor of reduced glutathione. There have so far been mixed reports of the beneficial effective of NAC on FEV1 and exacerbation rates. Systematic Reviews' showed that NAC could reduce COPD exacerbations vs placebo. Conversely, the BRONCUS (Bronchitis Randomized on NAC Cost-Utility Study) randomized, double-blind, placebo-controlled, 3-year study failed to demonstrate the beneficial effect of NAC on FEV 1 and exacerbation

frequency. More recently the 1-year HIACE (The Effect of High Dose N-acetylcysteine on Air Trapping and Airway Resistance of COPD), patients aged 50 to 80 years with stable COPD were randomised to NAC 600 mg bd or placebo after 4-week run-in. Lung function parameters and exacerbation and admission rates were measured. A significant reduction in exacerbation frequency (0.96 times/y vs 1.71 times/y, P =0.019), and a tendency toward reduction in admission rate (0.5 times/y vs 0.8 times/y, P 5 .196) with NAC vs placebo.

Macrolide antibiotics

Macrolide antibiotics have been shown to have beneficial effects on neutrophil numbers and are therefore thought to exhibit and anti-inflammatory effect through this mechanism. In addition, they have recently been shown to restore HDAC2 activity; as such an erythromycin derivative is currently under development for this purpose.

2.4.2 Co-morbidities

Co-morbidities are an important factor in determining the outcome of any treatment as it has been shown in general that people with multiple co-morbidities often have worse outcomes (such as deaths and hospitalisations) from treatment than those without. Other than asthma, discussed previously, no specific co-morbidity was identified that would have a specific impact on the efficacy of ICS in COPD. However it has been shown that a measure of co-morbidities, such as Charlson score, does affect the outcome from COPD treatment with higher Charlson scores associated with increased risk of death (Karoli and Rebrov, 2012).

2.4.3 Socio-economic status

Lower socio-economic status has long been associated with lower life-expectancy (Stringhini et al., 2017)and it would therefore be expected that this would impact on outcomes with ICS use in COPD. In addition, lower socio-economic status is also linked to increased smoking or nicotine exposure (Chen et al., 2019)and could be an important co-factor in determining the outcome of ICS use in smokers with COPD.

2.4.4 Measuring efficacy of COPD treatments

In section 2.1.4 it was identified that a Delphi consensus for the outcomes evaluating eosinophil-guided treatment in COPD was available (Suehs et al., 2020). However, there is no such consensus for the more general outcome measures to be used to assess efficacy of treatments in COPD. Throughout the literature review in this chapter, most of the studies have used one or more of the following patient outcome measures; lung function (FEV_1), exacerbations in community or requiring hospitalisation, and mortality. Of these outcomes, only exacerbations and mortality were also identified in the Delphi consensus. Glaab et al. (2010) evaluates the strengths and limitations of the most commonly used outcome measures, including; lung function, dyspnoea, exercise capacity, St Georges' Respiratory Questionnaire (SGRQ), exacerbations and mortality. This review highlights that for many of these outcome measures, except lung function, there is no gold standard and therefore no single outcome measure can be recommended. Additionally, it is not possible to use all these outcome measures in observational research; it is unlikely that SGRQ, exercise capacity or dyspnoea are recorded in healthcare databases, which further limits their use in research.

2.5 Conclusions

Corticosteroids have been widely used in the treatment COPD despite lack of mechanism of action and little clinical benefit historically. Recent changes to national and international guidance on the use of ICS in COPD have indicated that not all people with COPD will benefit from ICS, however this guidance indicated that not enough was known about the factors which may cause this. The key factors that may determine if ICS will be an effective treatment for an individual have been considered in the literature review in this chapter.

With regards to eosinophils, it can be concluded that these may be an important factor in determining the efficacy of inhaled corticosteroids, but so far observational studies, some using the CPRD dataset, have been inconclusive. As there are methodological limitations in the way ICS use was classified and the time-frames used in this literature, different methods to investigate the effect of eosinophils may be beneficial.

Targeting ICS to people with asthma-COPD overlap has not been well studied as many researchers have excluded a co-diagnosis of asthma from their investigations. ACO has several features that indicate its diagnosis and treatment, including smoking, blood or sputum eosinophilia, airway reversibility and atopy which make it complex to study in isolation. However observational studies using healthcare databases could consider all these co-factors together.

Smoking has been found to potentially cause ‘steroid resistance’, and thereby theoretically make COPD less responsive to ICS therapy. However, there is currently no

systematic review or meta-analysis focussing on the effect ICS use has in smokers and non-smokers on patient outcomes such as exacerbation rates.

A few other factors that may determine ICS efficacy have been identified. The concomitant use of other medications, such as theophylline and macrolide antibiotics may increase the efficacy of ICS by reducing eosinophilic inflammation or reducing some of the causes of steroid resistance. Additionally, comorbidities and low socio-economic status may result in more detrimental outcomes from ICS treatment, especially as both are often co-factors to smoking status.

A Delphi consensus identified 12 outcomes for evaluating eosinophil-guided treatment, however there is no specific consensus guiding best practice for measuring outcomes of treatment in COPD more generally. Through much of the literature outcome measures used have included lung function, exacerbation rates and mortality, however these have strengths and limitations. Other methods, such as SGRQ and dyspnoea are also suitable outcome measures, however, are unlikely to be recorded in healthcare databases for observational studies.

2.6 Future direction

This thesis sets out to explore some of the gaps in the knowledge of the efficacy of ICS in COPD identified; in the next chapter a systematic review on the effect of smoking on outcomes with ICS use in COPD is undertaken. Following that, pharmaco-epidemiology using large healthcare datasets is discussed as a potential method to answer some of these questions. The broad questions this thesis aims to answer are:

1. The effect the variables identified in the literature review (smoking, asthma diagnosis, eosinophil counts) have on outcomes with ICS in COPD. Outcomes will include yearly exacerbations, lung function decline and mortality at extended time points
2. The suitability of a large UK healthcare database to investigate this aim

In the following chapter, the systematic review that was identified as a gap in the literature in this chapter on the effect of smoking on outcomes with ICS use in COPD is undertaken.

In Chapter four the use of the Clinical Practice Research Datalink will be discussed as the method of selecting a suitable cohort for investigation. In this chapter, the cohort will be defined and explored for its suitability for use in investigating the aims of this thesis stated above.

The following four chapters (chapters five to eight) will include the results of the research into the cohort identified. There will be one chapter dedicated to each of the four objectives stated above.

Chapter nine will bring all the results together in a discussion to draw conclusions on the effect factors, such as asthma diagnosis and smoking status, have on ICS outcomes. It will aim to answer the question that there may be suitable ways to identify patients to target ICS therapy towards who may get more benefit than others.

3. Systematic review: The impact of smoking status on the efficacy of ICS in COPD

As smoking is very common amongst people with COPD and it's known link to decline in lung function, the literature on the effect smoking status has on efficacy of ICS has been explored in depth here in a systematic review. The systematic review in this chapter was accepted for publication by BMJ Open in February 2020. No further relevant studies have been identified since the publication.

3.1 Introduction

Cigarette smoking is a causative factor in chronic obstructive pulmonary disease and it is estimated that worldwide, around 80% of people with COPD are current or ex-smokers.(Lamprecht et al., 2011, Schneider et al., 2010) In addition to contributing to an increased rate of lung function decline, recently it has been postulated that smoking may cause resistance to some drug treatments; most notably inhaled corticosteroids (Anthonisen et al., 2002, Barnes et al., 2004). Asthmatic patients who smoke often require higher doses of ICS for control of their disease (Thomson and Spears, 2005). The mechanism for this resistance has yet to be fully established.

ICS reduce exacerbation rates and possibly reduce the decline in lung function, as measured by forced expiratory volume in one second (FEV_1), in comparison to placebo for people with COPD (Vestbo et al., 2013). As a result, ICS have been a mainstay of COPD treatment for some time. However, there has been some controversy around the use of ICS; most notably that not all people with COPD benefit from their

use(Barnes, 2010, Suissa and Barnes, 2009), and the vast array of adverse effects that long-term use of these medicines cause. It is well-established that ICS are highly effective anti-inflammatory agents in asthma yet efficacy in COPD, even at high doses, remains debated. The reasons for this are likely to be complex and multifactorial, however resistance to ICS due to smoking is one possible factor.

One of the mechanisms by which ICS suppress inflammation in COPD is by acting on histone deacetylase-2 (HDAC-2) to inhibit the release of inflammatory mediators such as TNF-α and IL-8 that activate inflammatory cells (Culpitt et al., 2003). Several animal models and *in vitro* studies have shown that cigarette smoke reduces the activity and expression of HDAC-2 in alveolar macrophages by imposing an oxidative stress in the lungs (Marwick et al., 2009). Cigarette smoke contains several reactive oxygen species (ROS) and other noxious particles which generate ROS. Cigarette smoke also contains nitric oxide (NO) which combines with ROS to generate peroxynitrite. In mice exposed to cigarette smoke, peroxynitrite causes the nitration of HDAC-2, which consequently leads to a loss in HDAC-2 function (Marwick et al., 2009). This reduction in levels and function of HDAC-2 prevent ICS from exerting the anti-inflammatory effect, thereby causing steroid resistance (Ito et al., 2004).

It is not yet clear if smoking cessation reduces steroid resistance; it was noted that airway mucosal inflammation may persist even after smoking cessation (Gamble et al., 2007). However there are many other benefits that smoking cessation brings on disease control in COPD; including reduced disease progression and reduced exacerbation rates (Anthonisen et al., 2002). One small study found that there may even be a small element of steroid resistance caused by direct interaction of

environmental tobacco smoke and aerosolised corticosteroid particles; which may alter drug deposition in the lungs and a subsequent decline in steroid efficacy (Invernizzi et al., 2009).

Whilst there remains cellular observation of the resistance to ICS in smokers with COPD, as yet the clinical significance on patient outcomes, such as lung function and exacerbation rates, is still to be fully investigated; no systematic review of the evidence has been published.

3.1.1 Aim

The aim of this systematic review is to investigate the effect smoking status, or amount smoked, has on COPD outcomes with ICS use in comparison to either placebo or other inhaled therapies. This will be done by identifying and drawing conclusions from published literature.

3.2 Methods

This systematic review was registered with Prospero (https://www.crd.york.ac.uk/prospero/), registration number CRD42019121833. In addition, the full search strategy can be found in Appendix 1 Systematic review search strategy.

Literature search: This systematic review was conducted by an electronic database search in PubMed (Jan 2000-Jan 2020), Ovid Medline (Jan 2000- Jan 2020), Ovid Embase (Jan 2000-Jan 2020) and Cochrane Library (Jan 2000-Jan 2020). A structured search strategy including free text and MeSH terms related to randomized controlled trial, COPD, smoking and inhaled corticosteroids (budesonide, fluticasone, ciclesonide, mometasone and beclometasone) was used to retrieve literature for this systematic review. The reference lists of the retrieved papers were also searched to identify further relevant studies.

Inclusion criteria: Fully published randomised controlled trials (RCTs) evaluating the use of ICS (either alone or in combination with LABA) in COPD adults that stratified the participants by smoking status (including as a sub-group analysis) were included. Review articles, abstracts, papers which are not fully published or published in languages other than English were not included. Retrieved trials that included COPD patients with asthma, lung cancer and pneumonia were also excluded. Trials that did not stratify participants by smoking status or smoking pack-years were also excluded.

Data extraction: Information about the study characteristics which include the study design and length, settings, participants' age, diagnostic criteria for COPD, severity of

COPD, ICS type, dose and frequency, duration of the intervention and frequency of follow-up were extracted. An estimated effect of ICS on the outcomes reported was calculated for each participant subgroup. The outcome measures were: difference in mean change of lung function between subgroups, as measured by FEV_1, and rate ratio of yearly exacerbations.

Quality assessment: Risk of bias and quality assessment of all included studies was assessed using the Cochrane Collaboration tool for assessing risk. Where disagreement occurred, this was discussed and a consensus reached. Information extraction was completed by one researcher and confirmed by a second.

3.3 Results

Eight RCTs were identified for inclusion in this systematic Figure 3-1 . A further study by Bafadhel et al. (2018) was identified, but the data was not presented in a way that could be extracted for this systematic review and thus it's results have been discussed separately. On further inspection two of the RCTs, Hoonhorst *et al* and Snoeck-Stroband *et al*, were both post-hoc analyses of the Groningen Leiden Universities and Corticosteroids in Obstructive Lung (GLUCOLD) trial but it is not clear if the same patient group was analysed (Lapperre et al., 2009, Hoonhorst et al., 2014, Snoeck-Stroband et al., 2015). The way each study classified smoking status was different and thus both sets of results have been reported. Additionally, Bhatt *et al,* Hinds *et al and* Pascoe *et al all* reported a post-hoc analysis of the SUMMIT, FLAME and IMPACT studies respectively (Pascoe et al., 2019, Bhatt et al., 2018, Hinds et al., 2016).

The eight RCTs included in this systematic review were heterogeneous in nature with respect to their stratification of smokers, study drug used and outcomes. Stratification of smokers broadly fell into two categories: current smoker versus ex-smoker in five studies (Hoonhorst et al., 2014, Zheng et al., 2007, Bhatt et al., 2018, Wedzicha et al., 2016, Pascoe et al., 2019) or heavier smoker versus lighter smoker in the remaining studies (Hinds et al., 2016, Pauwels et al., 1999, Snoeck-Stroband et al., 2015). The study drugs used were either budesonide or fluticasone (propionate/furoate); six studies used fluticasone in combination with a Long Acting Beta Agonist (LABA), either salmeterol (Snoeck-Stroband et al., 2015, Hoonhorst et al., 2014, Wedzicha et al., 2016, Zheng et al., 2007) or vilanterol (Hinds et al., 2016, Bhatt et al., 2018, Pascoe et al., 2019), and the remaining two used fluticasone (Snoeck-Stroband et al., 2015) or

budesonide alone (Pauwels et al., 1999). The outcomes reported were either change in lung function (measured by FEV_1) in five studies (Pauwels et al., 1999, Hoonhorst et al., 2014, Snoeck-Stroband et al., 2015, Zheng et al., 2007, Bhatt et al., 2018), or yearly exacerbation rates in four studies (Bhatt et al., 2018, Wedzicha et al., 2016, Pascoe et al., 2019, Hinds et al., 2016); one study reported both. Where lung function was reported, there were differences in the way in which FEV_1 was measured; Pauwels *et al* reported median of the post-bronchodilator FEV_1 slope (ml/year), Bhatt *et al*, Hoonhorst *et al* and Snoeck-Stroband *et al* reported post-bronchodilator FEV_1, and Zheng *et al* reported pre-bronchodilator FEV_1. There were also minor differences patient characteristics, disease severity and study length. All of the included studies were parallel group, double-blind and placebo-controlled RCTs. A summary of the characteristics of the trials is reported in Table 3-1

Effect on lung function

In total, 17,999 participants were included in the trials reporting lung function as the outcome. Bhatt *et al* was by far the largest trial with over 16,000 participants. The number of participants enrolled in each trial and general trial characteristics are shown in Table 3-1. All five trials were funded by pharmaceutical companies.

There were a variety of primary outcomes reported, including: change in median post-bronchodilator FEV_1 over time, inflammatory cell counts and mean pre-bronchodilator FEV_1. Follow-up was carried out at least every 3 months. The changes in post-bronchodilator FEV_1 in each study (except Zheng *et al* where pre-bronchodilator FEV_1 is reported) are summarised in Table 3-2 . Although each study used the same measurement of lung function (FEV_1), it was represented as either: mean (mL), median

slope (mL/year) or interquartile median (mL). The pre-bronchodilator FEV_1 is reported for Zheng *et al* as the authors did not stratify post-bronchodilator FEV_1 by smoking status. In addition to differences in outcome measure, the lack of data on number of participants in each smoking arm in some trials (Pauwels et al., 1999, Snoeck-Stroband et al., 2015) means that no meta-analysis between the study results was possible.

The overall effect of smoking on the efficacy of ICS is summarised in Table 3-2 In studies where participants were categorised by pack-year history (Pauwels et al., 1999, Snoeck-Stroband et al., 2015), heavier smokers using ICS had a greater deterioration in FEV_1 in comparison to lighter smokers using ICS. This ranged from -22ml/year to -75ml/year. However, when categorised by smoking status (Hoonhorst et al., 2014, Zheng et al., 2007, Bhatt et al., 2018) there were mixed results: current smokers' FEV_1 ranged from -600ml to +110ml over the study period in comparison to ex- or never-smokers; no statistical significance was reported with these results.

Effect on exacerbation rate

Three trials, Wedzicha et al (2016), Hinds et al (2015) and Pascoe et al (2019), evaluated the rate ratio of yearly COPD exacerbations at 52 weeks in comparison to the alternative treatment arm and one, Bhatt et al (2018), the percentage change in exacerbations, as indicated in Table 3-3 (Pascoe et al., 2019, Bhatt et al., 2018, Hinds et al., 2016, Wedzicha et al., 2016). Hinds *et al* was a post-hoc cluster analysis of the Effect of Indacaterol/Glycopyronium versus Fluticasone propionate/Salmeterol on COPD Exacerbations (FLAME) trial where the participants were sorted into clusters, the cluster of participants included in this systematic review had eosinophil counts of ≤2.4% and treatment was with either fluticasone propionate/salmeterol (ICS/LABA) or

indacterol/glycopyrronium (LABA/Long Acting Anti-muscarinic, LAMA) (Dransfield et al., 2013). Wedzicha *et al*, Bhatt *et al* and Pascoe *et al* were multicentre studies which compared fluticasone furoate/vilanterol (ICS/LABA) to vilanterol (LABA) or placebo. Each study classified smoking status differently: Wedzicha *et al*, Bhatt *et al and* Pascoe *et al* classified participants as a current smoker or ex-smoker. Hinds *et al* classified them by pack-years smoked; ≤46 pack-years or >46pack-years thus making direct comparison between the results difficult. In total there were 27,460 participants.

The additional study not included in this systematic review, Bafadhel et al (2018), reported that smoking status was a predictor of response to budesonide/formoterol in reducing exacerbations; ex-smokers had a lower exacerbation ratio (versus formoterol alone) than current smokers(Bafadhel et al., 2018). However, the results were stratified by eosinophil count and the data could not be extracted to make a meaningful comparison to the other RCTs discussed here.

All four studies reported that current or heavier smokers in the ICS treatment arm were associated with a higher exacerbation rate than ex-smokers or lighter smokers. One study reported that LABA alone was less effective at reducing yearly exacerbation rates than ICS/LABA if pack year history is equal to, or less than 46 (RR 1.29; CI 1.02-1.58) (Hinds et al., 2016). But LABA alone was more effective if pack years >46 (RR 0.81; CI 0.63-1.06), however this result was not statistically significant. Two studies reported that overall, participants who were current smokers in the ICS treatment arm had less favourable outcomes in terms of exacerbations (RR 0.83 & 0.99; CI 0.74-0.92 & 0.87-1.12) than ex-smokers (RR 0.92 & 1.20; CI 0.83-1.01 & 1.10-1.33) (Pascoe et al., 2019, Wedzicha et al., 2016). The final study showed that exacerbation rates were reduced

with ICS/LABA versus placebo and that this effect was greater in ex-smokers than current smokers (36% versus 19%, p=0.013) (Bhatt et al., 2018).

Quality assessment

Each of the eight included studies were assessed using the Cochrane Collaboration's tool for assessing the risk of bias (Figure 3-2) Overall the quality of all included trials was high, however the main limitation was lack of information on how the random allocation was made and how this was concealed. Several trials had other sources of bias; although randomisation was undertaken in the original trial, the post-hoc analyses reported in this systematic review used a sub-set of the original participants and therefore it cannot be determined if the original randomisation process holds. In addition, Hoonhorst (2014) and Snoeck-Stroband (2015) were powered to detect change in CD8 count, not lung function. Only 114 patients were recruited in the parent trial and it is unlikely that these were sufficiently powered to detect a change in lung function. Bhatt *et al* was a post-hoc analysis of the SUMMIT study, however the results were published as a 'letter to the editor' and not as a peer-reviewed paper. The original SUMMIT trial was peer-reviewed and thus the results were included in this systematic review due to the robustness of the original data and significant number of participants it included.

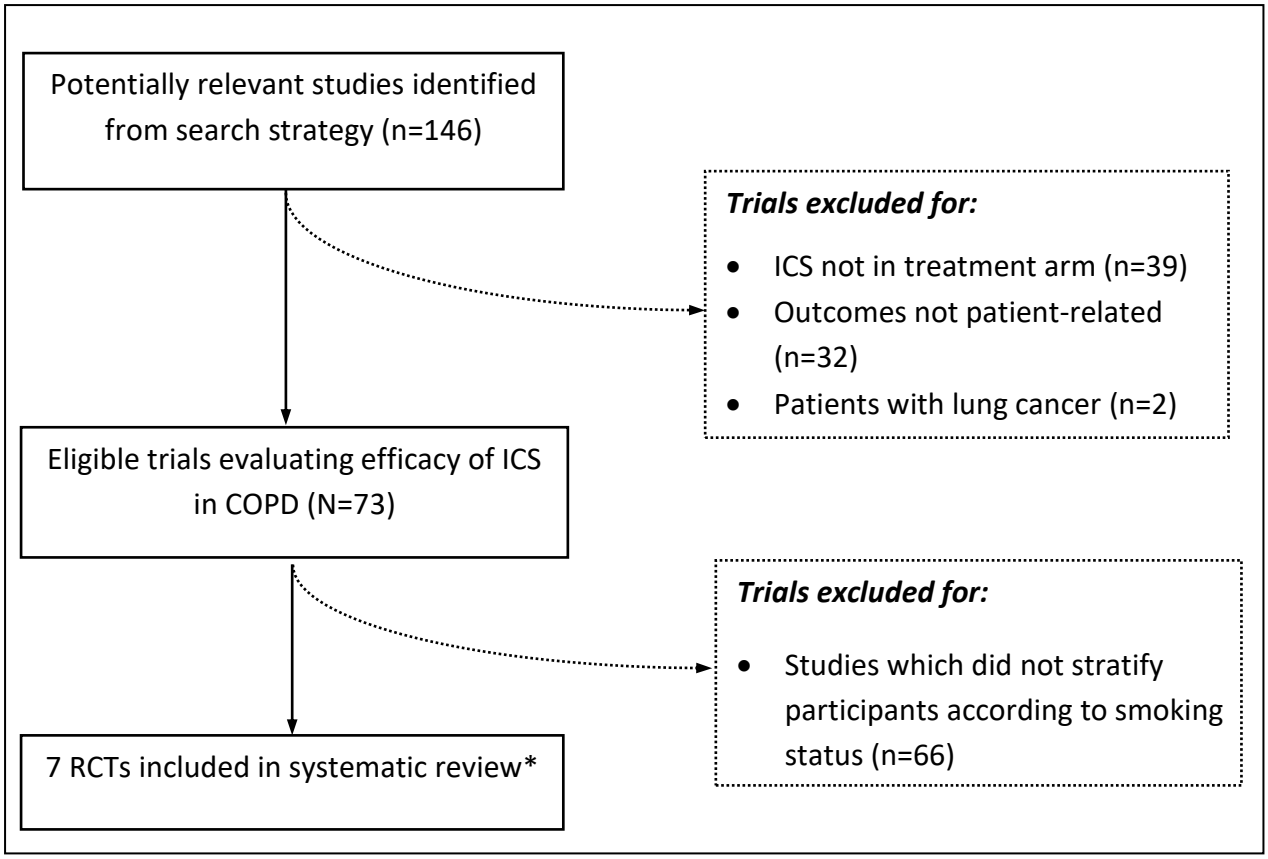

Figure 3-1 Exclusion of studies identified in the search strategy
*A further RCT was identified that was published outside of the time period, but was thought to be important to include, taking the total to eight.

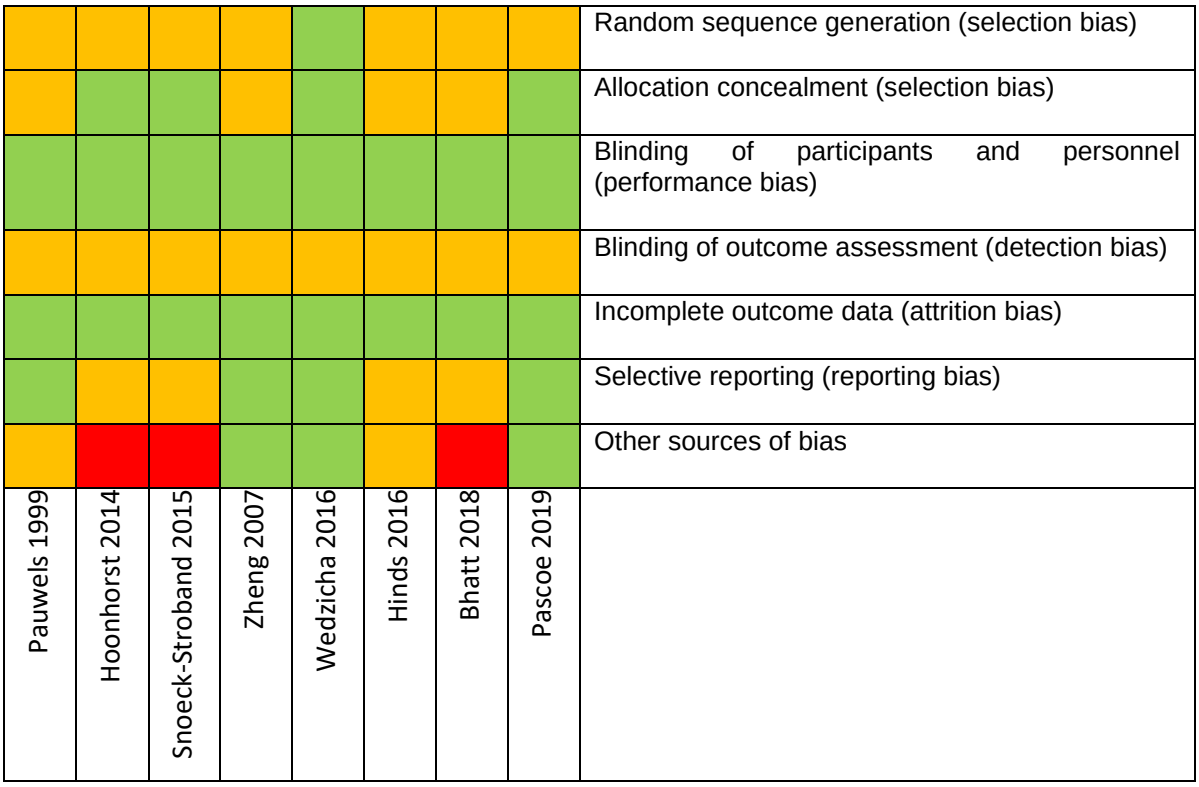

Figure 3-2. Quality assessment of included studies using Cochrane Collaboration tool for assessing risk of bias.
Red = high risk of bias; amber = uncertain/cannot tell; green = low risk of bias

Study	Design and trial length	COPD diagnosis criteria and severity	Age range (years)	Intervention	Treatment duration and follow-up frequency	Primary efficacy outcome	Other outcomes
Pauwels 1999	Parallel, double-blind, placebo-controlled, international, multicentre (9 European countries); 3.5 years	Spirometry test 50% < FEV_1 < 100%	30-65	Budesonide 400µg twice daily (n=458) Placebo (n=454)	3 years; Every 3 months	Change in post-bronchodilator FEV_1 over time (ml/yr)	None
Zheng 2007	Parallel, double-blind, placebo-controlled, multicentre (China); 6.5 months	Spirometry test 25% < FEV_1 < 69%	40-79	Fluticasone propionate/ Salmeterol 500/50µg twice daily (n=297) Placebo (n=148)	6 months; Week 0,2,4,8,12,16,20 and 24	Pre-bronchodilator FEV_1 (ml)	Post-bronchodilator FEV_1 (L) Health status Night-time awakenings Supplemental salbutamol use
Hoonhorst 2014 AND Snoeck-Stroband 2015	Post-hoc analysis. Parallel, double-blind, placebo and active controlled, single centre (Netherlands); 7 years	Spirometry test 30% < FEV_1 < 80%	45-75	Fluticasone propionate (FP) 500µg twice daily or FP/Salmeterol 500/50µg twice daily (n=35) FP 500 µg twice daily (6 months) + Placebo (24 months) (n=55) Placebo (n=17) Fluticasone propionate 500 µg twice daily (n=26) Placebo (n=24)	2.5 years; Every 3 months	Inflammatory cell counts in bronchial biopsies (10^7/m2) and induced sputum (10^4/ml)	Post-bronchodilator FEV_1 (L) Dyspnoea score Health status

Wedzicha 2016	Parallel, double-blind, non-inferiority, multicenter (43 countries worldwide) ; 52 weeks	Spirometry test 25% < FEV_1 < 60%; mMRC≥2; ≥1 exacerbation in past year	≥40	Indacterol/glycopyrronium 110/50µg (n=1680) Salmeterol/fluticasone propionate 50/500µg (n=1682)	Exacerbations at week 52	Annual rate of COPD exacerbations	None
Hinds 2016	Post-hoc analysis. Randomised, double-blind, parallel group, 52-week, multicentre study (16 countries worldwide)	FEV_1 of ≤70% predicted and a (FVC) ratio of ≤0.7 after bronchodilator use; ≥1 exacerbation in previous year	≥40	Fluticasone furoate/Vilanterol 50/25µg OR 100/25µg OR 200/25µg twice daily (n=1092) Vilanterol 25µg (n=386)	52 weeks	Annual rate of moderate to severe exacerbations	None
Bhatt 2018	Post-hoc analysis. Randomised, double-blind, 52-week, multicentre (43 countries worldwide)	FEV_1 of 50-70% predicted and a (FVC) ratio of ≤0.7 after bronchodilator use; ≥10 pack-year smoking history	40-80	Fluticasone furoate/Vilanterol 100/25µg (n=4121) Fluticasone furoate 100µg (n-4135) Vilanterol 25µg (n=4118) Placebo (n=4111)	3, 6, 9 and 12 months	Change in post-bronchodilator FEV_1	Annual rate of moderate to severe exacerbations SGRQ
Pascoe 2019(Pascoe et al., 2019)	Post-hoc analysis. Randomised, double-blind, parallel, 52-week, multicentre	CAT score ≥10, FEV_1 ≤50% and ≥1 mod/severe exacerbation in last year OR FEV_1 50-80% and ≥2 mod/severe exacerbation in last year	≥40	Fluticasone furoate/Vilanterol 100/25µg (n=4125) Umeclidinium/Vilanterol 62.5/25µg (n=2065)	52 weeks	Annual rate of moderate to severe exacerbations	SGRQ

Table 3-1 Summary of characteristics of included trials

µg= micrograms, bd= twice daily, ml/yr= milliliters per year, mMRC = modified Medical Research Council dyspnoea scale, CAT score = COPD assessment test

	Period	Study	Smoking status	Change in FEV_1*		Estimated effect of ICS on FEV_1 outcomes*	P value	Estimated effect of smoking on FEV_1 outcomes in ICS users*	P value
				ICS	Placebo				
Smoking: pack-year	0-6 months	Pauwels 1999	Subjects with ≤36 pack-yr history^	30	-90	120	<0.001	-50	#
			Subjects with >36 pack-yr history^	0	-70	70	0.57		
	9-36 months	Pauwels 1999	Subjects with ≤36 pack-yr history^	-47	-71	24	0.08	-22	#
			Subjects with >36 pack-yr history^	-67	-65	-2	0.65		
	0-30 months	Snoeck-Stroband 2015**	Subjects with ≥42 pack years^	-28	-63	35	0.242	-75	0.023
			Subjects with <42 pack years^	18	-92	110	0.037		
Smoking: smoking status	0-6 months	Hoonhorst 2014*	Smokers (n=41)	-100	200	-300	-	-600	#
			Ex-smokers (n=31)	100	-200	300	-		
	6- 30 months	Hoonhorst 2014**	Smokers (n=41)	-90	-300	210	-	+110	#
			Ex-smokers (n=31)	0	100	-100	-		
	0-6 months	Zheng 2007	Never-smoked (n= 52)	261	141	120	0.3592	-	-
			Ex-smokers (n= 297)	177	6	171	0.0068	+51	#
			Current smokers (n=96)	112	-85	197	0.0022	+26/+77	#
	0-12 months	Bhatt 2018	Smokers (n=7678)	-	-	22	0.038	-	-
			Ex-smokers (n=8807)	-	-	30	0.005	+8	#

Table 3-2 Effect of ICS on FEV_1 categorised by smoking status.

*Change in FEV_1 reported. Values are in ml, except for Pauwels (1999) and Snoeck-Stroband (2015) data are expressed as mL/yr **These results are from the same original RCT – GLUCOLD study [19]; number of participants in each study group not reported; #P value cannot be calculated from data

Period	Study		Yearly exacerbations (95% CI)		Rate ratio*	95% CI
			ICS	Alternative		
0-52 weeks	Wedzicha 2016	Current smoker (n=658, 647)	-	-	0.83	0.74-0.92
		Ex-smoker (n=998, 1004)	-	-	0.92	0.83-1.01
0-52 weeks	Pascoe 2019	Current smoker (n=1421, 726)	-	-	0.99	0.87-1.12
		Ex-smoker (n=2704, 1339)	-	-	1.20	1.10-1.33
0-52 weeks	Bhatt 2018	Current smoker (n=7678)	-	-	19%^	7-29%
		Ex-smoker (n=8807)	-	-	36%^	27-43%
0-52 weeks	Hinds 2016	>46 pack years (n=587)	1.62 (1.29-2.02)	1.32 (1.00-1.76)	0.81	0.63-1.06
		≤46 pack years (n=891)	0.66 (0.54-0.81)	0.85 (0.67-1.08)	1.29	1.02-1.58

Table 3-3 Effects of ICS on yearly exacerbation.

*Rate ratio of yearly exacerbations: <1 favours the alternative; >1 favours ICS, except Bhatt et al where % reduction in exacerbations versus placebo was reported. ^Fluticasone furoate/vilanterol versus placebo, no difference was seen for Fluticasone furoate versus placebo or Vilanterol versus placebo

3.4 Discussion

Heavier smokers, with a greater pack-year history, were less likely to benefit from ICS use in terms of lung function and yearly exacerbation rates than those who were lighter-smokers. When categorised in terms of smoking status, i.e. smoker or ex-smoker, the majority of participants who were ex-smokers showed a greater increase in lung function and decrease in exacerbations over current smokers with ICS use. No definitive conclusions can be drawn from these data due to the lack of statistical significance reporting for most of the results and differences in stratification of smoking status and measurement of lung function. For generalisability of results, the participants had a wide range of severity of COPD, however the most severely affected (FEV_1<30% predicted) were underrepresented. In addition, although changes in lung function and exacerbation rates were found, the magnitude of these changes are unlikely to be clinically significant.

In the studies that stratified participants by pack years smoked, dividing participants into groups of >/≤36 pack years or >/≤42 pack years was not justified; there were no documented reason why these divisions were set but may be because this was a post-hoc analysis of the results and the original participants were not stratified according to smoking status. Furthermore, in most studies smoking status was self-reported by the participants at the beginning of the study. There was no objective measure used and change in smoking status through the study was not accounted for.

Effect on lung function

The effect of smoking on outcomes from ICS use on lung function were mixed and depended upon how smoking was defined. The decline in FEV_1 found in the trials stratifying smoking by pack-years ranged from 22ml/year to 75ml/year; implying that a greater number of pack years smoked resulted in a greater decline in lung function. By comparison, the trials that stratified by current smoking status found mixed results.

Of the studies that stratified by pack years smoked, the largest study (Pauwels *et al*) showed that those with >36 pack years receiving ICS had an FEV_1 decline of 50ml/year (median slope of FEV_1 used) over those with a lighter smoking history at six-months. In the longer term, Pauwels *et al* again reported a greater decline in lung function at 36 months in heavier smokers using ICS than lighter smokers, albeit by a reduced amount (22ml/year). Snoeck-Stroband *et al* also found a similar result (75ml/year decline, p=0.023), however was a very small study and a high risk of bias in the way participants were selected from the original trial.

Of the studies that stratified by smoking status, the smallest study (Hoonhorst *et al*) reported a decline in FEV_1 in smokers over ex-smokers. However, the size of the study and the original reporting of FEV_1 in litres to only two significant figures make these results unreliable and imprecise. Furthermore, the lung function of smokers receiving placebo increased from baseline to six months; a result that is inconsistent with the wealth of literature on effects of smoking. However, the three remaining trials all reported the opposite result; ex-smokers receiving ICS had less decline in lung function than smokers (8ml to 110ml). However the largest of these trials (Bhatt *et al*),

accounting for over 16,000 participants, showed only an 8ml increase which although statistically significant is not clinically important.

Effect on exacerbations

A clearer result was seen for effect on exacerbations; all studies reported a lesser decrease in yearly exacerbation rates when ICS was given to heavy or current smokers versus ex-smokers and lighter smokers; implying that ICS are less effective in heavier smokers. In addition, the large participant numbers and reporting of confidence intervals makes us more certain that these are true results. However, in each set of results the 95% confidence interval of the rate ratio crosses the threshold of one, making it possible that there is no difference between the comparison groups.

It was expected that smoking with ICS use would show a clearer impact on exacerbation rates than lung function; ICS are already known to have a larger impact on reducing rates of exacerbations than in slowing the decline of lung function (Burge et al., 2000). However it should be noted that in Wedzicha *et al* the effect of ICS/LABA was less than the alternative treatment of LAMA/LABA which may suggest ICS are of more limited efficacy in reducing exacerbation rates than other inhaled therapies, regardless of smoking status.

The outcome of this systematic review is consistent with the literature, indicating that steroid resistance of smokers to the effects of ICS may be present (Irusen et al., 2002, Culpitt et al., 2003, Marwick et al., 2009, Nowak et al., 1999, Ito et al., 2004). However, just as there is uncertainty in the literature as to whether smoking cessation reverses this resistance (Gamble et al., 2007, Invernizzi et al., 2009), there is uncertainty here

as to if smoking status effects outcomes with ICS. More work is needed to determine the pack-year quantity at which it would be expected that smoking would cause steroid resistance and if smoking cessation reduces steroid-resistance. Furthermore, studies that report effect of smoking as a primary outcome and are adequately powered to detect this are needed. For now, clinicians should be aware that patients who are heavier smokers or current smokers may not respond as expected to ICS and that other inhaled therapies may be more beneficial.

3.5 Conclusion

In COPD, current or heavy smokers (over 36 pack years) may not gain the same benefit from ICS use on lung function and exacerbation rates as lighter or ex-smokers do. This could be due to 'steroid resistance' caused by smoking, or other factors, such as difference in; severity of disease, co-prescribed medicines (such as bronchodilators) and methodology between trials. In practice this means that practitioners should consider smoking status before prescribing ICS due to potentially reduced efficacy; however further work is needed with greater patient numbers to determine if there is an effect of 'steroid resistance' in current smokers.

4. Methods: Cohort selection and data management

4.1 Introduction

As highlighted in chapter two and three, further investigation into the features of people with COPD that may, or may not, respond to ICS is needed. There are different methodologies by which this can be done, for example, randomised controlled trials or cohort studies. There are limitations to these types of studies in terms of recruiting enough participants to adequately power the research. Additionally, the time and financial pressures of this type of study often mean that these only relatively short-term follow-up (up to three years) is possible. Diseases such as COPD are chronic and thus the person will live with it for the rest of their lives; and if they are using ICS this will often be for most of this time. Hence, to fully understand the benefits of these medicines, over three years follow up is required.

Cohort studies can also be undertaken by using healthcare databases. These databases have the advantage of containing millions of patient records and real-world data, with follow up over extended time periods; in some cases, ten years or more.

The aim of this chapter is to explore the suitability of a healthcare database, the Clinical Practice Research Datalink, for this research and to define the study population.

4.2 Data source

Healthcare databases are in use globally as a means of recording patient demographics, disease episodes, therapies received, and costs associated with this. In the UK there are several primary care datasets where routine primary care data are recorded, such as the Clinical Practice Research Datalink (CPRD), the QResearch database and The Health Improvement Network (THIN). CPRD can provide linked clinical records with secondary care data from the Hospital Episodes Statistics (HES) database and other datasets such as the Index of Multiple Deprivation (IMD) and death registration data from the Office for National Statistics (ONS) (Herrett et al., 2015a). Used together, this information provides a full picture of a patient's healthcare journey. In studying COPD, it enables the researcher to understand the course of the disease, treatments received, and tests performed from diagnosis until death.

4.2.1 Recent advances in COPD research using databases

In 2004, Quality and Outcome Framework (QOF) targets were first set for COPD management. A QOF is a way of ensuring quality of patient treatment strategies in the UK as GPs are paid based on their attainment of the target set (England, 2022). A subsequent bonus of the introduction of these QOFs has been to improve recording of certain measurements of health and disease. Thus, the data available from CRPD has been more complete since their introduction. Outlined in Table 4-1 are the current QOF indicators relevant to COPD.

Therefore, any data analysis that uses these measures or outcomes will likely be more complete and therefore more representative of the wider COPD population. However,

data analysis for other measures may not be as accurate as the recording may be patchy resulting in missing data or the inability to use certain patients due to lack of data.

Indicator	Target recorded
The contractor establishes and maintains a register of patients with COPD	n/a
The percentage of patients with COPD (diagnosed on or after 1 April 2011) in whom the diagnosis has been confirmed by post bronchodilator spirometry between 3 months before and 12 months after entering on to the register	45-80%
The percentage of patients with COPD who have had a review, undertaken by a healthcare professional, including an assessment of breathlessness using the Medical Research Council dyspnoea scale in the preceding 12 months	50-90%
The percentage of patients with COPD with a record of FEV1 in the preceding 12 months	40-75%
The percentage of patients with COPD and Medical Research Council dyspnoea grade ≥3 at any time in the preceding 12 months, with a subsequent record of oxygen saturation value within the preceding 12 months	40-90%
The percentage of patients with COPD who have had influenza immunisation in the preceding 1 September to 31 March	57-97%
The percentage of patients aged 15 or over whose notes record smoking status in the preceding 24 months	50-90%

Table 4-1 COPD QOF indicators
Target recorded shown as a range as payment varies by percentage of target achieved. It should be noted that these indicators were updated in February 2019, introducing two new indicators and retiring two, however as this thesis presents data for the time period of the previous QOF indicators, those will be used here (England, 2022)

4.2.2 Clinical Practice Research Database

The CPRD is a large computerised database of anonymised, longitudinal medical records from a general practice primary care setting in the UK. The CPRD contains data prospectively collected within primary care and is converted into a coded database by the CPRD team.

The original database was formed in 1987 and was significantly smaller than it is today. After changing ownership and names several times, the data is now hosted and managed by the Medicines and Healthcare Products Regulatory Agency (MHRA).

The database is now extremely large, including over 11.3 million patients in 2015, approximately 6.9% of the estimated UK population with records collected from 674 primary care practices throughout the UK. (Herrett et al., 2015b) This database population is considered to be reasonably representative of the demographic characteristics of the UK population and is considered a valid source of data for epidemiological drug safety, but has been used increasingly for pharmacoepidemiology studies. Many studies have used the CPRD to investigate prescribing outcomes in COPD and can be searched for in the CPRD bibliography (MHRA, 2023).

The information recorded in CPRD, as part of routine GP practice, is based on Read codes, and product codes for prescriptions. Read codes are coded clinical terms, maintained by the UK Terminology Centre (UKTC). (Data.gov.uk, 2015) The CPRD recode these Read codes as medical codes in the data. Product codes are unique identifiers of either generic or branded medical products and provide information on formulation and strength. The CPRD organises the data into several files to record

different types of information about the medical services provided in the primary care setting (Table 4-2). The patient records are linked by individual an anonymised patient identification number.

File	Summary of contents
Patient	Basic patient demographics and patient registration details for the patients
Practice	Details of each medical practice, including geographical region
Staff	Medical practice staff details, including type of practitioner
Consultation	Information about the type of consultation enmtered by the GP
Clinical	Contains medical history, including signs, symptoms and diagnosis. Uses Read codes
Additional clinical	Information entered in structured areas of the GP's software, linked to events in clinical file
Referral	Patient referrals to external care centres
Immunisation	Records of immunisations
Test	Records of tests undertaken and the result
Therapy	Details of all prescriptions for medicines and medical appliances

Table 4-2 Summary of the data files available in CPRD
Taken from CPRD GOLD data specification file

The CPRD provides an acceptability indicator for the data to indicate when the practices records were considered to be up to research quality. This assessment is undertaken centrally by CPRD using their own algorithm, essentially using a check list of data quality markers determined as practices periodically submit their patient data for processing.

The CPRD group has obtained ethical approval from a Multi-Centre Research Ethics Committee (MREC) for all purely observational research using CPRD data. However, any studies using the CPRD data which are destined for publication or for which it is intended to communicate the results to third parties, must receive Independent Scientific Advisory Committee (ISAC) approval on the scientific quality of the protocol before proceeding. The protocol for this PhD study was granted ISAC approval on the in October 2018, protocol number 17_047R.

4.2.3 Current COPD research using CPRD

To date, CPRD has been used in several studies for COPD research. One recent study using CPRD to investigate people with COPD was to assess longitudinal incidence rates for community acquired pneumonia (CAP) in COPD patients or risk factors for pneumonia onset (Mullerova et al., 2012) A cohort of COPD patients aged over 45 years, was identified in CPRD between 1996 and 2005, and annual and 10-year incidence rates of CAP evaluated. A nested case-control analysis was performed, comparing descriptors in COPD patients with and without CAP using conditional logistic regression generating odds ratios (OR) and 95% confidence intervals (CI). The COPD cohort consisted of 40,414 adults. During the observation period, 3149 patients (8%) experienced CAP, producing an incidence rate of 22.4 (95% CI 21.7 to 23.2) per 1000 person years.

Boggon *et al* characterised the COPD population in the CPRD database by age, sex, smoking status and severity of COPD. There were a total of 62,747 COPD patients aged 40 or over with at least nine months registration on the COPD register (Boggon et al.,

2013). Of these; 53% were male, 88.2% were current or ex-smokers and the severity of COPD (as determined by FEV_1) can be seen in Table 4-3.

Severity of COPD	% of COPD population
Mild (>80%)	4.3
Moderate (50-79%)	16.6
Severe (30-49%)	32.3
Very severe (<30%)	12.9
Unknown	33.8

Table 4-3 Severity of COPD of all patients in the CPRD database
Severity of COPD as measured by percentage predicted FEV_1

A few studies have used CPRD to review the use of inhaled corticosteroids in COPD; including looking at mortality, adverse events and treatment strategies. Soriano *et al* compared the three year survival rates of COPD patients who used an ICS/LABA combination of fluticasone propionate (FP) and salmeterol with patients who used other bronchodilators, but not an ICS or LABA (Soriano et al., 2002). They found that the FP/salmeterol user's survival at three years was 78.6%, versus 63.3% in the reference group. The authors of this study used a nested case control study for their analysis; matching 1045 patients using FP/salmeterol with 3620 COPD patients who were not. They matched for age, sex, smoking status, history of co-morbities and other respiratory medications used.

An analysis of the risk of non-vertebral fractures amongst FP/salmeterol users in the COPD population using CPRD (Miller et al., 2010), showed no association between the average daily dose of ICS and the odds of a non-vertebral fracture occurring. The authors identified subjects in CPRD that were over 45 years of age, diagnosed between

2003 and 2006 and had over one year of data. They excluded any patient with a history of cystic fibrosis or lung cancer. They used OXMIS and READ codes to identify these patients and matched them to controls from the cohort based on age, gender, number of years in the cohort and GP practice at a ratio of approximately 1:2 (a case-controlled study). They calculated the average daily dose of FP/salmeterol received by analysing prescription records for number of days prescription supplied for and dosing on these days.

Two recent, and relevant study investigated the effect of blood eosinophils on outcomes with ICS use, in terms of exacerbation rates (Oshagbemi et al., 2018, Oshagbemi et al., 2019a). Although this study investigated an overlapping area with this thesis, there were some important methodological differences. These methodological differences are most apparent around the selection of the cohort, and the way use of ICS and exacerbations of COPD were defined; this will be discussed later on in this chapter. In addition, the authors did not investigate lung function as an outcome, which will be a key outcome of this thesis. However, the results of this study provide a useful benchmark for discussion of the results presented in this thesis.

4.2.5 Hospital Episode Statistics

HES data contains records for individual patients to record admissions, outpatient appointments and accident and emergency attendances at English NHS hospitals from 1 April 1989 and outpatient attendance data from 2003 (Digital, 2022). The CPRD data is linked via the anonymous patient identification number to Hospital Episode Statistics (HES) data, for patients registered at practices in England (not the whole UK) who have

consented to this linkage with HES data. The proportion of the UK CPRD that had consented to data linkages including HES in 2015, was 58% (Herrett et al., 2015a)

The HES data records use the International Statistical Classification of Diseases and Related Health Problems, version 10 (ICD-10) clinical coding and Office of Population Censuses and Surveys, Classification of Interventions and Procedures version 4 (OPCS4) procedural coding. Single or multiple episodes may be included in a single hospitalisation (known as a "spell" in HES). The data is arranged in files relating to hospitalisation episodes, and other files for events that are linked to specific episodes such as the primary diagnosis for the hospitalisation, or individual episodes. No details about medicines received at hospital are recorded.

4.2.6 Index of Multiple Deprivation

The IMD contains GP-practice level data about the socio-economic status of the postcode area the GP practice is based in. It is assumed that a patient registered with a particular GP practice lives in the same postcode area; this clearly makes assumptions, however, is a good proxy for determining the socio-economic status of patients. The scale is reported in quintiles, with 1=lest deprived and 5=most deprived.

4.2.7 Office of National Statistics data

ONS data contains details of death registrations in the UK. It is a rich source of data on both the data and recorded cause of death. This allows the researcher to differentiate, for example, between a death from all-causes and that from respiratory illness. Patients registered in the CPRD dataset can be linked to the ONS data to determine date and cause of death.

4.2.8 Suitability of database use in relation to current research questions

The work done by Boggon *et al* shows that there is good recording of demographic data, including lung function tests (Boggon et al., 2013). They found that over 65% of patients had lung function recorded in the database. This along with HES data and GP exacerbation rates are vital for any research into COPD (regardless of using database analysis techniques or primary data collection) as they are currently among the only clinically proven ways of showing benefit from medication. Other measures often used to demonstrate benefit from medication for COPD are patient-reported quality of life, for example using the St Georges Respiratory Questionnaire (SGRQ) score. However, this score is not recorded in the CPRD dataset currently. In addition, since 2004 the introduction of the QOF indicators, including the need to record spirometry) have improved recording of these vital COPD indicators. However, data from prior to 2004 may be less complete.

Both cohort, and nested case controlled studies have been shown to be valid methods of analysing data sets from healthcare databases in multiple studies. (Boggon et al., 2013, Mullerova et al., 2012, Soriano et al., 2002, Miller et al., 2010)

Advantages and disadvantages

CPRD is a rich source of data which includes excellent prescription records and links to secondary care records to enable a full follow up of a patient's treatment. It is possible to tell when a drug was first prescribed, when it was stopped (and often the reason for stopping) and the dose it was prescribed at. However, the limitation here is that it is unknown if the patient took this prescription to be filled and subsequently took the medication in the manor intended on the prescription. Furthermore, only primary care

prescribing data is included, prescribing in secondary care is not available, neither is an emergency supply of medicine acquired at a pharmacy. Therefore, there is the possibility that medicines could be accessed from elsewhere.

One limitation of the CPRD dataset is that all records are manually entered at the time of the healthcare consultation (e.g. by a doctor, nurse or other healthcare professional) and therefore susceptible to human error. The large number of records available and techniques of data-cleaning can minimise the effect this will have on the outcomes. Furthermore, human error will be a random occurrence.

Additionally, the data is intended to be a medical record of treatment and thus not specifically for research, therefore only data that is relevant to the current treatment at the time of recording is available. Hence studies using this data need to be designed to use the data that is available and may have to make compromises and use proxy measures for variables instead of direct measures.

Another disadvantage of this database when used for prescribing data is that prescribing by the GP is not random; the decision to prescribe a certain drug will be influenced by a myriad of factors, including co-morbidities, current drug therapy and patient choice. Therefore, cohort and case-controlled studies carried out in this dataset still fall short of the gold-standard RCT as patients cannot be randomised to a treatment and thus other measures must be used to minimise confounding factors.

Despite these limitations, the large volume of available data outweighs many of these limitations since it allows the impact of any anomalies in the data on the conclusions to be minimised, especially when the conclusions are drawn at a population level.

However, any limitations that may cause bias in the results must be considered when making conclusions and their effect minimised in the study design. Furthermore, the advantage of using CPRD data is that it represents 'real-world' prescribing and outcomes over many years. This is something that cannot be readily replicated in RCTs.

4.3 Aims and objectives

In order to research the relationship between patient factors, such as smoking status, blood eosinophil counts and asthma diagnosis, and outcomes for people with COPD taking ICS, the study cohorts and variables must be defined and characterised in the CPRD dataset. The quality of the available data should be explored to ensure the suitability of this dataset for the research purposes.

This chapter assesses the availability of data for the variables that are believed to effect outcomes of ICS, such as age, severity of COPD, smoking status, asthma co-diagnosis, eosinophil counts and comorbidities, and explore the recording of these outcomes in the dataset. The objectives include:

- To define and justify the data source (CPRD, HES, ONS and IMD data linkage) used in the study
- To define and select the study cohorts (with a COPD diagnosis) from the dataset
- To define the variables in the cohort data related to patient characteristics that are associated with outcomes of ICS use
- To define the outcome measures of ICS use
- To understand the quality and basic characteristics of the variables, outcomes and patient cohorts

4.4 Methods

4.4.1 Study design

This section describes the methods used to define the patient cohort and how variables and outcome measures were derived and developed for each patient, for each year that they were included in the cohort study. The methods used in the cohort study to investigate the primary outcomes of this thesis are described in the individual results chapters five to eight.

Time periods

Patient records from CPRD were extracted in September 2017 and includes data between 1st January 2004 to 31st December 2016. This study period was selected to cover at least a ten-year period, plus its linkages to HES and ONS for which dataset release 16 was available up until 31st October 2014. The IMD data available was from 2010 and 2015. In addition, the earliest date data was extracted from was set at 2004, even though data since 1988 is available. The older CPRD data is less complete and changes in treatments, available medicines and practices have been introduced over time may make conclusions drawn from this data less relevant to current practice.

4.4.2 Selecting the study population

COPD population in CPRD

This study included people with COPD aged over 35 years at first diagnosis who had received at least one prescription for a COPD-related medication within four weeks of this diagnosis and had a spirometry result at any time within their registration in the database.

In order to define a COPD diagnosis in the CPRD database, patients were identified and defined according to numerical codes used by CPRD relating to COPD [appendix 2] in addition to being prescribed at least one medicine from the COPD product list [appendix 3] within four weeks of the diagnostic code. The code list for COPD was developed by searching for terms including “chronic”, “pulmonary”, “respiratory”, “lung”, “bronchitis” and “emphysema”. All COPD related codes from the clinical files were retrieved from the CPRD database. Similarly, the COPD product code list was developed by searching for terms including “bronchodilator”, “corticosteroid” and all inhaled medications, including nebulized medication in the therapy files retrieved from the CPRD database. In addition, the code lists generated were compared and amended based on previous validations of COPD cohort identification in CPRD. (Quint et al., 2014, Rothnie et al., 2016)

From the list of patients defined above, only those that were from up standard (UTS) practices and acceptable on 1st January 2004 were included. The following data files for each patient were extracted, between 1st January 2004 to 31st December 2016 (further detail on these files is available in Table 4-2): patient file, therapy file, clinical file, test file, referral file and additional file.

This data was then be processed to give the final cohort; each patient met the following inclusion criteria:

1. Over 35 years of age at diagnosis
2. At least one year of registration in the dataset before first diagnosis and treatment of COPD
3. Had HES data available (see below for details)

All patients were followed from the index date to the end of the study period unless they were lost to follow-up or died prior to this date. The index date was defined as when a patient entered the study; either the start date of the study period (1st January 2004) or the start of the year when the patient first met the inclusion criteria. The end of follow up date was the date patients exited the study; either the study end date (31st December 2016), or before the start of the year when patients no longer met all of the inclusion criteria. Some patients may have re-entered the cohort if they again met the criteria. Patients were only included for the calendar years when they met the inclusion criteria. For each patient, the time variant study variables were measured repeatedly over each calendar year between 2004 and 2016 for the years that they met the inclusion criteria.

HES, ONS and IMD data linkage

The COPD cohort identified above was linked to the HES, ONS and IMD data. Patients who were treated within the HES consenting practices (a list of HES consenting practices is available from the CPRD) were identified by screening the last 3 digits of the patient identifier (refers to the practice ID) and matching these practice ID's with the HES consenting list. Patients with practice ID's that did not match were excluded. The same was done for ONS and IMD data. Data linkage set 16 from the MHRA was used.

4.4.3 Identifying ICS use in the cohort

Problems in identifying ICS use

There is no acknowledged definition of a person using ICS for COPD, or for other lung diseases due to variation in doses and adherence. Many respiratory patients use ICS for less than 50% of the time and stop using it after only six months of treatment. (Breekveldt-Postma et al., 2004). Other studies have put adherence with ICS at just 30-60% of patients. (Dekker et al., 1993, Jackevicius et al., 1997, van Ganse et al., 1997). Furthermore, compliance with any long-term medicine, such as for conditions such as hypertension and heart disease, is known to be poor. (Caro et al., 1999, Catalan and LeLorier, 2000).

Compliance with a long-term medicine is a complex area and there are many definitions, including 'adherence' and 'persistence'. Adherence with a medication can be defined as a medication possession ratio (MPR) of ≥80%. Persistence may be defined as medication refills consistent with ongoing use of the medication. A way to measure this is by Continuous Measure of Medication Gaps (CMG). A CMG of <20% is considered persistent. This is calculated by subtracting total days' supply obtained throughout study period from total number of days of observation period (gives number of days of treatment gaps); total days of treatment gaps is then divided by number of days of observation period. The mean of each patient's CMG value provides an overall study non-adherence value based on lack of available medication; 0% reflects complete adherence and 100% reflects complete non- adherence. (Raebel et al., 2013) In addition ICS are prescribed at a variety of doses, according to response, with different drugs within the class being of differing potencies. This is similar to the

manner in which opiates are prescribed; therefore, the Daily Defined Dosage (DDD) is also a measure that could be considered for use. This has previously been studied by Svendson et al (Svendsen et al.) in opiate usage and may be a suitable method of assessing the amount of ICS a patient has received over a year.

How ICS use was defined

Given the wide range of adherence to ICS and the complexity in defining it, both the CMG and DDD approaches were used to produce a range of definitions (as outlined in Table 4-4) to allow each group to be investigated separately.

ICS use was defined for each patient for each year they met the cohort criteria above. This was done by developing a code list, including all steroid-containing inhalers, by searching for the drug terms: “beclometasone”, “budesonide”, “fluticasone”, “ciclesonide” and “mometasone” [appendix 5]. In addition, the code list generated was compared and amended based on previous validations of ICS products in CPRD (Oshagbemi et al., 2018). If a patient switched between ICS in a calendar year, this was considered consistent use of ICS.

The specific drug prescribed, and the daily dose were identified. In order to compare daily doses across all of the ICS, an equivalence to beclometasone was calculated using SIGN 2016 asthma guideline as per Table 4-5 (James and Lyttle, 2016). Once all doses were calculated as beclometasone equivalence, the DDD was calculated based on beclometasone dose. The DDD of beclometasone is 0.8mg (WHO, 2017).

Category of ICS use	Definition
Strict ICS user	Over 80% persistence (≤20% CMG) with a prescription in each quarter of the year. OR adherence of: DDD ≥292
Intermediate ICS user	Over 50% persistence (≤50% CMG) with a prescription in at least 3 of the 4 quarters. OR adherence of: DDD ≥182
Wider ICS user	Over 10% persistence (≤90% CMG) in at least one quarter of the year. OR adherence of: DDD >28
Non-ICS user	Less than 10% persistence (≥90% CMG) in no more than one quarter. OR adherence of: DDD ≤28

Table 4-4 Definitions of ICS use
Using the Continuous Measure of Medication Gaps and Daily Defined Dosage methods. Beclometasone equivalence is defined in table 4-5.

Drug	ICS prescribed	Beclometasone equivalence factor
Beclometasone	*All except Fostair and QVAR*	1
	Fostair and QVAR	2
Budesonide	*All except DuoResp*	1
	DuoResp	1.25
Fluticasone	*All*	2
Mometasone	*All*	2
Ciclesonide	*All*	1.25

Table 4-5 Beclometasone equivalence factor
Dose equivalence calculated by multiplying daily steroid dose by the beclometasone equivalence factor (James and Lyttle, 2016).

The strict-, intermediate- and wide-ICS user groups all overlap and thus can be combined in various ways to look at ICS use in a wide versus strict definition, and to compare between, for example low-ICS use and high-ICS use.

4.4.4 Defining lung function

Lung function was recorded using spirometry as FEV_1, either a percentage of the patient's predicted value, or as an absolute value in litres. To be useful, both methods of recording were needed. In order to do this the conversion equations in Figure 4-1. This requires the patients' age, sex and height to be known. For age and sex this was simple as is well recorded in the dataset, however for height there was a significant amount of missing data. Where data was missing for height, population statistics were used to input average height given the patients' age and sex. These equations are not perfect, there is no one agreed method of calculating percentage predicted lung function and all models used rely on using population data to make their predictions.

Male

$FEV_1\ \% = FEV_1 Litres/(height \times (27.63 - (0.112 \times age))/1000)*100$

Female

$FEV_1\ \% = FEV_1 Litres/(height \times (21.78 - (0.101 \times age))/1000)*100$

Figure 4-1 Equations to calculate FEV_1% from FEV_1L
Height measured in centimetres. Based on (deF. BALDWIN et al., 1948)

4.4.5 Defining exacerbations

Defining exacerbations in CPRD

As there is no definitive indicator of a COPD exacerbation in CPRD, proxy markers must be utilised; such as use of antibiotics and oral corticosteroids. Rothnie et al. (2016) produced a validated method of defining a COPD exacerbation in CPRD, which will be used in this thesis. This strategy resulted in a positive prediction value (PPV) of 85.5%

(82.7–88.3%) and a sensitivity of 62.9% (55.4–70.4%). The following combination of approaches gives the most reliable result:

1. Both a prescription for OCS and antibiotics on the same day [appendix 6a and 6b] OR
2. Symptom definition (2 or more or cough, breathlessness, sputum) [appendix 6c] with prescription for either OCS or antibiotic
3. A diagnostic code for an exacerbation of COPD [appendix 6d] OR
4. A diagnostic code for LRTI [appendix 6e]

Defining exacerbations in HES

The number of hospitalisations per year per patient due to a COPD exacerbation were defined in the HES cohort via the use of ICD-10 codes. Only hospital episodes where a COPD exacerbation was listed as the primary cause of the hospitalisation were included. An exacerbation occurring prior to a patient receiving the initial diagnosis of COPD were excluded. The two ICD-10 codes included were:

J44.0: Chronic obstructive pulmonary disease with acute lower respiratory infection

J44.1: Chronic obstructive pulmonary disease with acute exacerbation, unspecified

4.4.6 Defining other variables

Smoking status

Within the CPRD data a patient could be recorded as being: a current smoker, a non-smoker or an ex-smoker. The smoking status was recorded for each patient for each year of their inclusion in the cohort. If they had multiple different statuses recorded for a year, if any of these statuses were ‘current smoker’, the patient was recorded as

a smoker for that year regardless of the other statuses recorded. The number of cigarettes smoked per day was also included, where known.

Eosinophil blood count

Eosinophil blood count was recorded in CPRD, either a percentage of the patients' total white cell count, or as an absolute value in cells/Lx10^9. As both measurements are useful, each was also re-calculated as the other missing measurement. This was done using the equation in Figure 4-2. A patient was defined as having either high or normal eosinophil counts as follows: High eosinophil count = $\geq$0.4/Lx10^9 *or* $\geq$2%; normal eosinophil count = <0.4/Lx10^9 *or* <2%.

Eosinophil% = 100*(eosinophil count/Lx10^9)/(White cell count/Lx10^9)

Figure 4-2 Conversion eosinophil between absolute counts and percentage of WCC

Asthma co-diagnosis

An asthma diagnosis was defined as per Nissen et al. (2017) by the presence of one of the asthma diagnostic codes [appendix 7]. The PPV for asthma diagnosis using only a specific asthma code was reported as 86.4% (95% CI 77.4% to 95.4%). However no sensitivity testing was carried out in this study.

A dummy variable was created to indicate a patient also had asthma if the patient had one recording of an asthma diagnosis during their inclusion in the study.

Comorbidities

There are four methods of measuring comorbidity that are considered to be valid and reliable; the Charlson Index, the Cumulative Illness Rating Scale (CIRS), the Index of Coexisting Disease (ICED) and the Kaplan Index. (de Groot et al., 2003) The Kaplan index was developed for diabetes research, and the CIRS does not consider specific disease diagnosis. The ICED considers both disease severity (mortality) and disability. The Charlson Index is generally used to study mortality but is the most extensively studied commonly used method to create a summary measure of comorbidity. Therefore, the Charlson comorbidity index (CCI) (Charlson et al., 1994, Charlson et al., 1987) was chosen to measure patient comorbidity status in this study at baseline. CCI is a sum of the presence of 17 classes of diseases, weighted according to their association with 1-year all-cause mortality, this is a validated method to predict patient mortality, but was used within this study to indicate the patients' health, which may influence outcomes from COPD. COPD is one of the conditions measured within the CCI, so all patients in this study cohort should have at least one condition identified in their CPRD records. To calculate the Charlson comorbidity score a method used by Khan et al. (2010) was adapted; ICD9 codes were translated into a list of Read codes that could be used to identify these same comorbidities using the CPRD data. The medcodes produced by Khan et al from the Read codes refer to the old GPRD database and therefore had to be converted to the medcodes now used in CPRD [appendix 8]. The Read codes were identified in the *clinical*, *referral* and *consultation* files in the CPRD during the year when the patient was first included in the study period and a dummy variable was created to indicate whether a read code for each condition was present or not. When comorbidity was present, the dummy variable was set to equal one. For each

comorbidity, the dummy variable was multiplied by the assigned index value (weighting) and these added up to form a total score for the year for each patient. The score was then adjusted for age, by the addition of one point for each decade of life over the age of 50 at time of first diagnosis.

Deaths

ONS mortality data was used to determine the date and cause of death. Cause of death was either determined to be all-cause, or respiratory cause, based on the ICD-10 code. Table 4-6 below summarises the ICD-10 codes used.

ICD-10 code	Descriptor
J00-J06	Acute upper respiratory infections
J09-J118	Influenza and pneumonia
J20-J22	Other acute lower respiratory infections
J30-J39	Other diseases of upper respiratory tract
J40-J47	Chronic lower respiratory diseases
J60-J70	Lung diseases due to external agents
J80-J84	Other respiratory diseases principally affecting the interstitium
J85-J86	Suppurative and necrotic conditions of lower respiratory tract
J90-J94	Other diseases of pleura
J95-J99	Other diseases of the respiratory system

Table 4-6 ICD-10 codes for respiratory-cause mortality.

Index of Multiple deprivation

The English Index of Multiple Deprivation from 2010 and 2015 was included. This is a composite measure derived from of a number of indicators covering different aspects ('domains') of material deprivation: housing, employment, income, access to services, education and skills, crime, and living environment. Patients were classified based on the location of their GP practice into one of five quintiles. One being the least deprives and five being the most deprived.

4.4.7 Missing data

It was expected when using healthcare database data, that missing data would be found. Discounting cases that have missing data may introduce bias into the dataset and lose the richness of the data that is the reason for using a large healthcare database in the first place. The missing data was first assessed for its 'missingness', prior to inputting values, to determine if it was missing at random (MAR), missing not at random (MNAR) or missing completely at random (MCAR). This could be done by logistic regression, however this would only be applicable to a continuous variable such as lung function and not sex, smoking status or prescription details and therefore each variable was simply considered in turn whether it was likely to be MAR or MCAR. If data is MCAR then simple imputation methods are suitable to use, whereas if it is MAR then multiple imputation must be used. It was assumed that none of the data was MNAR.

There are many methods of inputting missing data, including simple imputation (such as last observation carried forward, imputing the mean value) and multiple imputation

(van Buuren et al., 1999, Rubin, 1976). It is accepted that multiple imputation using regression analysis is the most accurate method for inputting the missing data in either MAR or MCAR situations, however the remaining data must be complete for this to be most effective and it can therefore only be applied to one variable; in this study this was the lung function. The number of imputations was set at 20 based on the literature above to obtain the best estimate and the Stata MICE command was used to do this.

It was anticipated the missing eosinophil data would be MNAR as patient may have eosinophils measured because it is suspected they are high. Additionally, it was anticipated that a high proportion of eosinophil data would be missing, therefore this data would not be imputed at this stage.

A summary of the imputations methods used is in Table 4-7.

4.4.7 Data analysis

Descriptive statistics were used to describe the baseline characteristics of the cohort and to summarise the characteristics of each variable and outcome. This was then compared with similar database studies and controlled trial studies to determine if the cohort and the methods of dealing with missing data and determining outcome variables, described above, produced valid results. Stata v15 was used for all data analysis.

Variable	How missing data was imputed
Sex	Very few missing, randomly assigned male or female
Height	Population average for sex and age used
Prescription details e.g. dose, frequency	Many were determined from the data already available (e.g. number of doses per inhaler, daily doses prescribed). Otherwise it was assumed that one inhaler would last 28 days
Smoking status	Last observation carried forward or carried backward for each patient year. If a patient never had a smoking status recorded, they were assumed to be a non-smoker
Amount smoked	Last observation carried forward or carried backward for each patient. In cases where this was not recorded, the mean cigarettes smoked per day for the smoking-cohort was imputed
Lung function in year 1	Multiple imputation using regression analysis. Based on sex, age at diagnosis, smoking status, exacerbations per year and ICS use.
Lung function in subsequent years	Multiple imputation using chained equations. Based on sex, age at diagnosis, smoking status, exacerbations per year and ICS use.
Eosinophils	Too much missing data was present, therefore a nested cohort of patients with ≥1 eosinophil recording was created

Table 4-7 How missing data was imputed

4.5 Results

A total of 62,642 people with COPD met the inclusion criteria for the study (Figure 4-3). This accounted for 314,523 patient follow-up years with a median follow-up of four years per patient. The mean age of COPD diagnosis was 66.6 years. 56,784 patients (90.6%) had two years of data, 47,080 patients (75.2%) had three or more years of data included in the study. At five years this dropped to 30,588 (48.9%) and at ten years 5,355 (8.5%). A detailed breakdown of the cohort demographics can be seen in Table 4-8.

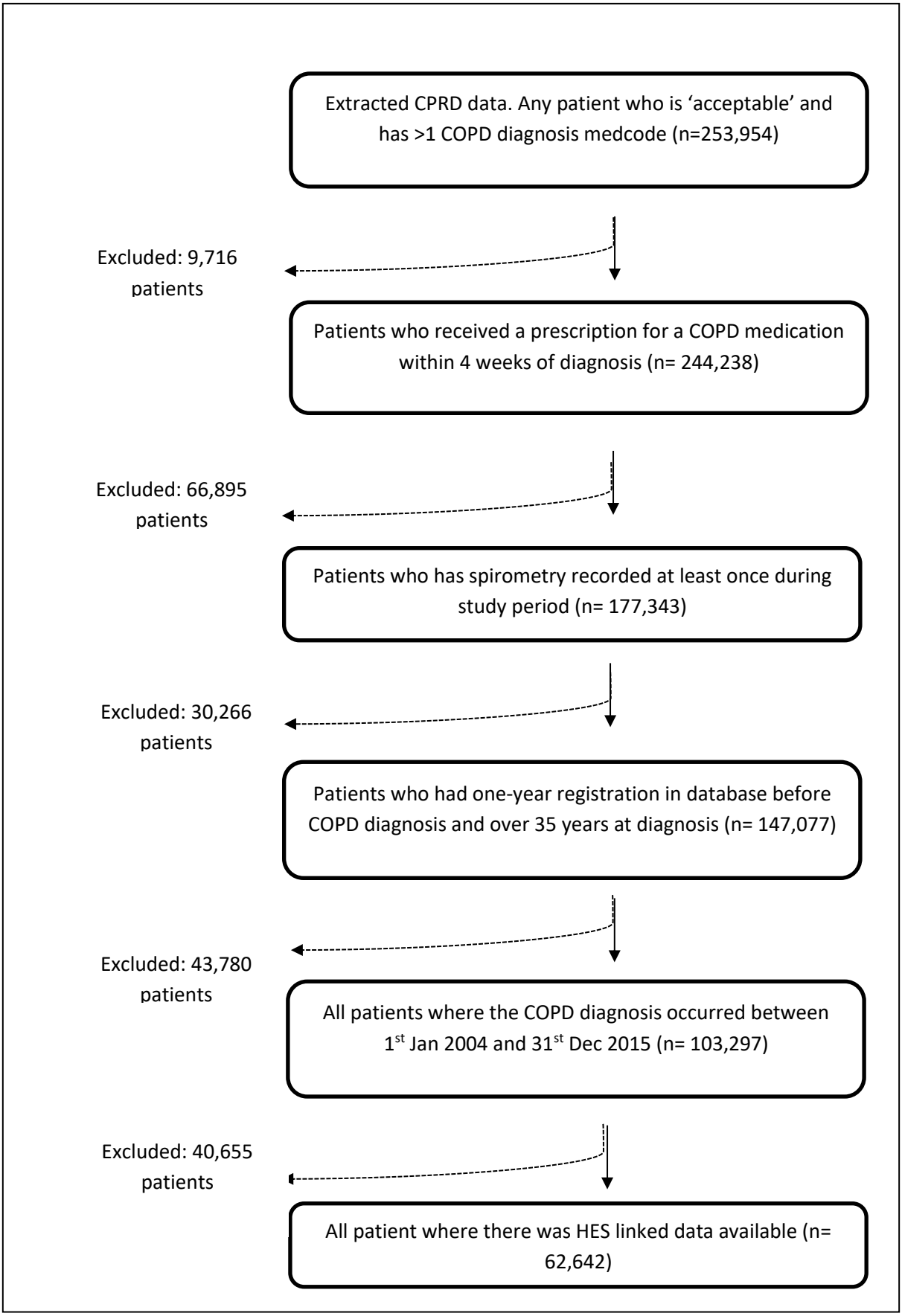

Figure 4-3. Identifying the study cohort

	Mean (S.D/%)
Age at diagnosis	66.6 (11.5)
Sex (female)	30,021 (48.1%)
Years follow up*	4 (3-7)
Baseline lung function	
(% predicted)	63.26 (18.45)
Litres	1.71 (0.68)
Exacerbations per year	
Total	1.24 (1.07)
In community	1.21 (1.02)
Requiring hospitalisation	0.03 (0.023)
Deaths during study period	10,055 (16.1%)
Charlson score at baseline*	4 (2-5)
Asthma diagnosis	28,889 (46.1%)
Smoking status at baseline	
Current smoker	26,904 (42.9%)
Ex smoker	25,428 (40.6%)
Non smoker	10,308 (16.5%)
Amount smoked per day for current smokers	12.99 (11.36)
ICS use at baseline:	
Strict ICS user	16,560 (26.4%)
Intermediate ICS user	4,510 (7.2%)
Wider ICS user	11,515 (18.4%)
Non-ICS user	30,057 (48.0%)
Other respiratory medications at baseline^:	
SAMA	4,770 (7.6%)
LABA	9,076 (14.5%)
LAMA	6,890 (11.0%)
Theophylline	461 (0.7%)
OCS	1,635 (2.6%)

Table 4-8 Demographics of the COPD cohort identified in CPRD

*median, IQR; ^With over 50% persistence per year, except OCS where >28 days therapy per year was included.

4.5.1 Patient variables breakdown

Age

The mean age of the cohort at the time of diagnosis was 66 years (SD 11.5). The lowest age at diagnosis was 35; this was the same as the minimum age to be included in the cohort as below which a diagnosis of COPD would be unlikely. The oldest person to receive a diagnosis of COPD during the study period was 110.

Sex

Recording of sex was missing for 3,805 patients. After random imputation of sex, 30,021 (48.1%) of the cohort were female.

Charlson Score

The median score Charlson co-morbidity index score was 4 (interquartile range 2-5). The histogram in Figure 4-4 shows the distribution of Charlson score in the cohort.

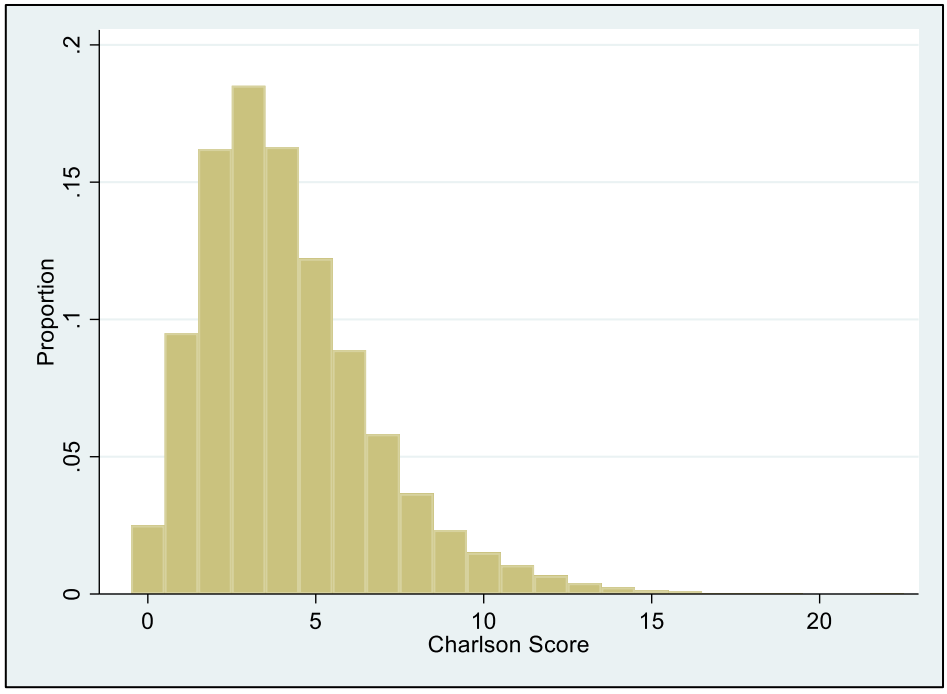

Figure 4-4. Proportion of patients in each Charlson score group at baseline

ICS use

In total, the number of patients with at least one prescription of an inhaled steroid during the study period was 32,585 (52.0%). However only 21,070 (33.6%) of these patients had at least one year of ICS use with over 50% persistence. Of those with 50% persistence, there was a total of 149,225 patient years of ICS use; the mean number of years ICS use was 3.57 (S.D. 2.69). The mean beclometasone equivalent daily dose for all patients with at least one prescription for ICS was 740 micrograms (S.D. 772mcg). The mean for those with over 50% persistence was 1351 micrograms (S.D. 641mcg). There were 16,560 patients who had ICS use with over 80% persistence in their first year of inclusion in the study. Of these patients, the drop-off to less than 80% persistence, or leaving the study, year on year was steady, as demonstrated in Figure 4-5.

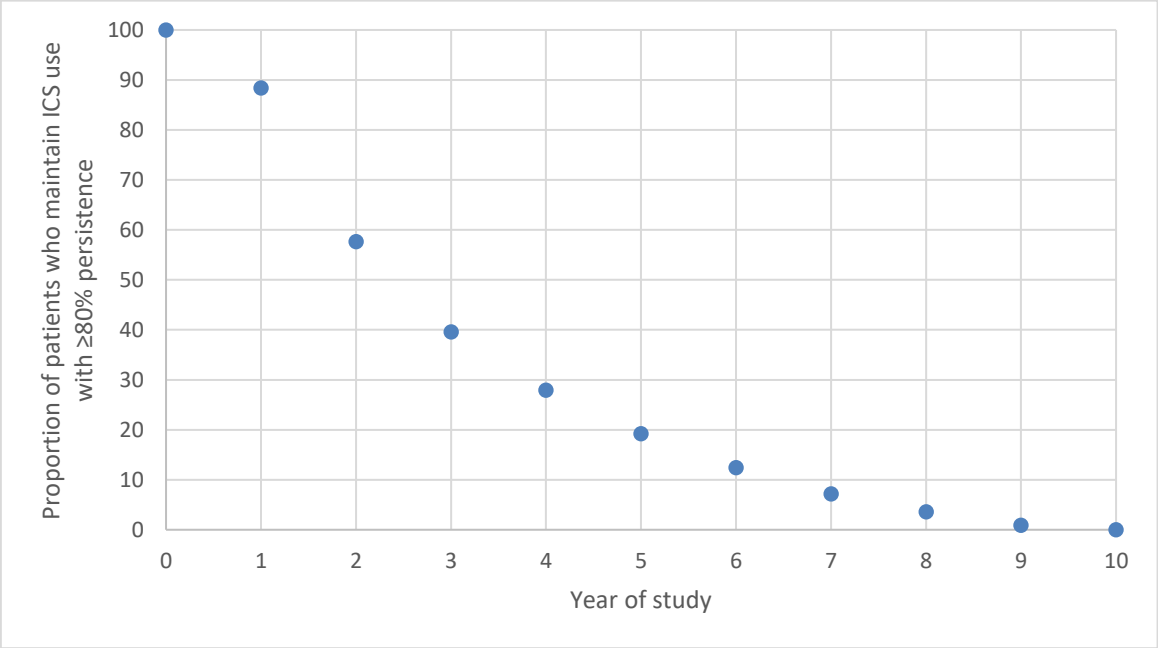

Figure 4-5. Patients maintaining ICS use with 80% persistence or higher year on year
After having an initial persistence of ≥80% at the baseline: either through reduction of persistence or leaving the study

Other medications

As per Table 4-8 all the other categories of medications usually used to treat COPD were prescribed for the cohort. It is important to note that the prescribing of these medications may be alone, or in combination with other inhaled therapies; for example, ICS/LABA or LAMA/LABA combinations. Use of SABA medication, such as salbutamol, was not recorded in this study as it was assumed most patients would be prescribed this and additionally, the use of such medication varies greatly so 'persistence' would not be a meaningful measure.

Smoking status

Smoking status was missing for 22 patients (0.04%), however 26,904 (42.9%) were recorded as smoking at baseline. A further 10,308 (16.5%) were recorded as non-smokers and the remaining patients were ex-smokers. Of the smokers, the mean amount smoked per day was 13.7 cigarettes (SD= 8.61).

Asthma diagnosis

In the cohort, 28,889 (46.1%) people also had an asthma diagnosis at some point during, or prior to, the study.

Eosinophils

There was a significant amount of missing data with regards to eosinophil measurements. There were 28,749 patients (45.9%) who had no eosinophil measurement during the study. This equated to 235,083 patient years (74.7%) with missing eosinophil data.

Lung function

Missing data was also problematic for lung function measurements. FEV_1(% predicted) had 154,651 patient years missing (49.2%); FEV_1(x10^9Litres) had 155,723 patient years missing (49.5%). It should be noted that the data was classified as missing if the patient had no recorded lung function in that year, a year was excluded if the data was missing because the patient had died or transferred out of the study. However, each patient had at least one spirometry recording during the study. Patients who had missing lung function data in year one had this successfully imputed using multiple imputation, details of this are in Table 4-9.

Patient's baseline lung function in terms of severity of their disease, as per GOLD guidance (Vestbo et al., 2013) is in Table 4-10

Measurement	Mean before imputation (S.D.)	Mean after imputation (S.D)
FEV_1 litres Missing = 18,916	1.713 (0.679)	1.706 (0.614)
FEV_1 % Missing = 18,927	63.31 (18.28)	63.38(15.59)

Table 4-9 Mean lung function before and after multiple imputation

Severity of COPD (FEV_1 % predicted)	% of COPD population
Mild (>80%)	12,114 (19.3%)
Moderate (50-79%)	35,632 (56.9%)
Severe (30-49%)	12,342 (19.7%)
Very severe (<30%)	2,554 (4.1%)

Table 4-10. Baseline severity of COPD, as per GOLD classification

Exacerbations

75,461 exacerbations occurred during the study period. Mean total exacerbations per patient per year was 1.24 (SD 1.07). The maximum number of exacerbations a single patient experienced in a single year was 22. Most of these exacerbations (1.21/patient/year) were mild or moderate, being treated in the community.

Index of Multiple Deprivation

At the patient's baseline, the number of patients in each IMD quintile was as per Table 4-11.

Quintile	Number of patients
1 (least deprived)	7,431
2	12,699
3	12,975
4	14,458
5 (most deprived)	15,079

Table 4-11. Number of patients in each quintile of IMD according at their baseline, according to 2010 IMD data.

Deaths and transfers out

There were 10,055 deaths (16.1%) over the study period. The number of deaths and transfers out per year of the study can be seen in Table 4-12 and Figure 4-6.

Year of study	Deaths (cumulative)	Transfer out and deaths (cumulative)
1	1,101	1,101
2	2,706	7,465
3	4,171	17,028
4	5,540	25,534
5	6,681	33,195
6	7,752	39,914
7	8,517	45,721
8	9,114	50,464
9	9,565	54,388
10	9,854	57,576
11	10,000	60,017
12	10,055	61,722

Table 4-12 Cumulative deaths and transfers out of study

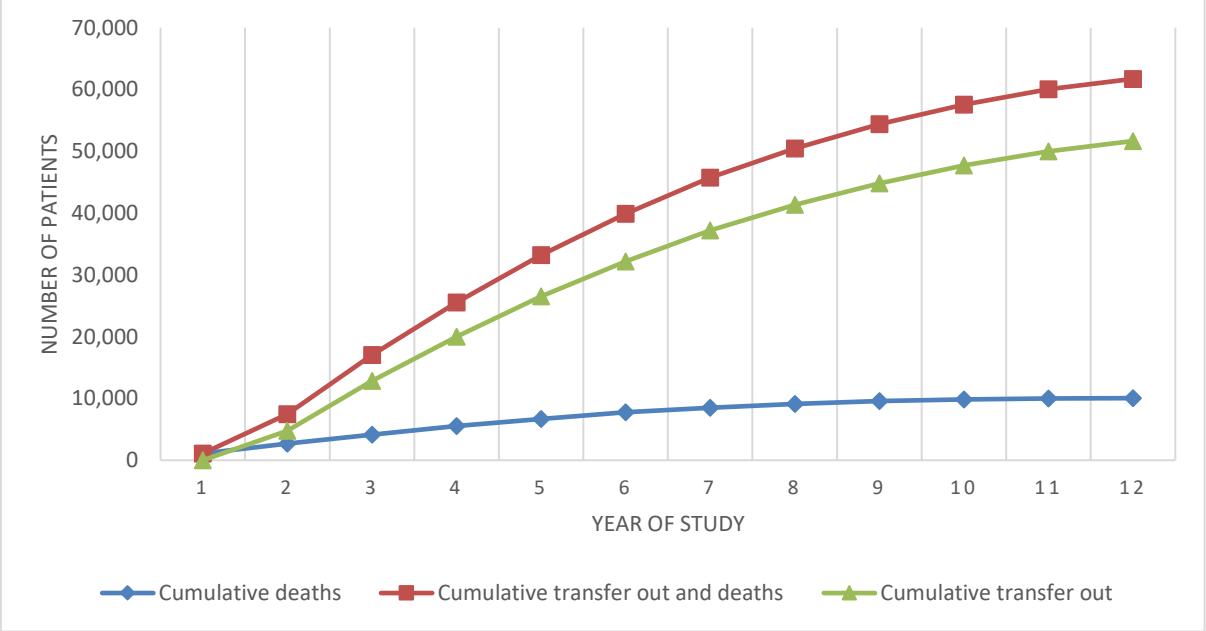

Figure 4-6 Cumulative death and transfers out over the study period

4.6 Discussion

4.6.1 Suitability of using CPRD data

This chapter aimed to define the COPD cohort, variables and outcomes of treatment within the CPRD dataset, to justify its further use for the research proposed in this thesis.

COPD cohort

A cohort of people with COPD, including their primary care data and hospital admission data, has successfully been defined using the CPRD dataset. Data available for each person included; age, sex, medications prescribed, COPD exacerbations per year, hospitalisation for COPD exacerbations, lung function and eosinophil counts. There was also data available on asthma status, smoking status, socio-economic group and co-morbidities. The preliminary investigations of the variables in CPRD for the study cohort showed that a large sample size (62,642 patients) and sufficiently large follow up period of up to 12 years for individual patients was available. Two or more years of data were available for 90% of patients and three or more years of data were available for 75% of patients, which will allow outcomes over an extended time period to be studied later in this thesis. Therefore, the CPRD is a suitable data set for this purpose of this study.

In a similar study by Quint et al. (2014) a similar method was used to define their COPD cohort and ended up with a cohort of 71,780 patients. They found a PPV of 89.4% when a combination of medical code, spirometry and medication was used. The two most notable differences between their cohort and the one presented here are firstly, that

they did not include HES data and thus they have a larger cohort of patients as they were not limited to only patients registered in England. Secondly, the medical codes used to define a COPD diagnosis were more restrictive than those used in this study. Having compared both medical-code lists, there is rationale for either the inclusion or exclusion of some of the codes. For example the codes used in this study include 'COPD follow-up', 'COPD self-management plan given' and other similar terms. Although these codes are not directly diagnostic of COPD, they may capture patients who have COPD (along with spirometry and COPD medications) but have not had a recording of a more definitive diagnosis of COPD by their GP; perhaps because the diagnosis was made elsewhere (e.g. hospital). Other more minor differences include a different time-frame for inclusion of participants in both studies.

In a further study by Whittaker et al. (2019b) using the cohort defined by Quint above, the baseline characteristics of the their cohort compared to the one presented here were similar; for example in terms of the age (66 years) and sex (46.4% female) of the participants. In addition, Whittaker found that the split amongst baseline severity of COPD (in terms of airflow obstruction) was almost identical to that found here.

Additionally a study by Mullerova et al. (2012) using a COPD cohort to investigate exacerbations defined a the cohort in a different way from this study and by Quint, however it still reported similar demographics in terms of smoking status and sex.

In all of the studies discussed above, and the one presented in this chapter, there are variations in asthma diagnosis; ranging from 19% to 46.1%. Much of this variation is due to the difficulty in differentiating an asthma diagnosis from COPD, both in the CPRD data and by doctors themselves. However, this heterogeneity is noted in other

studies, which do not use CPRD data. As identified in the literature review of chapter two (section 2.2.1), the prevalence of asthma is thought to lie between 20-40% of the COPD population, with some reports as high as 66% (Uchida et al., 2018). It can therefore be concluded that the method of defining the COPD cohort used here is consistent with the literature in terms of method used and baseline patient characteristics.

Definition of ICS use

Defining the use of ICS within the CPRD data was challenging; there is currently no literature to support a definitive method. Other studies using CPRD which have used ICS as a study criteria, for example the study by Whittaker et al, discussed above, or Oshagbemi et al. (2019b) used a definition of at least one prescription for ICS in a year or 'current' ICS use versus 'never' use. These are wide definitions and not helpful for the aims of this thesis when considering that all ICS have different potencies and dose regimens. Other studies, outside of CPRD, have indicated that ICS are used by around 50% of the COPD population, in agreement with the results of this study (Price et al., 2014, Burgel et al., 2014). However, no definition of what constituted an user of ICS could be found.

The method presented here to define usage of ICS was based on opioid use, as discussed in method section of this chapter (section 4.4.3) and allows different levels of ICS use (in terms of both adherence and dose received) to be investigated. As there is no agreed definition, it seems sensible to continue with the groupings of: non-user, wider-user, intermediate-user and strict-user of ICS to allow these groups to be compared to each other in terms of the outcomes: lung function, exacerbations and

eosinophil counts. Clinically this is helpful to prescribers as consider their individual patient's usage before making prescribing decisions.

Lung function data availability

As mentioned previously, the breakdown of patients per GOLD classification of airflow restriction broadly matches that reported in other studies. This is important to note as due to missing data, these results were imputed using multiple imputation and it has given a reliable result. In this chapter, missing lung function data was only imputed where needed for the first year of a patient's registration, latter years with missing lung function data will be imputed using the Stata MICE procedure prior to data analysis in subsequent chapters in this thesis.

Definition of COPD exacerbations

The definition of exacerbations used here was as that presented by Rothnie et al. (2016). Overall, the yearly number of exacerbations per patient found in this chapter was near identical to those reported in the widely cited ISOLDE trial (Burge et al., 2000). Furthermore it is comparable to other published literature of 0.5-4 exacerbations per patient per year (Seemungal et al., 2009).

In terms of hospitalisations for a COPD exacerbation, there is limited data on the frequency of exacerbation requiring hospitalisation. It has been reported that 10% of exacerbations require hospitalisation (Donaldson et al., 2008). This would give a prediction of 0.12 hospital exacerbations per patient per year in this study's cohort, approximately four-fold the actual figure. The study reporting 10% was a small study following 109 patients for 4 years and thus the margin for error may be wide. Furthermore, the study presented here has only included a hospital admission for

COPD if it resulted in an in-patient stay, rather than just and A&E admission. There may be some exacerbations that were missed.

Overall the methods of defining a COPD exacerbation in the community and requiring hospitalisation can be considered as producing results consistent with the literature and are suitable for use in the rest of this thesis.

Eosinophil data availability

Due to the high number of missing data and as there are some patients who have never had a measurement of eosinophils reported it was decided it would be inappropriate to impute the missing data here. It was expected that the eosinophil data would be missing, not a random as eosinophils would be more likely to be measured if the doctor suspected the level to be high, thus making multiple imputation inaccurate. Instead, the patients who do have at least one measurement will be treated as a nested cohort when it comes to data analysis in subsequent chapters of this thesis.

Charlson score data

There is variation in the literature as to the expected Charlson Score of people with COPD. It is reported as being around 2.5 in two studies (Echave-Sustaeta et al., 2014, Aramburu et al., 2019) and in another, nearly 90% of patients had a score of 3 or more (Ho et al., 2017). The median score of 4 here seems at the higher end of the literature, however in the first two studies it is unclear if the Charlson score was age-adjusted as it was in this study, which would result in a higher score. Furthermore, it is likely the

method used in this study overestimated the Charlson score because of the use of medcodes as proxies for the comorbidities, rather than any further clinical confirmation of the comorbidity.

IMD availability

It was found that in this cohort, many patients are resident in the more deprived quintiles; 29,537 (47.2%) which was expected. COPD disproportionately affects those of lower socio-economic status due to a higher incidence of smoking and employment where lung diseases are more prevalent (e.g. historic mining). As such, IMD is likely to be a confounding factor in outcomes for those patients with COPD and should be included in all analysis.

4.6.2 Strengths and limitations

A large patient cohort has been identified in this study which will give power to study outcomes from treatment of COPD. In addition, there are many cases where over three years follow up is present; this is beneficial as many of the trials already published investigating outcomes with COPD have been performed for a maximum of three years. All the variables previously identified in the literature review (chapter two) that may affect outcomes to ICS use in COPD were identified from the CPRD data. Although some patient level observations were missing, many were reasonably well recorded such as the patient's age, gender, ICS drug prescribed, and other COPD drugs prescribed.

The main limitation of the CPRD dataset is the lack of availability of eosinophil counts for all patients. Therefore, a nested cohort study of the patients with at least one measurement will be needed. Furthermore, the patchy recording of lung function has meant that methods of imputing the missing values has been undertaken. However, the method of multiple imputation was used to complete the lung function data and as discussed previously is the most accurate way to input missing data and it seems to have given results similar to that achieved in other studies.

Patients' smoking status appears to be reasonably well recorded in the cohort. This was expected since there are QOF points available for having this information recorded for COPD patients. However, a patient may have multiple entries for smoking status as their smoking status changes over time, or they may have their smoking status recorded again in a different year and this will need to be accounted for in subsequent use of the data.

An asthma diagnosis within the cohort is not well defined and seems to be at the higher end of what is found in the literature. There appears to be no more suitable way of defining it currently.

The exacerbations of COPD that were identified in the data can be confidently relied upon, however there may still be exacerbations that could not be identified. This may be due in part to patients keeping 'rescue packs' of antibiotics and steroids at home, ready to take without consulting the GP, should an exacerbation occur. Or could be due to a patient attending A&E for treatment of their exacerbation and neither receiving GP or in-patient care for the episode.

4.7 Conclusion

The CPRD and HES datasets are suitable for use in this research. The overall demographics of the COPD cohort are consistent with the COPD population reported in other studies and there is sufficient follow up time to give meaningful results. The method of defining exacerbations rates also gives results consistent with exacerbations rates reported elsewhere.

Investigating the effect of eosinophil counts on outcomes with ICS therapy will need to use a nested cohort, rather than the full cohort, due lack of recording of eosinophil counts in the dataset. Furthermore, missing lung function data will need to be imputed using chained equations prior to subsequent data analysis.

5. Cohort Study: Random Effects Panel Data Model

5.1 Introduction

Now that a cohort of patients with COPD has been defined within the dataset, modelling can be undertaken to investigate the impact of factors such as an asthma diagnosis, smoking status and eosinophil counts on outcomes from COPD in people using ICS over time. As was identified in the previous chapter, there are some variables, such as ICS usage and smoking that vary considerably over time. Cross-sectional studies, and even repeated cross-sectional studies are unable to fully account for these changes as they make comparisons at specified time points without the acknowledgement that the changes observed at one time-point may be dependant on what was observed a prior time-point. Panel data modelling can account for the variability of variables over time that have an impact on the outcome of interest and the magnitude of that impact by using linear regression.

5.1.1 Panel data

Models for panel data must accommodate the fact that observations for the same patient over time are unlikely to be independent of one another, for example; lung function at year five will be dependent on lung function in the preceding four years. Panel data allows you to control for variables you cannot observe or measure, such as differences in inter-patient physiology or co-morbidities and variables that change over time. There are two panel data models which could be used; fixed-effects or random-effects.

Fixed versus random effects model

The *fixed effect* assumption is that the individual-specific *effects* are correlated with the independent variables. Hence the fixed-effects model should be used whenever analysing the impact of variables that vary over time; this was not the case here, as for example sex and asthma diagnosis will not vary. The rationale behind random effects model is that, unlike the fixed effects model, the variation across entities is assumed to be random and uncorrelated with independent variables included in the model: as there are differences across patient cases that influence the dependent variable (such as patient physiology) then random effects should be used. Another advantage of random effects is that you can include time invariant variables, such as sex.

There is a test to determine if the fixed effects or random effects model should be used; the Hausman specification test. If the test rejects, then random effects model is biased, and fixed effects is the correct model to use. Unfortunately, it is not possible to perform the Hausman test in Stata when there is data included from multiple imputation. Therefore, based on what is known about the variables being studied and because the aim is to understand the amount of variability in the outcomes (lung function, yearly exacerbations and mortality), a random-effects model will be used.

5.2 Aims and objectives

An exploration of the effect of patient variables on the outcomes of COPD over the study period use via random effects panel data analysis.

Patient variables: smoking status, blood eosinophil levels and asthma. Lung function at diagnosis, sex, age at diagnosis, co-morbidities (Charlson index), other COPD medication (LAMA, theophyllines), duration of ICS use, OCS use

Outcomes: lung function (FEV_1), exacerbations per year (in community and requiring hospital treatment), respiratory deaths

Time frame: Panel data model at year 3, 5, 10 after COPD diagnosis or index date

5.3 Methods

The cohort developed in chapter four was used in the cohort study. This was a prospective cohort study design rather than repeated cross-sections as this allows a patient to join the study at any date where they meet the criteria, rather than being censured to a specific date.

All patients with at least one year of data were analysed at year three, five and ten years from their enrolment. This is because panel data looks at a stable cohort over a timeframe; it cannot deal with censured data. Each patient's year of diagnosis was assigned 'year1' to 'yearx' regardless of which calendar year it was. Dependent variables were FEV_1%, exacerbations (hospital and community), respiratory deaths. Independent variables are as described in Table 5-1.

In addition, the nested cohort of patients with at least one blood eosinophil count were also analysed and reported separately.

A sub-group analysis smoking status was performed. Some variables derived from the CPRD data were not time dependent and hence these variables could not be included in the modelling since any variables that are consistent over time are lost during the modelling calculations (during first differencing). To consider the effect of these variables, the model must be repeated for subgroups of the cohort for each time dependent characteristic. The cohort was divided by smoking status (smoker, ex-smoker or non-smoker) and by amount smoked (≥20 cigarettes/day and <20 cigarettes/day).

Outcome measures: Lung function and exacerbations

The "xtreg" command in Stata was used to analyse the data for the lung function and yearly exacerbation dependant variables. The xtreg command fits a regression model to the data. The independent variables were gender, diagnosis age, Charlson score, daily beclomethasone dose, beclometasone persistence, LAMA persistence, SAMA persistence, cigarettes per day, OCS persistence, deprivation score, LABA persistence, theophylline persistence, asthma diagnosis and either yearly exacerbations or lung function.

Outcome measures: Deaths

The "xtprobit" command in Stata was used for the outcome of deaths as it is a binary dependant variable and a probit regression model was therefore needed. The independent variables were gender, diagnosis age, charlson score, daily beclometasone dose, beclometasone persistence, LAMA persistence, SAMA persistence, cigarettes per day, OCS persistence, deprivation score, LABA persistence, theophylline persistence, asthma diagnosis and yearly exacerbations. Lung function could not be included in this model due to the missing data if a person died.

Variable name	Time dependant	Variable description
Gender	No	As recorded by GP surgery in the dataset (1=male; 2=female)
Age of diagnosis	No	Age at time of first recorded diagnosis of COPD in the dataset
Charlson score	No	Charlson Co-morbidity Index
Daily beclomethasone dose	Yes	Inhaled daily steroid dose, converted to a beclomethasone dipropionate equivalent
Persistence	Yes	Adherence to prescribed ICS, as defined by Continuous Measure of Medication Gaps. Reported as percentage (100% = complete adherence to prescribed dosage)
LAMA persistence	Yes	Adherence to prescribed LAMAs, as defined by Continuous Measure of Medication Gaps. Reported as percentage (100% = complete adherence to prescribed dosage)
SAMA persistence	Yes	Adherence to prescribed SAMAs, as defined by Continuous Measure of Medication Gaps. Reported as percentage (100% = complete adherence to prescribed dosage)
Cigarettes	Yes	Estimated number of cigarettes smoked per day, recorded by GP surgery in dataset
OCS persistence	Yes	Adherence to prescribed OCS, as defined by Continuous Measure of Medication Gaps. Reported as percentage (100% = complete adherence to prescribed dosage)
Deprivation index	No	Index of multiple deprivation in England in 2010 by GP practice postcode. Reported as quintiles (1= most deprived, 5= least deprived)
LABA persistence	Yes	Adherence to prescribed LABAs, as defined by Continuous Measure of Medication Gaps. Reported as percentage (100% = complete adherence to prescribed dosage)
Theophylline persistence	Yes	Adherence to prescribed theophyllines, as defined by Continuous Measure of Medication Gaps. Reported as percentage (100% = complete adherence to prescribed dosage)
Asthma	No	Concomitant diagnosis of asthma
Total exacerbations	Yes	Total (community and hospital) exacerbations per year
FEV_1 percent	Yes	Lung function reported as percentage of forced expiratory volume exhaled in one second
Eosinophils	Yes	Blood eosinophil count
Smoking	Yes	Smoking status each year. Classified as: 1=current smoker; 2=ex-smoker; 3=never-smoker

Table 5-1 Explanation of the variables included in the panel data models

5.4 Results

Demographics for the cohort were presented in chapter four.

5.4.1 Lung function

Increased number of co-morbidities (Charlson score), higher socio-economic status (deprivation index), and asthma diagnosis had the largest effect on increasing lung function at 3, 5 and 10 year time points (Table 5-2, Figure 5-1, Figure 5-2).

The variable that had the most significant effect on decreasing lung function was higher number of exacerbations per year. Smoking, increased age at diagnosis and greater COPD medication use were all associated with decreased lung function, but the effect was much smaller.

There was no significant change in effects of the variables at the three time points studied, as shown by the overlapping 95% confidence intervals.

	Three years Patients = 47,080; observations = 91,273. Rho = 0.61001305. R-squared: Overall = 0.0555			Five years Patients = 30,588; observations = 91,388. Rho = 0.64005461. R-squared: overall = 0.0530			Ten years Patients = 5,355; observations = 30,359. Rho = 0.61885813. R-squared: overall = 0.0565		
	Coefficient	95% Confidence interval		Coefficient	95% Confidence interval		Coefficient	95% Confidence interval	
Age of diagnosis	-0.1694618	-0.1849281	-0.1539954	-0.1258613	-0.145328	-0.1063945	-0.0004463*	-0.0473978	0.0465052
Charlson score	0.4021765	0.3343824	0.4699706	0.4419963	0.3543749	0.5296176	0.4615786	0.2382723	0.6848849
Cigarettes	-0.0755995	-0.0876003	-0.0635986	-0.0500906	-0.0621048	-0.0380764	-0.0001396*	-0.0166638	0.0163847
Deprivation index	0.2056164	0.1058782	0.3053547	0.2520569	0.1299467	0.3741671	0.5818456	0.3032306	0.8604606
Asthma	1.666184	1.388766	1.943603	1.660668	1.321341	1.999995	1.973823	1.149005	2.798642
Total exacerbations	-0.8947109	-0.9991816	-0.7902403	-0.6742669	-0.7712606	-0.5772732	-0.4615594	-0.6275514	-0.2955674
Daily beclomethasone dose	-0.0022691	-0.0024349	-0.0021034	-0.0016826	-0.0018353	-0.00153	-0.0011024	-0.0013483	-0.0008566
Persistence	-0.0000813*	-0.0001744	0.0000117	-0.0000693*	-0.0001577	0.0000191	-0.0000658*	-0.0001517	0.0000201
LAMA persistence	-0.0002788^	-0.0004425	-0.0001152	-0.0002032^	-0.0003455	-0.0000609	-0.0034694#	-0.0067368	-0.0002019
SAMA persistence	-0.0110335	-0.0129245	-0.0091424	-0.0051526	-0.0066861	-0.0036191	-0.0044081	-0.0062226	-0.0025937
OCS persistence	-0.0275498^	-0.044097	-0.0110026	-0.0680535	-0.083023	-0.0530839	-0.062455	-0.0808192	-0.0440908
LABA persistence	-0.0090581	-0.011878	-0.0062381	-0.0076308	-0.0098175	-0.0054441	-0.00563^	-0.0091022	-0.0021577
Theophylline persistence	-0.0310612	-0.0427939	-0.0193285	-0.0371145	-0.0468271	-0.0274018	-0.0377394	-0.0519614	-0.0235173

Table 5-2 Random effects panel data model for lung function (FEV_1 percent) outcome at years 3, 5 and 10

p=0.000 unless stated; *=p>0.05; #=p≥0.01; ^=p≥0.001

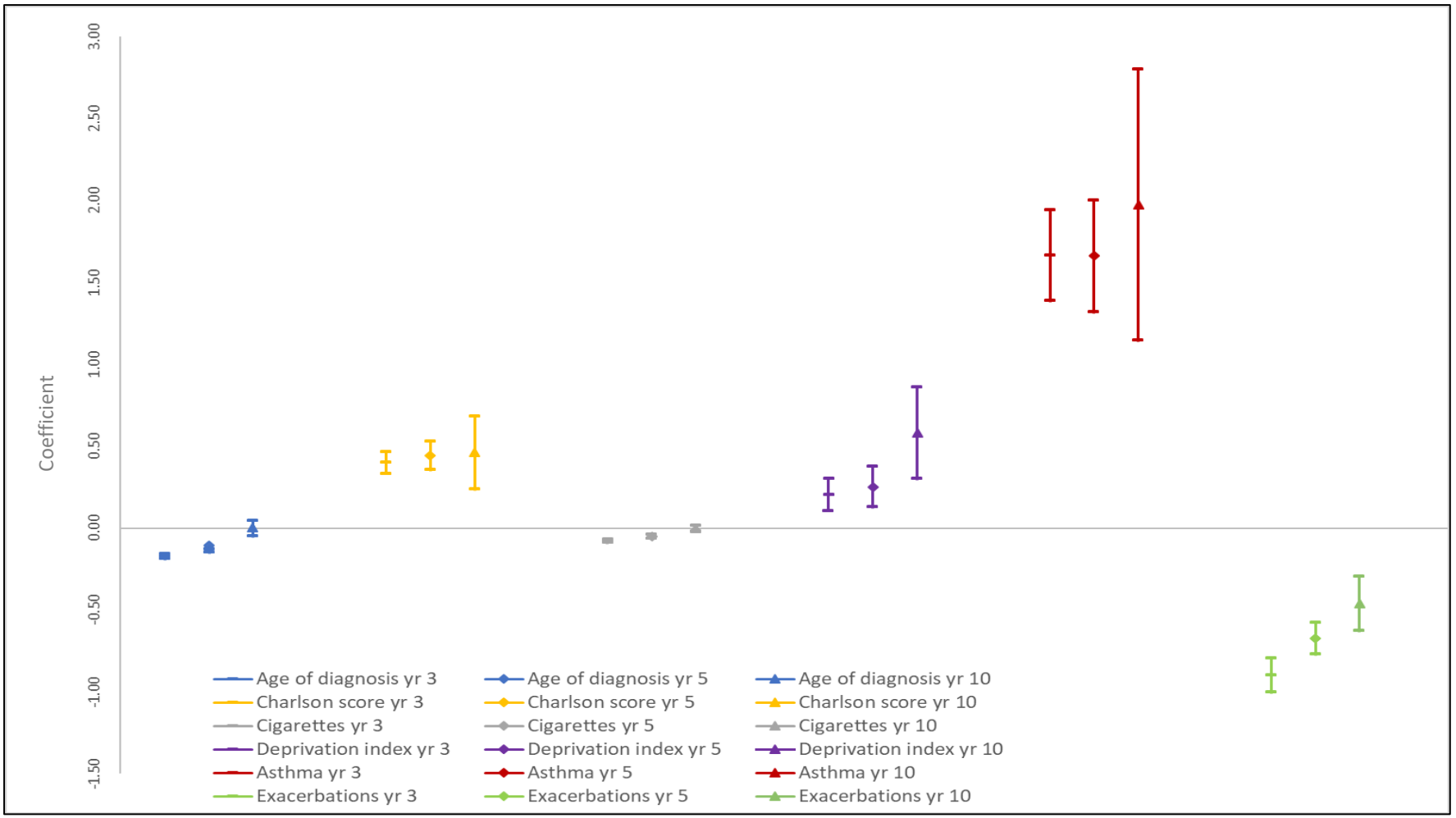

Figure 5-1 Variable coefficients at 3, 5 and 10 years for lung function (FEV_1 percent) outcome.
With 95% confidence interval bars

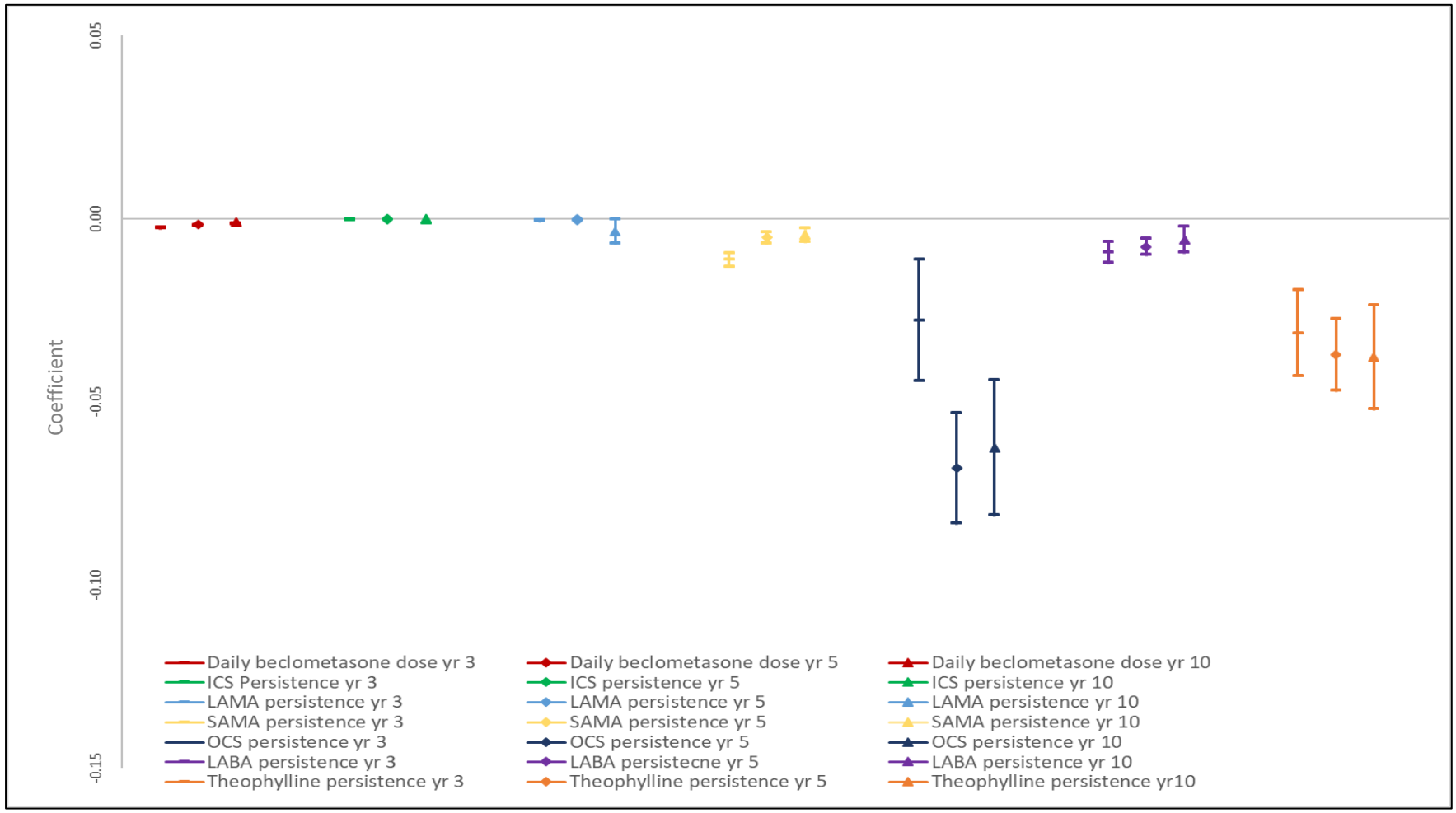

Figure 5-2 Variable coefficients at 3, 5 and 10 years for lung function (FEV_1 percent) outcome.
With 95% confidence interval bars

5.4.2 Exacerbations

All variables, with the exception of increased age at diagnosis and higher lung function, are associated with an increased number of community exacerbations per year (Table 5-3 to Table 5-5, Figure 5-3 and Figure 5-4).

Exacerbations in the community were most affected by Charlson score, deprivation index and asthma diagnosis whereas hospital exacerbations showed little change with any of the variables. On closer examination, asthma diagnosis was associated with more exacerbations in the community and less in hospital, whereas the other variables showed the same direction of exacerbation change for both community and hospital-based exacerbations.

Mostly there is no significant change in the variables over time, however asthma and OCS use did have a significant change from year three to year ten. At year ten, several the variables did not show statistically significant impact on hospital exacerbations.

	Community Patients = 47,080; observations: 91,273. Rho 0.49335035. R-squared: Overall = 0.0351			Hospital Patients = 47,080; observations: 91,273. Rho = 0 .0738377. R-squared: Overall = 0.0152		
	Coefficient	95% Confidence Interval		Coefficient	95% Confidence Interval	
Gender	0.0849322	0.0700913	0.0997731	0.0047617	0.0025634	0.00696
Age of diagnosis	-0.0047379	-0.0055984	-0.0038774	0.0001934^	0.0000641	0.0003228
Charlson score	0.0307931	0.0270462	0.03454	0.0020953	0.0015388	0.0026517
Cigarettes	0.0003575*	-0.0003557	0.0010707	0.0002069^	0.0000847	0.0003291
Deprivation index	0.0123158	0.0068078	0.0178237	0.0015293	0.0007161	0.0023425
Asthma	0.0591044	0.0437235	0.0744852	-0.0088871	-0.0111777	-0.0065965
FEV1 percent	-0.003201	-0.0035854	-0.0028166	-0.0004309	-0.0004961	-0.0003656
Daily beclomethasone dose	0.0000951	0.0000851	0.000105	0.0000151	0.0000134	0.0000168
Persistence	-0.0000001*	-0.0000007	0.0000005	0.0000000*	-0.0000001	0.0000002
LAMA persistence	-0.0000002*	-0.000012	0.0000007	-0.0000001*	-0.0000003	0.0000000
SAMA persistence	0.0003989	0.0002854	0.0005125	0.0000601	0.0000404	0.0000797
OCS persistence	0.0079555	0.0069623	0.0089487	0.0013954	0.0012199	0.0015708
LABA persistence	0.0007558	0.0005868	0.0009249	0.0000328#	0.0000003	0.0000622
Theophylline persistence	0.0014104	0.0007263	0.0020946	0.000308	0.0001961	0.0004199

Table 5-3 Random effects panel data model for community and hospital exacerbations per year up to year 3

p=0.000 unless stated; *=p>0.05; #=p≥0.01; ^=p≥0.001

	Community			Hospital		
	Patients = 30,588, observations = 91388. Rho = 0.48734913. R-squared: overall = 0.0358			Patients = 30,588, observations = 91388. Rho = 0.05538188. R-squared: overall = 0.0148		
	Coefficient	95% Confidence Interval		Coefficient	95% Confidence Interval	
Gender	0.0837456	0.0656848	0.1018064	0.0050258	0.002731	0.0073206
Age of diagnosis	-0.0052718	-0.0063423	-0.0042013	0.0001044*	-0.0000348	0.0002435
Charlson score	0.0350999	0.0303167	0.0398831	0.0013989	0.0007899	0.0020079
Cigarettes	-0.0002355*	-0.0010028	0.0005319	0.0001558#	0.0000274	0.0002843
Deprivation index	0.0179771	0.0113184	0.0246357	0.001291^	0.0004475	0.0021345
Asthma	0.0479737	0.0294006	0.0665468	-0.0074971	-0.00987	-0.0051243
FEV1 percent	-0.0030076	-0.0034161	-0.002599	-0.0005186	-0.0005846	-0.0004526
Daily beclomethasone dose	0.0000868	0.0000769	0.0000966	0.0000149	0.0000132	0.0000165
Persistence	-0.0000000*	-0.0000007	0.0000006	0.0000000*	-0.0000001	0.0000001
LAMA persistence	-0.0000001*	-0.0000106	0.0000007	0.0000000*	-0.0000001	0.0000001
SAMA persistence	0.0001851	0.0000842	0.0002859	0.0000439	0.0000258	0.000062
OCS persistence	0.0071493	0.0061663	0.0081323	0.0012574	0.0010789	0.0014359
LABA persistence	0.0005606	0.0004171	0.0007041	0.0000318#	0.0000006	0.0000575
Theophylline persistence	0.0011485	0.000539	0.0017581	0.0003767	0.0002795	0.0004738

Table 5-4 Random effects panel data model for community and hospital exacerbations per year up to year 5

p=0.000 unless stated; *=p>0.05; #=p≥0.01; ^=p≥0.001

	Community Patients = 5,355; observations = 30,359. Rho = 0.5152202. R-squared: overall = 0.0276			Hospital Patients = 5,355; observations = 30,359. Rho = 0.01557679. R-squared: overall = 0.0184		
	Coefficient	95% Confidence Interval		Coefficient	95% Confidence Interval	
Gender	0.1159546	0.0731185	0.1587907	0.0027394*	-0.0014334	0.0069122
Age of diagnosis	-0.006741	-0.0093957	-0.0040863	-0.0000856*	-0.0003512	0.0001799
Charlson score	0.0396604	0.0270658	0.052255	0.0013062#	0.0000783	0.0025341
Cigarettes	0.0001849*	-0.0009113	0.0012811	-0.0000467*	-0.0002568	0.0001633
Deprivation index	0.0247243#	0.0090091	0.0404395	0.002745	0.0012161	0.0042739
Asthma	-0.0053507*	-0.0518715	0.0411701	-0.0052914#	-0.0097933	-0.0007894
FEV1 percent	-0.0018384	-0.0025692	-0.0011076	-0.0006284	-0.000747	-0.0005097
Daily beclomethasone dose	0.0000585	0.0000423	0.0000747	0.0000113	0.0000008	0.0000142
Persistence	0.0000000*	-0.0000007	0.0000005	0.0000000*	-0.0000001	0.0000001
LAMA persistence	0.0003144#	0.0000971	0.0005317	0.0001144	0.0000716	0.0001572
SAMA persistence	0.0001469#	0.000026	0.0002678	0.0000414^	0.0000172	0.0000656
OCS persistence	0.0007882*	-0.0004389	0.0020153	0.0013715	0.0011215	0.0016214
LABA persistence	0.0003928^	0.0001621	0.0006236	0.0000126*	-0.0000324	0.0000575
Theophylline persistence	0.0005857*	-0.0003385	0.00151	0.0003703	0.0002228	0.0005179

Table 5-5 Random effects panel data model for community and hospital exacerbations per year up to year 10
p=0.000 unless stated; *=p>0.05; #=p≥0.01; ^=p≥0.001

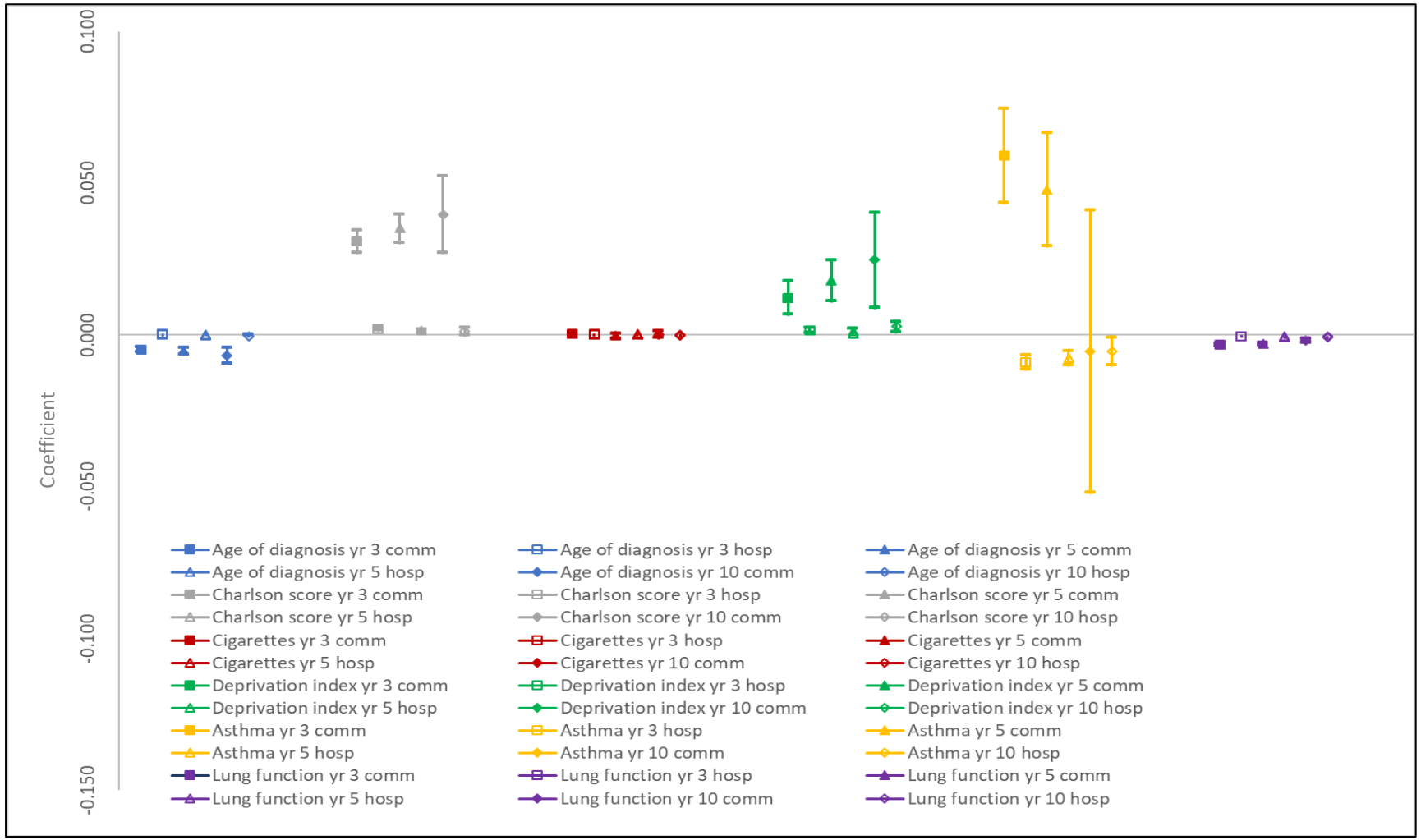

Figure 5-3 Variable coefficients for community and hospital exacerbations at 3, 5, and 10 years.
With 95% confidence interval bars

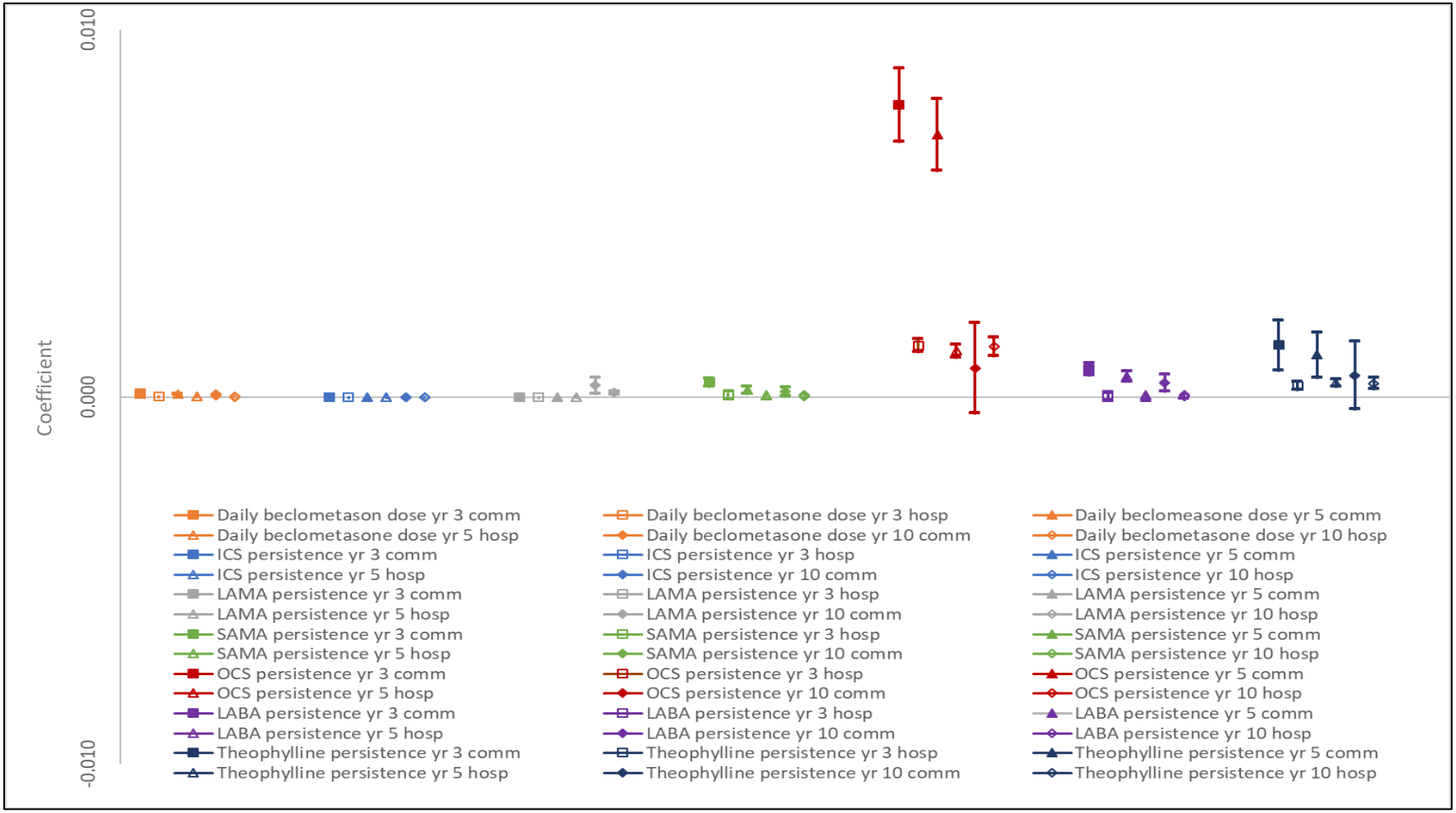

Figure 5-4 Variable coefficients for community and hospital exacerbations at 3, 5, and 10 years.
With 95% confidence interval bars

5.4.3 Respiratory deaths

Lower risk of respiratory death is associated with: being a non-smoker, higher socio-economic status (deprivation index), and asthma co-diagnosis (Table 5-6, Figure 5-5and Figure 5-6). Higher risk of respiratory death is associated with increased co-morbidities (Charlson score) and increased age at diagnosis.

Increased yearly exacerbations seemed to be associated with less deaths at year 3, but this was not statistically significant by year ten. COPD medication in general did not show any statistically significant effect on respiratory deaths.

Other than asthma diagnosis and yearly exacerbations, the effect of each variable does not change at each time point.

	Three years Patients = 59,215; observations = 161,133. Rho = 0.9900304.			Five years Patients 55,894, observations 218,626. Rho = 0.9955228			Ten years Patients = 27,690, observations = 164,732. Rho = 0.9923006.		
	Coefficient	95% Confidence interval		Coefficient	95% Confidence interval		Coefficient	95% Confidence interval	
Gender	-0.8083786	-0.9282171	-0.6885402	-0.5795897	-0.6897954	-0.469384	-0.5259726	-0.6451854	-0.4067599
Age of diagnosis	0.0531097	0.0458726	0.0603468	0.0551737	0.0475478	0.0627995	0.0762608	0.0678782	0.0846433
Charlson score	0.2478861	0.2215281	0.2742441	0.0867717	0.065823	0.1077203	0.168646	0.1416649	0.1956271
Smoking status	-0.2097685	-0.2757523	-0.1437848	-0.1879516	-0.2464467	-0.1294565	-0.1512266	-0.2161486	-0.0863047
Deprivation index	-0.138197	-0.1826995	-0.0936944	-0.053604#	-0.091638	-0.0155699	0.0479301#	0.0049296	0.0909305
Asthma	-1.548502	-1.689118	-1.407886	-0.7861339	-0.9022848	-0.6699829	-0.3635451	-0.4848974	-0.2421928
Total exacerbations	-0.1390221	-0.1999234	-0.0781209	-0.0775165#	-0.129259	-0.025774	0.0301719*	-0.0193978	0.0797416
Daily beclomethasone dose	0.0001183#	0.0000332	0.0002035	0.0000006*	-0.0000657	0.0000773	0.0000597*	-0.0000123	0.0001317
Persistence	-0.0001292*	-0.0007081	0.0004497	0.0000006*	-0.0001106	0.0001218	0.0001275*	-0.0001861	0.0004411
LAMA persistence	0.0000009*	-0.0000626	0.0000811	0.0000004*	-0.0001256	0.0001334	0.000008*	-0.0000702	0.000087
SAMA persistence	0.0001611*	-0.0008676	0.0011899	0.0001201*	-0.0006006	0.0008408	-0.0000491*	-0.0007669	0.0006687
OCS persistence	0.0192975	0.0088042	0.0297908	0.001452*	-0.0046894	0.0075934	0.0013461*	-0.0047329	0.0074251
LABA persistence	-0.0036017	-0.0053935	-0.00181	-0.0011305*	-0.0025117	0.0002507	0.0001645*	-0.0010755	0.0014045
Theophylline persistence	-0.009431#	-0.0173568	-0.0015053	-0.00018*	-0.0064753	0.0061154	0.0013339*	-0.003202	0.0058698

Table 5-6 Random effects panel data model for respiratory-cause deaths at years 3, 5 and 10
p=0.000 unless stated; *=p>0.05; #=p≥0.01; ^=p≥0.001

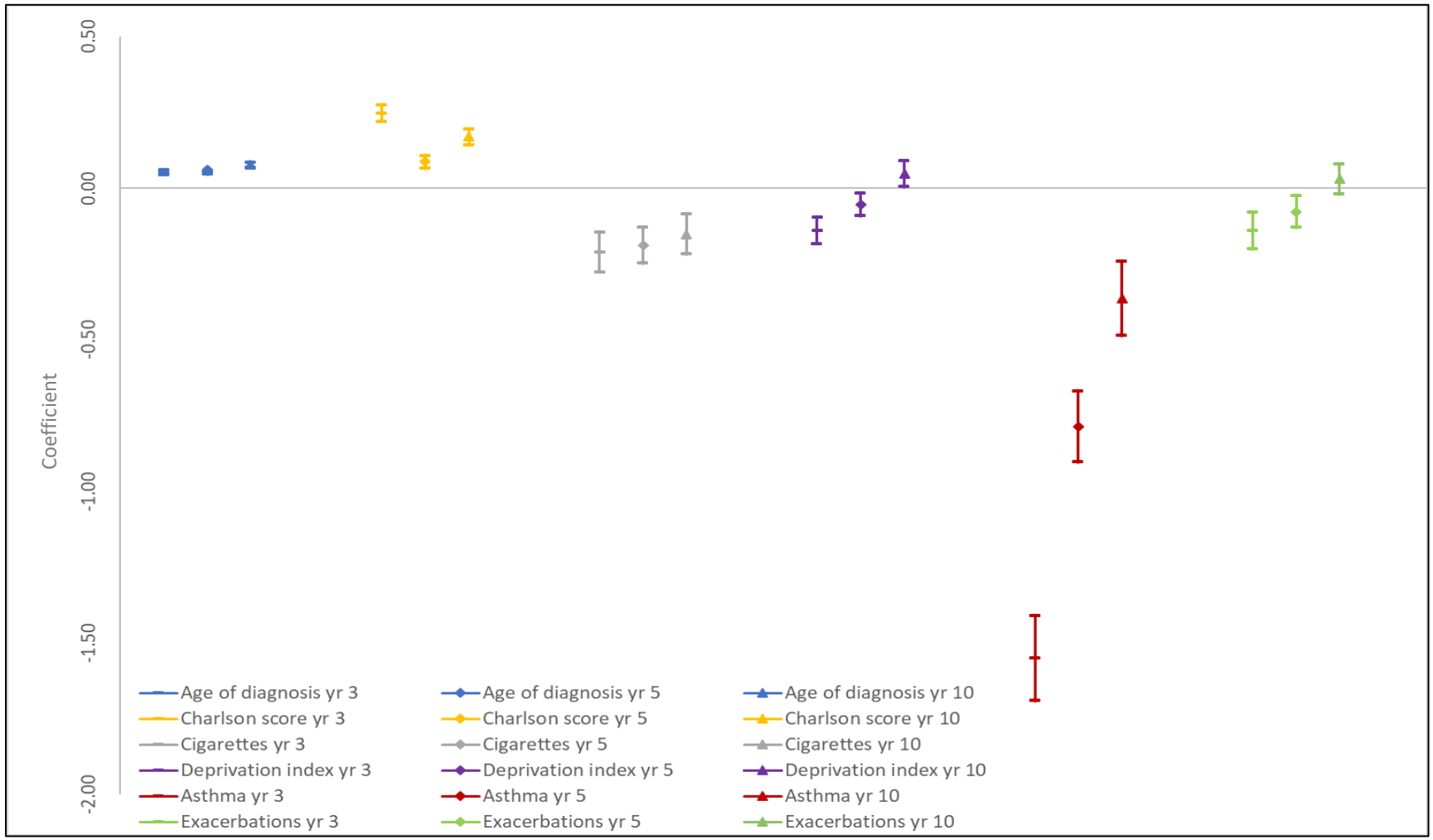

Figure 5-5 Variable coefficients for respiratory-deaths at 3, 5, and 10 years.
With 95% confidence interval bars

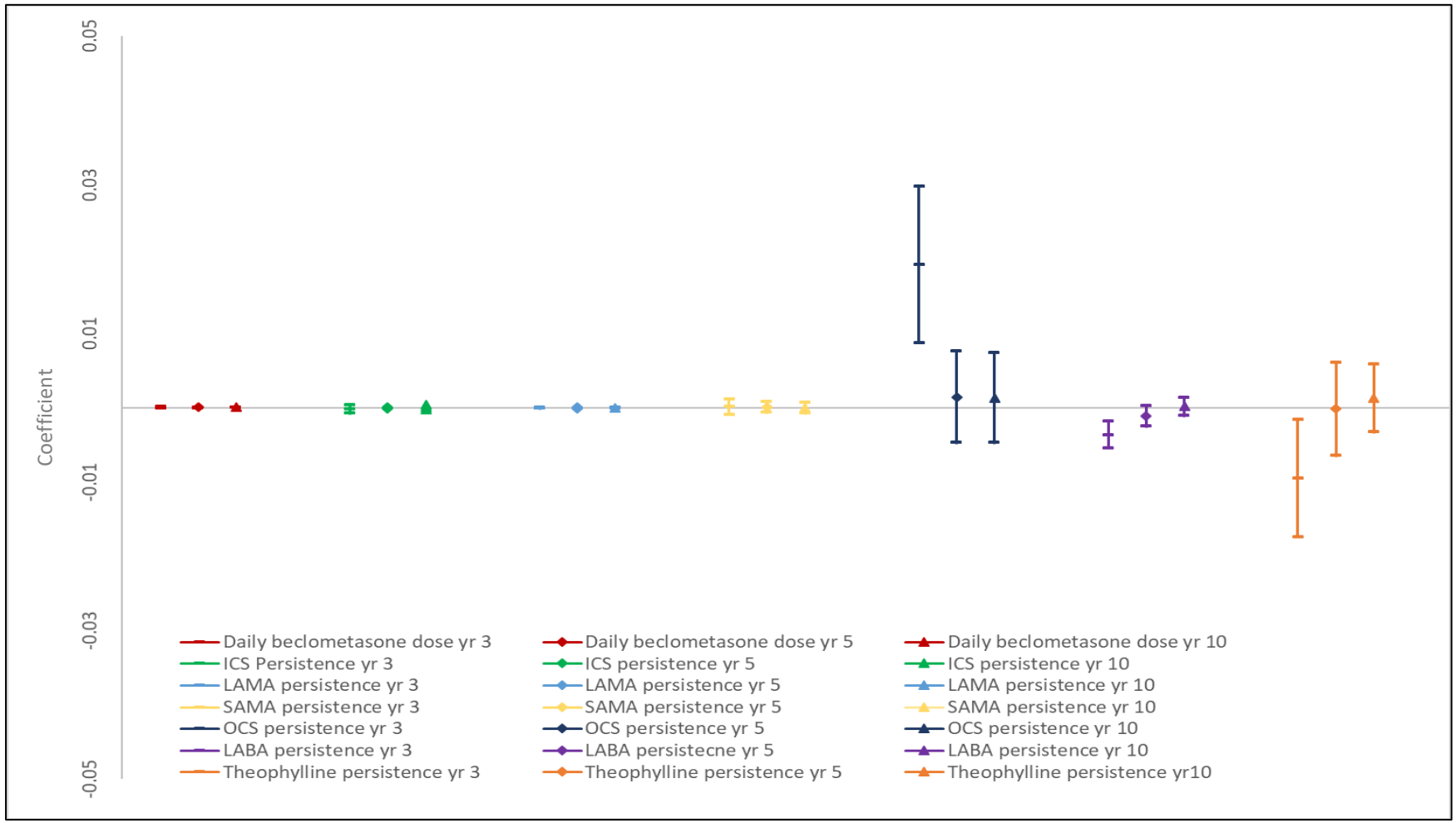

Figure 5-6 Variable coefficients for respiratory-deaths at 3, 5, and 10 years.
With 95% confidence interval bars

5.4.4 Nested Eosinophil cohort

As shown previously in this chapter, the majority of the effect seen from each variable on lung function, exacerbations and respiratory deaths did not change significantly at each time-point studied. Therefore, the five-year panel was used to investigate the nested-eosinophil cohort. The demographics of this cohort can be found in chapter four.

The nested eosinophil cohort showed that increased blood eosinophil count does not have a statistically significant impact on lung function or total yearly exacerbations (Table 5-7)

Including eosinophils in the model increases the effect asthma diagnosis has on lung function and yearly exacerbations in comparison to the five-year panels without eosinophils in Table 5-2 and 5-4 (2.19% versus 1.66%; 0.06 versus 0.05 respectively). Additionally, the negative effect increased cigarette smoking has on lung function and exacerbations is also increased (-0.11% versus -0.05%; -0.0004 versus -0.0002 respectively). The rest of the variables were mostly unchanged.

	Lung function Patients = 12,803; observations = 27,076. Rho = 0.72148279. R-squared: overall = 0.0597			Total exacerbations Patients = 12,803, observations = 27,076. Rho = 0.59067467. R-squared: overall = 0.0461		
	Coefficient	95% Confidence Interval		Coefficient	95% Confidence Interval	
Eosinophils	0.0531714*	-0.0122428	0.1185856	0.0003267*	-0.0042763	0.0049298
Gender	3.664594	3.091312	4.237877	0.0473129^	0.0147963	0.0798294
Age of diagnosis	-0.1074302	-0.1419011	-0.0729594	-0.0056492	-0.0076094	-0.003689
Charlson score	0.3820087	0.2428777	0.5211397	0.0383952	0.0305465	0.0462439
Cigarettes	-0.106238	-0.1343347	-0.0781412	-0.000358*	-0.0021249	0.001409
Deprivation index	0.4218906	0.2134176	0.6303636	0.0312153	0.0194365	0.0429942
Asthma	2.186211	1.595748	2.776673	0.0581301^	0.0245656	0.0916946
Total exacerbations	-0.6394731	-0.8235263	-0.45542	n/a	n/a	n/a
FEV1 percent	n/a	n/a	n/a	0.0001076	0.0000899	0.0001254
Daily beclomethasone dose	-0.0014831	-0.0017592	-0.0012069	0.0001815	0.0000409	0.0003221
Persistence	-0.0042858	-0.0064485	-0.002123	-0.0031537	-0.0039045	-0.002403
LAMA persistence	-0.0005841#	-0.0010708	-0.0000975	0.0000114*	-0.0000176	0.0000403
SAMA persistence	-0.0015831*	-0.0038712	0.0007051	-0.0000008*	-0.0001596	0.0001441
OCS persistence	-0.0607556	-0.081607	-0.0399043	0.0063794	0.0050118	0.0077469
LABA persistence	-0.0112656	-0.015913	-0.0066183	0.0005109^	0.0002094	0.0008123
Theophylline persistence	-0.051678	-0.0704055	-0.0329505	0.0018507^	0.00068	0.0030214

Table 5-7 Random effects panel data model for FEV_1% and total exacerbations up to year 5 in the nested eosinophil cohort
p=0.000 unless stated; *=p>0.05; #=p≥0.01; ^=p≥0.001

5.4.5 Smoking status breakdown

In the previous sections of this chapter, the variables that were shown to have most impact on COPD outcomes were: age at diagnosis, Charlson score, deprivation index, asthma diagnosis and smoking. Smoking status has been investigated further in this section due to the different methods of recording it. As in the previous section, the five-year panel was used to investigate further the effect of smoking.

Due to the nature of inhaled steroids, patients can be taking vastly different doses (unlike the other inhaled medications) and as already demonstrated in previous chapters, adherence to ICS is variable. Therefore, it is of more use to study the average beclomethasone daily dose a person is taking over a year. This can be calculated from the daily beclomethasone dose (as prescribed) and persistence (percentage of the year the patient has received a prescription for) as follows:

$$\frac{\text{(Daily beclomethasone dose x persistence)}}{100}$$

The average daily beclomethasone doses for smokers, ex-smokers and non-smokers were 657mg, 748mg and 722mg respectively.

5.4.5.1 Lung function

Smokers had a larger decrease in lung function as average daily beclomethasone dose, LABA and OCS use increased than non-smokers, however these effects were very small. Conversely, greater LAMA and LABA use were associated with less decline in lung function in smokers than non-smokers. In all cases, the 95% confidence intervals for

each variable, when comparing smokers and non-smokers overlapped, meaning that there may be no true difference (Table 5-8, Figure 5-7 and Figure 5-8)

	Smoker Patients = 14,009; observations = 34,598. Rho = 0.62964825. R-squared: overall = 0.0615			Ex-smoker Patients = 6,131; observations = 12,686. Rho = 0.60175441. R-squared: overall = 0.0357			Non-smoker Patients = 17,017; observations = 44,104. Rho = 0.68935327. R-squared: overall = 0.0362		
	Coefficient	**95% Confidence interval**		**Coefficient**	**95% Confidence interval**		**Coefficient**	**95% Confidence interval**	
Age of diagnosis	-0.2330928	-0.2629862	-0.2031994	-0.1135959	-0.1574531	-0.0697387	-0.0952827	-0.124423	-0.0661424
Charlson score	0.5678316	0.430025	0.7056382	0.1887354*	-0.0082927	0.3857636	0.3583128	0.2357006	0.480925
Deprivation index	0.2797383^	0.0974093	0.4620673	0.362659#	0.0765533	0.6487646	0.2120993^	0.0379353	0.3862634
Asthma	0.9854515	0.4723082	1.498595	0.1136437*	-0.7224529	0.9497403	1.413815	0.9344298	1.893201
Total exacerbations	-0.6898515	-0.8454957	-0.5342073	-0.9110132	-1.190225	-0.6318012	-0.7436562	-0.8845913	-0.602721
Mean daily beclomethasone dose	-0.0006464	-0.0007903	-0.0005025	-0.000043*	-0.000087	0.0000016	-0.0002772	-0.000368	-0.0001864
LAMA persistence	-0.0002299#	-0.0004298	-0.00003	-0.0002973*	-0.0006746	0.0000799	-0.0003234^	-0.0005844	-0.0000625
SAMA persistence	-0.0051103	-0.0074149	-0.0028056	-0.0115915	-0.0167306	-0.0064523	-0.0047756	-0.0071029	-0.0024484
OCS persistence	-0.1279273	-0.1612405	-0.0946142	-0.0606539^	-0.095417	-0.0258908	-0.0623658	-0.0820812	-0.0426504
LABA persistence	-0.0101626	-0.0134325	-0.0068928	-0.0211351	-0.0278225	-0.0144477	-0.0148544	-0.0183475	-0.0113613
Theophylline persistence	-0.0471066	-0.0620898	-0.0321233	-0.0315569#	-0.0568132	-0.0063007	-0.0429209	-0.0579053	-0.0279365

Table 5-8 Random effects panel data model by smoking status for lung function (FEV_1%) up to year 5

p=0.000 unless stated; *=p>0.05; #=p≥0.01; ^=p≥0.001

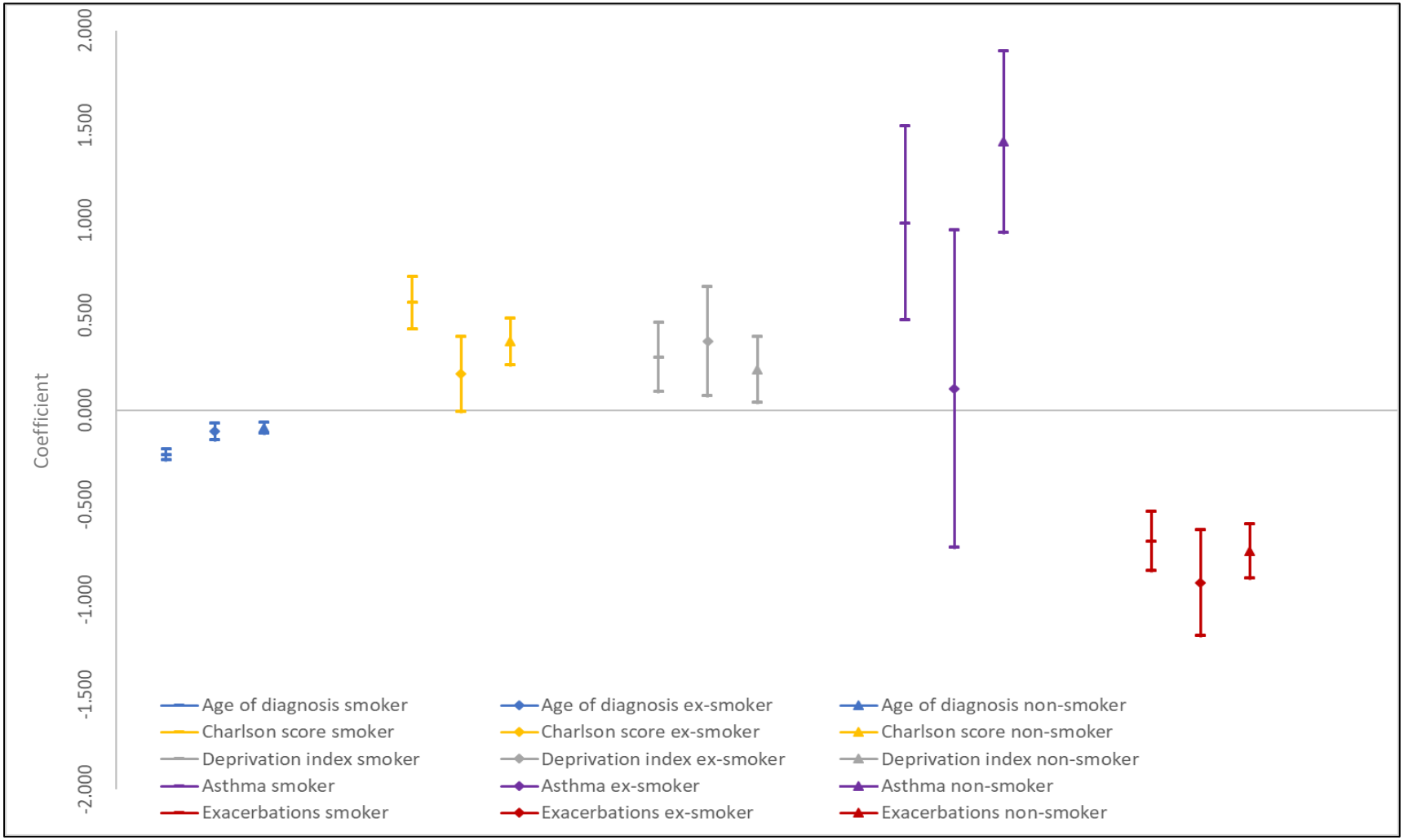

Figure 5-7 Variable coefficients by smoking status for lung function at year 5

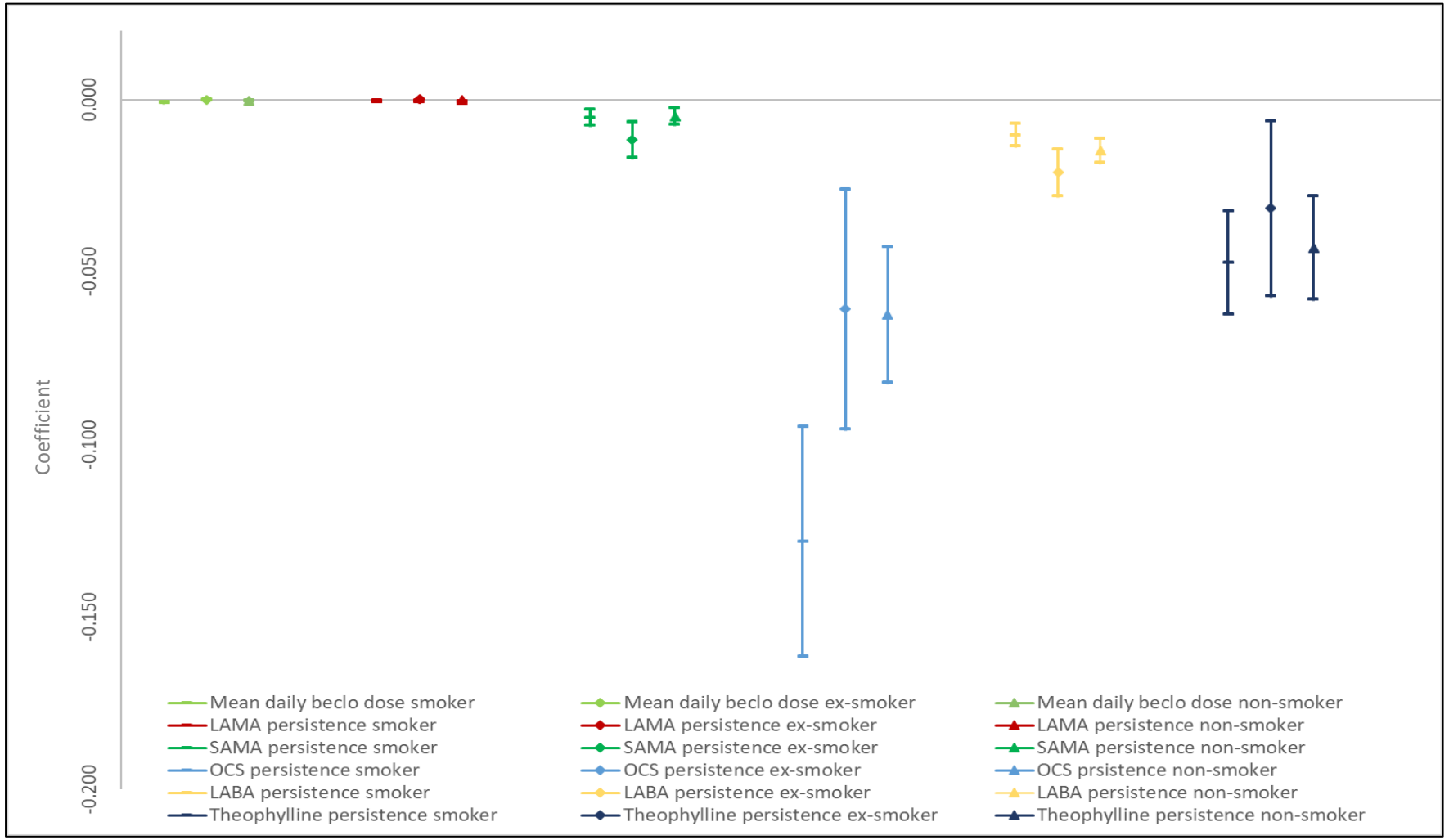

Figure 5-8 Variable coefficients by smoking status for lung function at year 5

5.4.5.2 Exacerbations

For people who smoke, increasing average daily inhaled beclomethasone dose and OCS persistence, is linked to a higher exacerbation rate than those that do not smoke. However, the result is very small and the 95% confidence intervals overlap so there may be no true difference (Table 5-9, Figure 5-9 and Figure 5-10).

Those that had asthma exacerbated more frequently despite being ex- or non-smokers and taking a higher average daily inhaled steroid dose than smokers. Again, the 95% confidence intervals are overlapping, so there may be no true effect.

5.4.5.3 Respiratory deaths

The majority of the variables show no statistically significant effect on respiratory deaths in smokers, ex-smokers or non-smokers (Table 5-10).

	Smoker Patients = 14,009; observations = 34,598. Rho = 0.4248232. R-squared: overall = 0.0435			Ex-smoker Patients = 6,131; observations = 12,686. Rho = 0.50834329. R-squared: overall = 0.0365			Non-smoker Patients = 17,017; observations = 44,104. Rho = 0.52875926. R-squared: overall = 0.0337		
	Coefficient	95% Confidence interval		Coefficient	95% Confidence interval		Coefficient	95% Confidence interval	
Gender	0.1268368	0.0991666	0.1545071	0.023725*	-0.0208147	0.0682647	0.0734993	0.0471563	0.0998424
Age of diagnosis	-0.0061383	-0.0078091	-0.0044675	-0.0036384^	-0.0061835	-0.0010933	-0.0035753	-0.0051927	-0.0019579
Charlson score	0.0438911	0.0362356	0.0515466	0.038882	0.0274808	0.0502832	0.0316618	0.0248826	0.038441
Deprivation index	0.0095959*	-0.0005379	0.0197296	0.022455^	0.0058906	0.0390193	0.0252405	0.0156167	0.0348644
Asthma	0.0441449^	0.0155468	0.072743	0.1242117	0.0757103	0.172713	0.0537942	0.0272342	0.0803541
Lung function	-0.0036711	-0.0043535	-0.0029887	-0.0038036	-0.0048759	-0.0027312	-0.0038833	-0.0044794	-0.0032872
Mean daily beclomethasone dose	0.0000468	0.0000369	0.0000568	0.0000002*	-0.0000027	0.0000031	0.000022	0.0000158	0.0000281
LAMA persistence	-0.0000001*	-0.0000129	0.0000128	0.0000089*	-0.0000146	0.0000326	-0.0000079*	-0.0000241	0.0000083
SAMA persistence	0.0002315^	0.0000727	0.0003902	0.000241*	-0.0000782	0.0005601	0.0001699#	0.000015	0.0003247
OCS persistence	0.0181278	0.0158924	0.0203632	0.0070502	0.0048749	0.0092254	0.0069234	0.005594	0.0082528
LABA persistence	0.000378^	0.0001507	0.0006053	0.0012521	0.0008384	0.0016659	0.0011022	0.0008725	0.0013319
Theophylline persistence	0.0021785	0.0012003	0.0031567	0.0017818#	0.0002611	0.0033025	0.0017389	0.0007925	0.0026854

Table 5-9 Random effects panel data model by smoking status for total exacerbations up to year 5

p=0.000 unless stated; *=p>0.05; #=p≥0.01; ^=p≥0.001

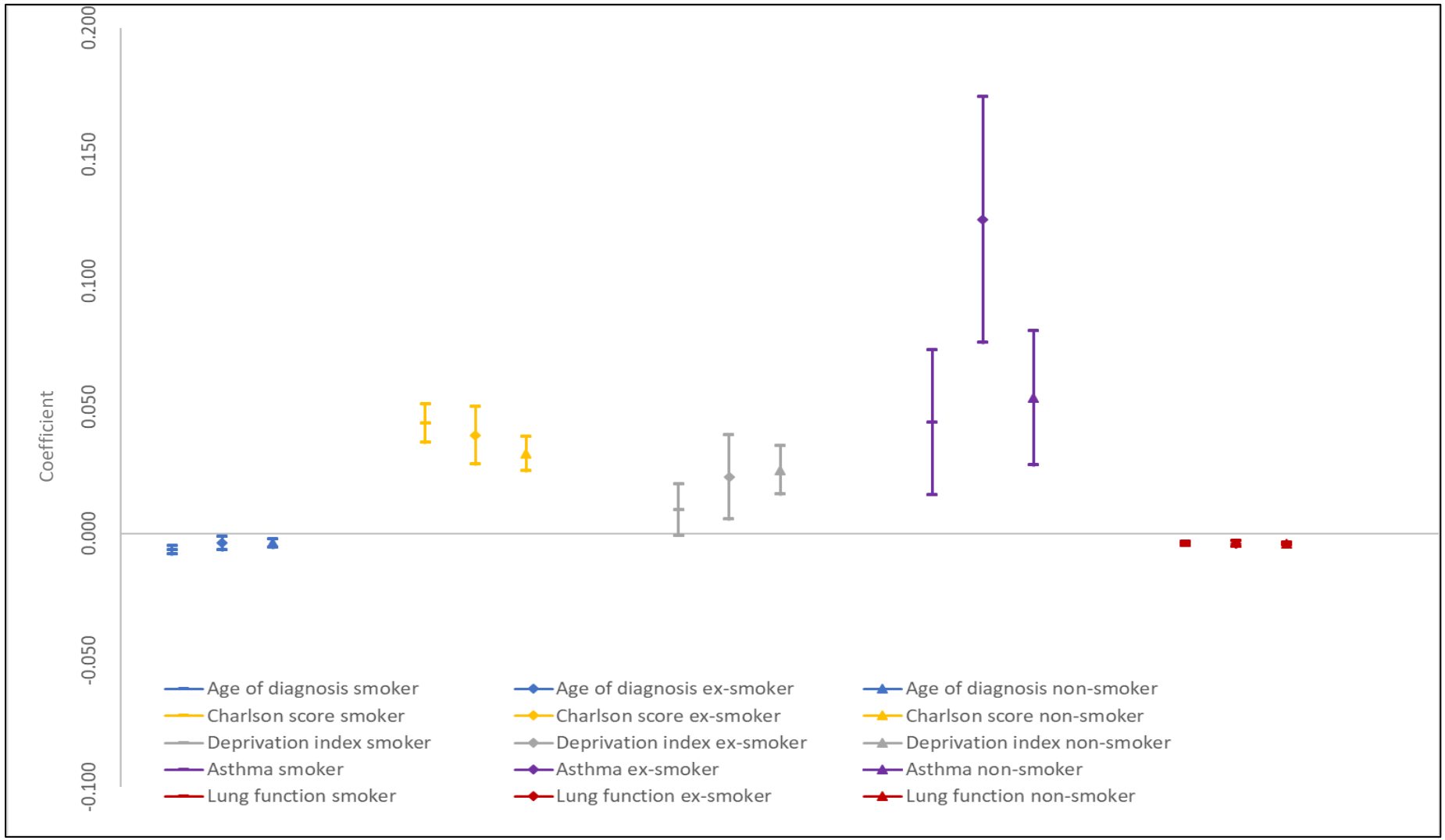

Figure 5-9 Variable coefficients by smoking status for total yearly exacerbations at year 5

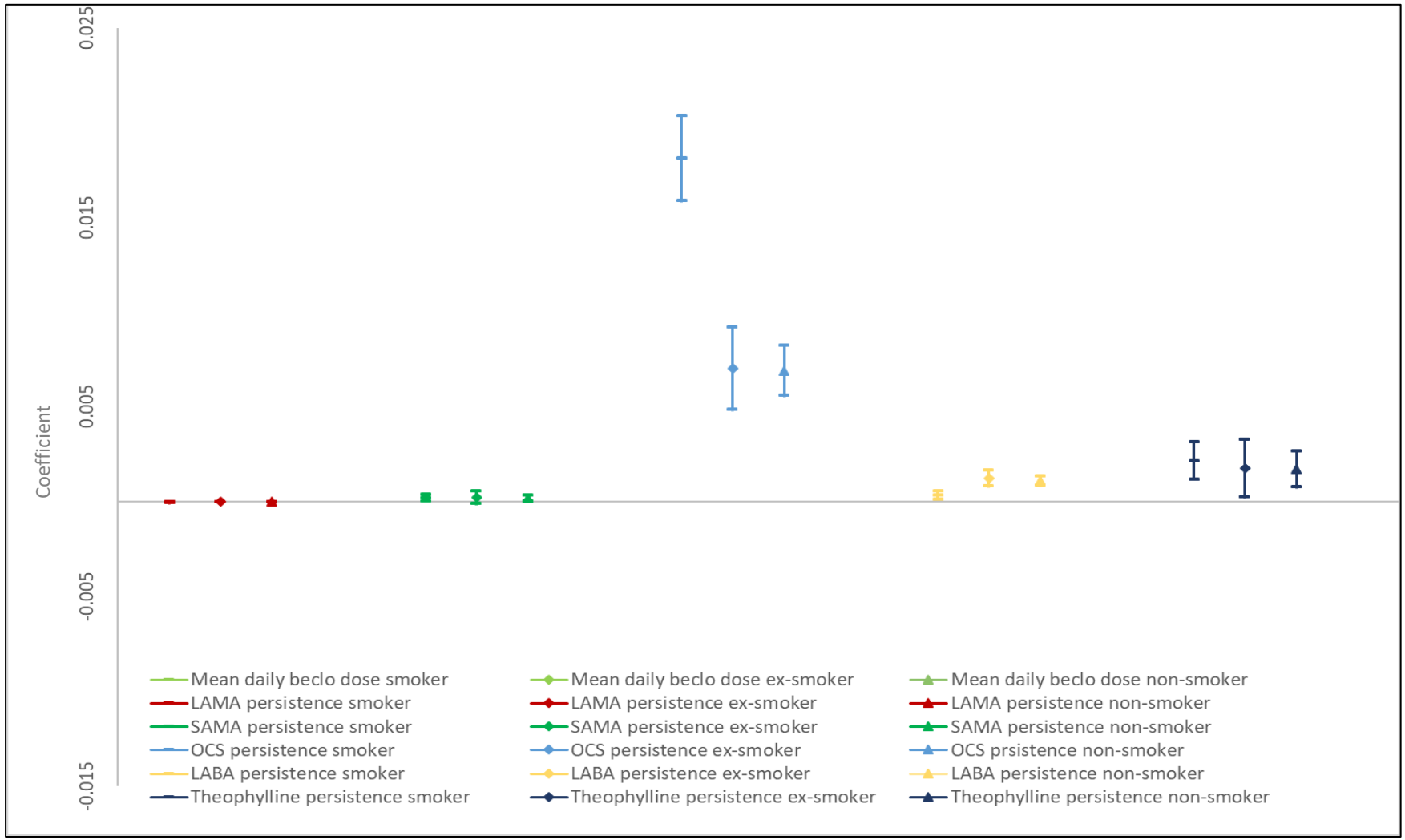

Figure 5-10 Variable coefficients by smoking status for total yearly exacerbations at year 5

	Smoker Patients = 26,059; observations = 83,004. Rho = 0.9732081.			Ex-smoker Patients = 12,335 observations = 34,599. Rho = 0.50834329.			Non-smoker Patients = 31,290; observations = 101,021. Rho = 0.9899641.		
	Coefficient	95% Confidence interval		Coefficient	95% Confidence interval		Coefficient	95% Confidence interval	
Gender	-0.7984861	-0.9291082	-0.6678639	-0.7878481	-1.012098	-0.5635986	-0.5007259	-0.6225041	-0.3789478
Age of diagnosis	0.0698624	0.0614992	0.0782255	0.0972711	0.0799988	0.1145433	0.0687078	0.0602643	0.0771512
Charlson score	0.2207071	0.1908489	0.2505654	0.2420815	0.1941615	0.2900015	0.1520995	0.126737	0.177462
Deprivation index	-0.01358*	-0.0602721	0.0331122	-0.0158091*	-0.0966896	0.0650714	-0.0375355*	-0.081894	0.006823
Asthma	-0.3819759	-0.5174372	-0.2465146	-0.9910379	-1.219699	-0.7623765	-0.6635402	-0.7887988	-0.5382815
Total exacerbations	0.0258058*	-0.0398763	0.091488	0.0039797*	-0.1007927	0.1087521	-0.0388338*	-0.0963921	0.0187244
Mean daily beclomethasone dose	0.0000142*	-0.0000443	0.0000726	0.0000038*	-0.0000344	0.000042	0.0000055*	-0.0000289	0.0000398
LAMA persistence	0.0000069*	-0.0001158	0.0001296	0.0000409*	-0.0000878	0.0001695	-0.0000015*	-0.0000977	0.0000947
SAMA persistence	0.0005075*	-0.0002079	0.001223	0.0009723*	-0.0003675	0.0023121	-0.0000202*	-0.0009436	0.0009033
OCS persistence	0.0030183*	-0.0062951	0.0123316	0.009517*	-0.0014214	0.0204554	0.0040213*	-0.0022728	0.0103155
LABA persistence	-0.0012961*	-0.0031183	0.0022204	-0.0004489*	-0.0031183	0.0022204	-0.0015398#	-0.00301	-0.0000695
Theophylline persistence	-0.0027291*	-0.0092716	0.0102169	0.0004726*	-0.0092716	0.0102169	-0.0000434*	-0.006199	0.0061121

Table 5-10 Random effects panel data model by smoking status for respiratory-cause deaths up to year 5

p=0.000 unless stated; *=p>0.05; #=p≥0.01; ^=p≥0.001

5.4.5.4 Heavy versus lighter smokers

Higher average daily beclomethasone doses in heavy smokers (20+ cigarettes a day) are associated with larger decreases in lung function and more exacerbations than in lighter smokers. Most of the other variables do not show statistical significance in the heavy smokers group, possibly because this group has low patient numbers (Table 5-11 and Table 5-12).

	Heavy smoker Patients = 1,720; observations = 4,956. Rho = 0.62254263 . R-squared: overall = 0.0662			Lighter smoker Patients = 28,868; observations = 86,432. Rho = 0.64629763. R-squared: overall = 0.0373		
	Coefficient	95% Confidence interval		Coefficient	95% Confidence interval	
Age of diagnosis	-0.2632969	-0.3499559	-0.1766379	-0.1083174	-0.1284493	-0.0881854
Charlson score	0.3936411#	0.0020298	0.7852524	0.4388016	0.3480904	0.5295128
Deprivation index	0.249007*	-0.2580986	0.7561126	0.2375698	0.1106492	0.3644904
Asthma	0.6810432*	-0.7498182	2.111905	1.412495	1.061725	1.763265
Total exacerbations	-0.822842	-1.264114	-0.3815696	-0.7202536	-0.8196704	-0.6208368
Mean daily beclomethasone dose	-0.0006621#	-0.0011697	-0.0001544	-0.0001096	-0.0001465	-0.0000727
LAMA persistence	-0.0002079*	-0.0011321	0.0007163	-0.0002335^	-0.0003778	-0.0000891
SAMA persistence	-0.0014288*	-0.0064469	0.0035893	-0.0054847	-0.0070984	-0.003871
OCS persistence	-0.1610436^	-0.259947	-0.0621403	-0.0730148	-0.0881535	-0.0578762
LABA persistence	-0.0147748^	-0.0257209	-0.0038288	-0.0134829	-0.0156338	-0.0113321
Theophylline persistence	-0.0424262*	-0.085578	0.0007256	-0.0412882	-0.0512726	-0.0313039

Table 5-11 Random effects panel data model by amount smoked for lung function up to year 5
p=0.000 unless stated; *=p>0.05; #=p≥0.01; ^=p≥0.001. Heavy smoker ≥ 20 cigarettes a day; lighter smoker <20 cigarettes a day

	Heavy smoker Patients = 1,720; observations = 4,956. Rho = 0.48709045. R-squared: overall = 0.0481			Lighter smoker Patients = 28,868; observations = 86,432. Rho = 0.48193353. R-squared: overall = 0.0334		
	Coefficient	95% Confidence interval		Coefficient	95% Confidence interval	
Gender	0.1884046	0.1132352	0.263574	0.0807742	0.0616819	0.0998665
Age of diagnosis	-0.0070816^	-0.0118296	-0.0023336	-0.0054457	-0.0065667	-0.0043246
Charlson score	0.0324525^	0.0111215	0.0537834	0.0371222	0.0320836	0.0421608
Deprivation index	0.0324932#	0.0049111	0.0600752	0.0193723	0.0123315	0.0264132
Asthma	0.0619362*	-0.0161797	0.1400521	0.0587368	0.0392409	0.0782327
Total exacerbations	-0.0035579	-0.0052772	-0.0018385	-0.003837	-0.0042687	-0.0034053
Mean daily beclomethasone dose	0.0000438^	0.0000114	0.0000761	0.0000068	0.0000042	0.0000094
LAMA persistence	-0.0000234*	-0.000082	0.0000352	0.0000010*	-0.0000084	0.0000104
SAMA persistence	0.000299*	-0.0000245	0.0006225	0.0002181	0.0001086	0.0003276
OCS persistence	0.0178302	0.0114748	0.0241856	0.0086182	0.0075917	0.0096446
LABA persistence	0.0003956*	-0.0002973	0.0010884	0.0010127	0.0008673	0.001158
Theophylline persistence	0.0016399*	-0.0010071	0.004287	0.0019246	0.0012799	0.0025694

Table 5-12 Random effects panel data model by amount smoked for total exacerbation up to year 5
p=0.000 unless stated; *=p>0.05; #=p≥0.01; ^=p≥0.001. Heavy smoker ≥ 20 cigarettes a day; lighter smoker <20 cigarettes

5.5 Discussion

5.5.1 Lung Function

The main finding was that the most significant impact on decreasing FEV_1 percentage was higher deprivation index, greater number of cigarettes smoked and greater number of exacerbations per year. This was expected; however, smoking did not seem to have as big a contribution to decreased lung function as would have been anticipated; -0.076 percentage points per cigarette smoked daily at year 3 (equating to approximately 1.5 percentage points for a person smoking 20 cigarettes per day). Previous studies have suggested that the rate of loss of lung function is in the region of 11-12ml/year for a smoker of 20 cigarettes a day (Xu et al., 1992, Burchfiel et al., 1995). This equates to approximately 1% loss in FEV_1 at year three for an average height 60-year old man.

It was unexpected that Charlson score and asthma co-diagnosis would contribute to improved lung function; 0.40% and 1.67% respectively at year 3. For asthma this finding is possibly explained by these people either having asthma (and not COPD) or asthma-COPD overlap. Asthma does not feature chronic, deteriorating lung function, as COPD does, so it is possible that the improved lung function comes as these people have received treatment after an exacerbation of asthma which temporarily lowered their FEV_1%. Charlson score is an indicated of mortality, so potentially would have no impact on lung function.

Increasing daily dose of ICS and increasing adherence to this and other medications seems to decrease the FEV_1%. This is unexpected; however, the decreases are very low

and not clinically significant; it could be explained by severity of the disease increasing and therefore increased doses of medication are given. In addition, as COPD is a progressive disease, the small decrease in lung function may be because the medications are mitigating a much larger decrease that would be noted if the disease was left untreated.

When observing the data at the three, five- and ten-year time points, there was no trend in change of the contribution each variable made over time. This was expected for the non-time dependant variables such as deprivation index. For the time-dependant variables (such as COPD medication use), this was also anticipated as the effect of each medication has not been shown to be cumulative. The dose may increase with time, however the effect of one dose unit (e.g. one milligram) would be constant.

The panel data model had a large constant, Rho was in the region of 0.62 and overall r-squared was around 0.055 at each time point; meaning that only a small amount of the change in lung function was explained by the variables. This was expected; a physiological function such as the lung function will be affected by many factors that cannot be either measured or altered; such as genetics and the environment.

5.5.2 Exacerbations

Overall, the majority of variables were associated with an increased number of community exacerbations per year. There was no significant difference in the variable coefficients at each time point; they stayed constant. The constants with the biggest effect were Charlson score, deprivation index and asthma co-diagnosis (0.031, 0.012

and 0.059 respectively at year three). Interestingly, cigarette smoking had very little impact on yearly exacerbations at year three and was not statistically significant. This was unexpected for smoking as it has been shown to cause more yearly exacerbations previously, as per the systematic review in chapter three of this thesis.

The impact on hospital-based exacerbations was very small for all variables and at year ten, a number of the variables did not show statistically significant impact. This is possibly because of the low number of hospital exacerbations, in comparison to community and therefore no conclusion can be drawn on the effect on hospital-based exacerbations here.

Asthma diagnosis had more of an effect on the number of exacerbations in community at years 3 and 5 than at year 10. This is an interesting observation, suggesting that initially co-diagnosis with asthma is associated with an increased likelihood of exacerbating in the community (note that at year 10 the asthma variable coefficient is not statistically significant). Increased persistence with OCS is associated with greater yearly exacerbations – probably because each exacerbation is treated with OCS and therefore those that frequently exacerbate end up on permeant OCS. None of the variables, were shown to be associated with decreasing the number of yearly exacerbations in a clinically significant way.

5.5.3 Respiratory deaths

As expected, higher Charlson score and higher deprivation-index were associated with increased likelihood of death. In this panel data analysis, smoking status had to be used instead of number of cigarettes smoked. Again, as expected never-smokers were less likely to die than current or ex-smokers. Asthma diagnosis was associated with less likelihood of death and while unexpected may be explained by these people having asthma rather than COPD and therefore as asthma is not a progressive disease, less likely to die from it. Most of the medications did not have a significant effect on respiratory deaths, which is as expected.

5.5.4 Nested eosinophil cohort

Blood eosinophils were not shown to have any statistically significant impact on lung function or yearly exacerbations. This is possibly due to several factors, which will be discussed at depth in later chapters of this thesis. Low levels of reporting eosinophils in the dataset and testing being incidental may contribute to this. Additionally, most literature examining eosinophil count impact on COPD outcomes uses sputum eosinophils, rather than blood eosinophils. The link between blood eosinophils and COPD outcomes of exacerbations and lung function has not been established in observational studies, as per the literature review in section 2.1.4 of this thesis, which demonstrated that in most studies, no overall effect was seen.

Including eosinophils in the model increases the effect asthma diagnosis has on lung function and yearly exacerbations in comparison to the five-year panel without eosinophils (2.19% increase versus 1.66%; 0.06/year increase versus 0.05/year respectively). Additionally, the negative effect that increased cigarette smoking has on lung function and exacerbations is also increased (-0.11% versus -0.05%; -0.0004/year versus -0.0002/year respectively). The potential mechanism for the increased number, or severity, of exacerbations of asthma is well established (de Groot et al., 2015). The increased lung function is less expected, but as discussed earlier could be because some of the people in this cohort actually have asthma and not COPD (increased likelihood with higher eosinophil counts), so it would be expected that their lung function improves as their asthma is controlled.

Smoking has been shown to cause elevated blood eosinophil counts (Jensen et al., 1998) and therefore it is probable that these are covariates.

Further investigation into the impact a high eosinophil count has on predicting ICS efficacy is warranted as a panel data model is not the best method to find the small changes expected. As identified in section 2.1.4, other observational studies into this have been conducted using CPRD, however the method by which ICS use is defined in this thesis is novel and not previously investigated.

5.5.5 Smoking status breakdown

Lung function

Smoking is associated with a larger decrease in lung function as average daily beclomethasone dose increases than in non-smokers. This was expected as smoking is known to decrease lung function however may also be explained by steroid-resistance caused by smoking (Barnes et al., 2004), which will be explored further in subsequent chapters.

Ex-smokers did not show any statistically significant change. Greater LAMA and LABA use were associated with less decline in lung function in smokers than non-smokers. This is an interesting observation that has not been previously seen in the literature and is a point for further investigation, outside of the scope of this thesis.

Exacerbations

People who smoke and have a higher average daily inhaled beclomethasone dose have a higher exacerbation rate than those that don't smoke, which again was expected. However, the non-smokers had a higher mean daily beclometasone dose (722mg versus 657mg) which may have contributed to this finding. Those that had asthma

exacerbated more frequently despite being non-smokers and taking a higher average daily inhaled steroid dose. For ex-smokers the effect is not statistically significant, possibly due to the lower number of patients in this group. This observation is consistent with the known pathology of asthma being and exacerbation and remission disease.

Heavy versus light smokers

When categorised by amount smoked (heavy smokers ≥20 cigarettes/day, lighter smokers <20 cigarettes/day), higher average daily beclomethasone doses in heavy smokers are associated with larger decreases in lung function and more exacerbations than in lighter/non-smokers. Most of the other variables do not show statistical significance in the heavy smoker group, possibly because this group has low patient numbers. This indicates that recording of amount smoked per day is likely to be under-reported as it would be expected that many more patients would fall into this category.

5.5.6 Strengths and limitations

A cohort study using panel data has strengths in that it allows investigation of the impact of multiple covariates on a single outcome. However, this study has shown that the data in the 10-year panel is limited, with low numbers of participants and many results not reaching statistical significance. Additionally, particularly at the 10-year end point there is a high likelihood of survivor-bias in the results; meaning that those who have survived until year ten of the study may have done so because they are less likely to have exacerbations of COPD, or have better preserved lung function.

The model and variables used in this chapter did not account for a large proportion of the variation in outcomes of lung function, exacerbations and deaths, as noted by the high value of Rho and low R-squared. Additionally, the effect of many of the variables on the outcomes was small and therefore no conclusion can be drawn from this data.

The Hausman test could not be performed on this data because of the use of multiple imputation, and therefore it was assumed that a random-effects model should be used.

5.6 Conclusion

ICS and other medications for COPD were shown to have very little impact on any of the outcomes for treating COPD. Smoking and asthma have been shown in repeated analysis to have an impact on lung function, exacerbations and deaths. Asthma shows an interesting effect in that it lowers deaths and exacerbations and increases lung function. This could be because many of the people in this group actually have asthma rather than COPD, which in general is associated with better long-term outcomes. Part of the difficulty in studying COPD or asthma in CPRD is the difficult in getting an absolute diagnosis of one of the other and in fact it is increasingly recognised that there are many people with asthma-COPD overlap. Eosinophils have shown no statistically significant impact, possibly because of the low numbers of recording and small changes observed.

Furthermore, higher doses or greater persistence with COPD medications may indicate that the person has worsening disease and as such the medications are actually slowing the decline down, but a decline is still occurring.

Charlson comorbidity index and multiple deprivation index have also shown to have a significant impact on outcomes of COPD, as expected however as they are not changeable, they will not be studied further, but are important co-variables to, for example, smoking status.

This model is not the most appropriate way to investigate the small changes expected in outcomes such as exacerbation rates and lung function with medication, but it does indicate variables suitable for further investigation.

Overall, investigation of the impact of smoking status and its impact on COPD outcomes appears to be of the most interest. The panel data model does not show that smoking has a large impact on COPD outcomes, most of the changes seen would not be clinically significant. This was expected as there are many factors that will impact a person's lung function, exacerbation rate and mortality; some of which are described by the model, but many other variables that may determine a person's health were either not included because they would not be expected to make a significant impact (for example non-respiratory medications) or can't be included (e.g. genetics).

Panel data is not the best method to investigate specific effects of one or two variables, such as smoking status on the outcomes of COPD, but has shown the is potential for further in-depth investigation.

6. Prospective Cohort study: Lung function

6.1 Introduction

It was discussed in the literature review of this thesis how further studies are needed to identify cohorts within the population with COPD that may get more benefit from using ICS than others. Other literature suggests that people with a co-diagnosis asthma and high blood eosinophil counts are more likely to benefit from ICS use in terms of lung function and exacerbations. Conversely, current or heavy smokers were expected to benefit less from ICS use.

Traditionally to investigate associations between treatments and outcomes, randomised controlled trials have been used. These trials are the gold standard, however, are expensive and time consuming. Real-world data from healthcare databases provide an opportunity to investigate long-term outcomes from therapies and in a way that is applicable to the complexity with which people access healthcare. In chapter four of this thesis, the CPRD dataset and linked data was investigated for its suitability for use in COPD research. It was found that the CPRD dataset contained a rich source of information, suitable to investigate the impact of asthma, blood eosinophil levels and smoking on outcomes such as lung function, exacerbations and death. The CPRD data had good recording of factors such as smoking status. Linking this data with ONS mortality data and HES data resulted in good recording of number and causes of death and yearly exacerbations. However, recording of lung function was patchy but methods of imputing this missing data were discussed.

In chapter five, the impact of key variables on the COPD outcomes were explored in a panel data model and it was found that an asthma diagnosis and smoking had a substantial influence on lung function, exacerbations and mortality. This has formed the basis for further investigation into these variables on COPD outcomes with ICS use

6.2 Aims and objectives

The aim of the next three chapters is to explore how the key variables; smoking status, asthma co-diagnosis and blood eosinophilia affect the effectiveness of ICS use on COPD outcomes.

This chapter will focus on the lung function outcome, chapters seven and eight will focus on exacerbations and deaths respectively.

6.3 Method

A prospective cohort study design was utilised, and data analysed at years three, five and ten after the index date. The index date was defined as the date of first diagnosis of COPD, described in detail in section 4.4.2. The COPD cohort developed from the CPRD dataset in chapter four of this thesis was used.

The treatment arm was ICS use and compared with the control group of no ICS use (as defined below). The outcome measured in this chapter was lung function. This was measured as the change in lung function (FEV_1 in litres) from the baseline year to year three, five and ten. In subsequent chapters (seven and eight) the same methods were used but the outcome measures were exacerbations and deaths.

6.3.1 Definition of ICS use

As discussed in chapter four, there were difficulties in defining what constitutes a person taking ICS within the CPRD dataset due to the wide range of doses and number of prescriptions per year. The categories of ICS use that were defined in chapter four (strict, intermediate, wider and non-user) were also use in this study (Table 6-1). As the definition developed in chapter four only considered the use of ICS in a single year, it was modified to account for multiple years use for the outcome of lung function. The definitions for each year of analysis can be seen in Table 6-2. It was important to consider the use of ICS across all years of this study, instead of just the baseline year because of the heterogeneity in ICS use in the population; it could not be assumed that a person that started ICS in year one would continue to take it through the study and

conversely that someone who did not take it in year one would not subsequently take it in line with the 'strict' user group for the remaining nine years of the study.

Category of ICS use	Definition
Strict ICS user	Over 80% persistence (≤20% CMG) with a prescription in each quarter of the year. OR adherence of: DDD ≥292, or ≥233mg beclometasone equivalence/year
Intermediate ICS user	Over 50% persistence (≤50% CMG) with a prescription in at least 3 of the 4 quarters. OR adherence of: DDD ≥182, or ≥146mg beclometasone equivalence/year
Wider ICS user	Over 10% persistence (≤90% CMG) in at least one quarter of the year. OR adherence of: DDD >28, or >23mg beclometasone equivalence/year
Non-ICS user	Less than 10% persistence (≥90% CMG) in no more than one quarter. OR adherence of: DDD ≤28, or ≤23mg beclometasone equivalence/year

Table 6-1 Definitions of ICS use during each one-year period from entry date
Based on the method of Svendson et al (2012) for opiate usage.
CMG = Continuous Measure of Medication Gaps
DDD = Daily defined dosage

ICS group	Year 3	Year 5	Year 10
Strict user	At least 'strict' in 2 out of 3 years	At least 'strict' in 4 out of 5 years	At least 'strict' in 8 out of 10 years
Intermediate user	At least 'intermediate' in 2 out of 3 year	At least 'intermediate' in 4 out of 5 year	At least 'intermediate' in 8 out of 10 year
Wider user	At least 'wider' in all years, or 'intermediate/strict' in 1 or more	At least 'wider' in all years, or 'intermediate/strict' in 2 or more	At least 'wider' in all years, or 'intermediate/strict' in 4 or more
Non-user user	Non-user in all years or 'wider' in a maximum of 1 year	Non user in all years or 'wider' in a maximum of 2 years	Non user in all years or 'wider' in a maximum of 4 years

Table 6-2 Definitions of ICS usage group at each analysis year
Based on ICS definitions of 'strict', 'intermediate', 'wider' and 'non' user in table 6-1

6.3.2 Definition of covariates

Smoking

Smoking status: Patients were defined as a 'current' smoker if they were recorded as smoking at any time during the baseline year. All other patients were recorded as ex- or non-smokers.

Amount smoked: For all people recorded as current smokers at baseline, the mean number of cigarettes smoked per day over the time the patient was in the study was calculated. Patients were defined as being a heavier smoker if they smoked 20 or more cigarettes a day. Anyone who smoked less than 20 cigarettes per day was designated a 'lighter' smoker.

Asthma

A patient was defined as having an asthma co-diagnosis if they had an asthma medcode recorded during or before their baseline year (as defined in chapter four and Appendix 7).

Eosinophils

The eosinophil nested cohort was used. A patient was defined as having a high blood eosinophil count if they had a result during the baseline year of over 0.4x10^9/L. All other patients were recorded as having a normal blood eosinophil count.

6.3.3 Imputation of missing data

As discussed in chapter four, lung function was found to be missing at some time points for some patients from the dataset. This was imputed using the Multiple Imputation Using Chained Equations (MICE) function in Stata v15.

6.3.4 Propensity Score Matching

When using healthcare databases, unlike randomised controlled trials, there is no ability to decide beforehand which treatment group a patient should be allocated to in order to minimise the risk of bias in the outcomes from patient characteristics that are not being studied. In this study, in order to control for differences in baseline characteristics that may affect choice of therapy a patient receives and the outcomes of that therapy, propensity score matching was utilised. Propensity score is a technique that attempts to estimate the effect of a treatment, by accounting for the covariates that predict receiving the treatment; a score of between 0 to 1 given to each case. If propensity score matching is undertaken at the baseline, then the study can be thought of as prospective.

The choice of covariates to include in the propensity score model should be based on theory and previous findings (Rubin, 1997). Only variables that influence simultaneously the treatment status and the outcome variable and are unaffected by treatment should be included in the model. To ensure this, variables should either be fixed over time or measured before participation.

Once the propensity score for each case has been created, there are several matching methods that can be used. The most widely used are nearest-neighbour matching (with or without caliper) or stratification matching. Each method has strengths and weaknesses, in this study nearest-neighbour (NN) was used due to ease of use in Stata. This method matches treated and control cases by taking each treated case and searching for the control case with the closest propensity score, in conjunction with use of a caliper; this defines the maximum proximity from which the matching case must come. Matching just one nearest neighbour minimizes bias at the cost of larger variance, matching using additional nearest neighbours increase the bias but decreases the variance (Rubin, 1973).

The literature suggests that the optimal number of NN matches is between two and five (Austin, 2010). In this study the number of NN matches was initially set as five due to the larger size of the control group (non-ICS use) than the treatment group and a caliper of 0.05 was set. This was varied if not enough matches were found in a sequential manner until enough matches were found:

1. Nearest neighbour = 5, caliper = 0.05
2. Nearest neighbour = 5, caliper =0.1
3. Nearest neighbour = 2, caliper = 0.1
4. Nearest neighbour = 1, caliper=0.1
5. Nearest neighbour = 1, caliper=0.2

In this study, propensity score matching of cases was done based on the following patient characteristics at baseline: gender, age at time of COPD diagnosis, Charlson score, asthma diagnosis, smoking status, prescribed long or short acting muscarinic-antagonists and prescribed long acting beta-agonists. FEV_1 and yearly exacerbations

were also included but were omitted when the this was the outcome being investigated.

Other medication factors that may influence propensity score such as use of oral corticosteroids and theophylline use were not included as there were too few cases with these to be able to match on it. Matching was done at baseline to ensure this was a prospective cohort study.

6.3.5 Data analysis

After missing data were imputed and cases were propensity score matched, data analysis using the '*teffects*' command in Stata v15 was performed. The '*teffects*' command is like performing a statistical T-test on the outcomes; it fits a logistic model to the data and provides the magnitude of difference in outcome between the treatment and control groups, along with the p value. A logistic model was used for the outcomes of lung function and exacerbations due to them being continuous variables. However, for mortality a probit model was used due to the binary outcome of deaths; this is explained further in chapter eight.

An example of the command used in Stata v15 can be found in Figure 6-1

```
mi estimate, imputations (1/20) cmdok esampvaryok: teffects psmatch (FEV1yr3)
(ICSyr3 pc_pscore), caliper(0.05) nn(5)
```

Figure 6-1 Stata command for multiple imputation, propensity score matching and fitting of the logistic model

6.4 Results

6.4.1 Demographics

There were 62,642 patients included at baseline, divided amongst the four ICS-usage groups. A total of 47,080 patients were still in the study at year three, 30,588 at year five and 5,355 at year ten. A detailed breakdown of the patient demographics can be seen in Table 6-3.

The ICS groups were broadly similar in terms of sex, age at diagnosis, follow up duration, Charlson score and deaths. However, differences were seen in asthma co-diagnosis, lung function at baseline and smoking status. An asthma co-diagnosis was more likely with strict-ICS use than non-use. The non-ICS use group had a better baseline lung function than strict-ICS use, however by year 10 they were comparable. Finally, the non-ICS use group was more likely to be a current smoker than those who used ICS.

	Mean (S.D)			
	Strict	Intermediate	Wider	Non-user
Number of participants at baseline	16,560	4,510	11,515	30,057
Age at diagnosis (years)	66.5 (11.6)	66.6 (11.6)	66.0 (11.9)	66.8 (11.4)
Sex (female)	8,414 (50.8%)	2,263 (50.2%)	5,548 (48.2%)	13,796 (45.9%)
Years follow up*	5 (3-7)	5 (3-7)	5 (3-7)	4 (2-6)
Lung function /L				
Baseline	1.60 (0.60)	1.66 (0.60)	1.72 (0.61)	1.77 (0.62)
Year 3	1.58 (0.65)	1.64 (0.65)	1.66 (0.64)	1.70 (0.66)
Year 5	1.54 (0.64)	1.59 (0.64)	1.61 (0.63)	1.63 (0.63)
Year 10	1.51 (0.69)	1.55 (0.59)	1.57 (0.59)	1.54 (0.61)
Exacerbations per year				
In community baseline	1.23 (1.00)	1.12 (0.90)	1.05 (0.87)	0.96 (0.82)
Year 3	1.36 (1.13)	1.21 (0.98)	1.15 (0.95)	1.09 (0.95)
Year 5	1.37 (1.15)	1.24 (1.04)	1.20 (0.99)	1.15 (0.96)
Year 10	1.31 (0.93)	1.22 (0.94)	1.29 (0.97)	1.26 (0.95)
Hospitalisation baseline	0.04 (0.23)	0.03 (0.17)	0.03 (0.18)	0.02 (0.13)
Year 3	0.04 (0.25)	0.03 (0.19)	0.02 (0.20)	0.02 (0.16)
Year 5	0.05 (0.26)	0.04 (0.39)	0.03 (0.19)	0.03 (0.21)
Year 10	0.08 (0.37)	0.05 (0.24)	0.07 (0.34)	0.07 (0.39)
Deaths (all cause)				
Up to year 3	3,054 (18.4%)	833 (18.5%)	2,376 (20.6%)	7,338 (24.4%)
Up to year 5	6,443 (38.9%)	1,706 (37.8%)	4,590 (39.9%)	13,708 (45.6%)
Up to year 10	11,829 (71.4%)	3,203 (71.0%)	8,397 (72.9%)	22,272 (74.1%)
Deaths (respiratory)				
Up to year 3	803 (4.8%)	232 (5.1%)	591 (5.1%)	1,488 (5.0%)
Up to year 5	1,337 (8.1%)	387 (8.6%)	899 (7.8%)	2,232 (7.4%)
Up to year 10	1,989 (12.0%)	547 (12.1%)	1,332 (11.6%)	3,107 (10.3%)
Charlson score at baseline*	4 (3-6)	4 (3-6)	4 (2-5)	3 (2-5)
Asthma diagnosis	12,053 (72.8%)	2,871 (63.7%)	6,229 (54.1%)	7,736 (25.7%)
Smoking status at baseline				
Current smoker	5,989 (36.2%)	1,694 (37.6%)	4,626 (40.2%)	14,595 (48.6%)
Ex smoker	7,174 (43.3%)	1,916 (42.4%)	4,777 (41.5%)	11,561 (38.4%)
Non smoker	3,397 (20.5%)	900 (20.0%)	2,112 (18.3%)	3,899 (13.0%)
Amount smoked per day for current smokers	12.3 (8.10)	12.8 (8.37)	13.1 (9.10)	13.3 (11.0)

Other respiratory medications at baseline^:				
SAMA	2,076 (15.5%)	374 (8.3%)	639 (5.5%)	1,681 (5.6%)
LABA	7,202 (43.5%)	942 (20.9%)	599 (5.2%)	333 (1.1%)
LAMA	3,479 (21.0%)	477 (10.6%)	718 (6.2%)	2,216 (7.4%)
Theophylline	336 (2.0%)	33 (0.7%)	39 (0.3%)	53 (0.2%)
OCS	832 (5.0%)	115 (2.5%)	229 (2.0%)	459 (1.5%)
Loss to follow up+				
Year3	3,337 (20.2%)	902 (20.0%)	2,673 (23.2%)	8,650 (28.8%)
Year5	7,690 (46.4%)	2,040 (45.2%)	5,444 (47.3%)	16,880 (56.2%)
Year10	14,819 (89.5%)	4,000 (88.7%)	10,305 (89.5%)	28,163 (93.7%)

Table 6-3 Demographics of whole cohort (prior to propensity score matching)

Categories at baseline (year 0)

*Median (IQR)

^With over 50% persistence except OCS where dose of ≥5mg/day for ≥28 days/year

+Left study or death

6.4.2 Nested eosinophil cohort

The nested cohort with eosinophil data had a total of 33,893 participants at baseline. There were 30,076 participants remaining in the study at year three; 21,877 at year five and 4,309 at year 10. A detailed breakdown of the demographics of this group can be found in Table 6-4.

In comparison to the whole cohort, the nested eosinophil cohort had broadly similar demographics.

	Mean (S.D/%)			
	Strict	Intermediate	Wider	Non-user
Number of participants	9,047	2,481	6,108	16,257
Age at diagnosis (years)	67.4 (11.0)	67.3 (10.9)	67.0 (11.1)	67.7 (10.8)
Sex (female)	4,688 (51.8%)	1,266 (51.0%)	2,987 (48.9%)	7,606 (46.8%)
Years follow up*	6 (4-8)	6 (4-9)	6 (4-8)	5 (3-7)
Lung function /L				
Baseline	1.58 (0.59)	1.65 (0.59)	1.70 (0.59)	1.74 (0.59)
Year 3	1.58 (0.63)	1.64 (0.62)	1.66 (0.63)	1.68 (0.64)
Year 5	1.53 (0.63)	1.60 (0.63)	1.59 (0.62)	1.63 (0.63)
Year 10	1.50 (0.69)	1.59 (0.62)	1.57 (0.60)	1.55 (0.61)
Exacerbations per year				
In community				
baseline	1.27 (0.98)	1.16 (0.89)	1.11 (0.86)	1.02 (0.82)
Year 3	1.39 (1.14)	1.24 (1.00)	1.20 (0.98)	1.12 (0.96)
Year 5	1.40 (1.16)	1.27 (1.09)	1.24 (1.01)	1.16 (0.96)
Year 10	1.33 (0.91)	1.24 (0.97)	1.32 (0.98)	1.29 (0.98)
Hospitalisation				
baseline	0.04 (0.21)	0.02 (0.15)	0.02 (0.17)	0.01 (0.11)
Year 3	0.04 (0.24)	0.02 (0.18)	0.02 (0.17)	0.02 (0.15)
Year 5	0.04 (0.26)	0.04 (0.43)	0.03 (0.20)	0.02 (0.19)
Year 10	0.09 (0.39)	0.06 (0.26)	0.06 (0.32)	0.08 (0.40)
Deaths (all cause)				
Year 3	767 (8.5%)	196 (7.9%)	538 (8.8%)	2,116 (13.0%)
Year 5	2,382 (26.3%)	639 (25.8%)	1,624 (26.6%)	5,571 (34.3%)
Year 10	6,112 (67.6%)	1,671 (67.4%)	4,180 (68.4%)	11,667 (71.8%)
Deaths (respiratory)				
Year 3	278 (3.1%)	77 (3.1%)	174 (2.8%)	606 (3.7%)
Year 5	550 (6.1%)	166 (6.7%)	344 (5.6%)	1,063 (6.5%)
Year 10	1,081 (11.9%)	291 (11.7%)	680 (11.1%)	1,753 (10.8%)
Charlson score at baseline*	4 (3-6)	4 (3-6)	4 (2-6)	4 (2-6)
Asthma diagnosis	6,654 (73.5%)	1,630 (65.7%)	3,404 (55.7%)	4,434 (27.35)
Smoking status at baseline				
Current smoker	3,013 (33.3%)	881 (35.5%)	2,308 (37.8%)	7,542 (46.4%)
Ex smoker	4,106 (45.4%)	1,086 (43.8%)	2,694 (44.1%)	6,599 (40.6%)
Non smoker	1,928 (21.3%)	514 (20.7%)	1,106 (18.1%)	2,114 (13.0%)
Amount smoked per day for current smokers	12.3	13.2	13.2	13.4

Other respiratory medications at baseline^:				
SAMA	1,075 (11.9%)	204 (8.2%)	326 (5.3%)	889 (5.5%)
LABA	3,981 (44.0%)	529 (21.3%)	293 (4.8%)	171 (1.1%)
LAMA	1,894 (20.9%)	256 (10.3%)	388 (6.4%)	1,216 (7.5%)
Theophylline	188 (2.1%)	17 (0.7%)	20 (0.3%)	29 (0.25)
OCS	381 (4.2%)	61 (2.5%)	115 (1.9%)	241 (1.5%)
Loss to follow up+				
Year3	762 (8.4%)	192 (7.7%)	554 (9.1%)	2,309 (14.2%)
Year5	2,772 (30.6%)	729 (29.4%)	1,858 (30.4%)	6,657 (40.9%)
Year10	7,653 (84.6%)	2,066 (83.3%)	5,144 (84.2%)	14,721 (90.6%)

Table 6-4 Nested eosinophil cohort demographics (prior to propensity score matching)

*Median (IQR)

^With over 50% persistence except OCS where dose of ≥5mg/day for ≥28 days/year

+Left study or death

6.4.3 Lung function outcome: whole cohort

The effects of ICS use on lung function are summarised in Table 6-5. The effect of a patient using ICS over no ICS was a small decrease in lung function after three years of use in both the strict-ICS group (-39ml; 95%CI=-62 to -15, p=0.001) and intermediate/strict-ICS groups (-34ml; 95%CI=-55 to -13, p=0.002). The decrease in lung function was extended in both groups at the five-year time point; -72ml (-110 to -33; p=0.000) and -66ml (-102 to -29; 0.000) respectively. At year ten, the detrimental effect of ICS on lung function appears to be extended again, however was not statistically significant.

ICS usage	Year 3		Year 5		Year 10	
	FEV_1/L (*95% CI; p*)	Participants	FEV_1/L (*95% CI; p*)	Participants	FEV_1/L (*95% CI; p*)	Participants
Strict use versus non-use	-0.039 (-0.062 to -0.015; 0.001)	Treated: 15,981 Control: 17,038	-0.072 (-0.110 to -0.033; 0.000)	Treated: 9,088 Control: 8,351	-0.087 (-0.350 to 0.175; 0.514)	Treated: 1,849 Control: 609
Intermediate/strict use versus non-use	-0.034 (-0.055 to -0.013; 0.002)	Treated: 19,863 Control: 17,038	-0.066 (-0.102 to -0.029; 0.000)	Treated: 11,666 Control: 8,351	-0.212 (-0.709 to 0.284; 0.401)^	Treated: 2,387 Control: 609

Table 6-5 Change in lung function (FEV_1/L) for the whole cohort with ICS use versus no use

Change in FEV_1 recorded from baseline to year three, five and ten: Caliper = 0.05, NN=5; ^=caliper=0.05, NN=2

6.4.4 Smoking co-variate

When patients were sub-categorised by smoking status at the beginning of the study, the patients who were current smokers prescribed ICS had a larger decline in lung function compared to non- and ex-smokers prescribed ICS after three and five years (Table 6-6). Results after ten years were not statistically significant. The difference was greatest in the strict ICS use group at the five-year time point: current smokers/ICS had a 106ml (95% CI=-173 to -38; p=0.002) decline in lung function compared to current smokers/non-ICS users. Comparatively there was a lesser decline of 48ml (-91 to -5; 0.027) in ex-&non-smokers/ICS users versus ex-&non-smokers/non-ICS users. This gives an overall effect of smoking of an additional 58ml decline in lung function for strict ICS use at year five.

However, at all-time points and both categories of ICS use, there was significant overlap in the 95% confidence intervals between the smoker/ICS group and the ex-&non-smoker/ICS groups, as demonstrated by Figure 6-2.

In terms of amount smoked, the same trend was observed as for smoking status; those that were heavier smokers (≥20 cigarettes a day) had a greater decline in lung function than those that were lighter or non-smokers (<20 cigarettes a day) with ICS use at year three and year five. The same occurred at year ten but was not shown to be statistically significant. This can be seen in Table 6-6 and Figure 6-3.

ICS usage	Year 3		Year 5		Year 10	
	FEV_1/L (*95% CI; p*)	Participants	FEV_1/L (*95% CI; p*)	Participants	FEV_1/L (*95% CI; p*)	Participants
Strict use versus non-use	Current smoker: -0.058 (-0.095 to -0.022; 0.002) Ex/non-smoker: -0.025 (-0.060 to 0.011; 0.171)	Treated, smoker: 6,299 Control, smoker: 8,250 Treated, ex/non smoker: 9,682 Control, ex/non smoker: 8,788	Current smoker: -0.106 (-0.173 to -0.038; 0.002) Ex/non-smoker: -0.048 (-0.091 to -0.005; 0.027)	Treated, smoker: 3,602 Control, smoker: 3,894 Treated, ex/non smoker: 5,486 Control, ex/non smoker: 4,457	Current smoker: -0.062 (-0.273 to 0.148; 0.561)^ Ex/non-smoker: -0.145 (-0.408 to 0.119; 0.281)^	Treated, smoker: 724 Control, smoker: 316 Treated, ex/non smoker: 1,125 Control, ex/non smoker: 293
	≥20 cigarettes/day: -0.069 (-0.130 to -0.009; 0.025) <20 cigarettes/day: -0.035 (-0.061 to -0.010; 0.007)	Treated, ≥20/day: 1,692 Control, ≥20/day: 2,443 Treated, <20/day: 14,289 Control, <20/day: 14,595	≥20 cigarettes/day: -0.100 (-0.208 to 0.009; 0.071) <20 cigarettes/day: -0.068 (-0.110 to -0.026; 0.002)	Treated, ≥20/day: 979 Control, ≥20/day: 1,177 Treated, <20/day: 8,109 Control, <20: 7,174	≥20 cigarettes/day: -0.164 (-0.395 to 0.068; 0.166)* <20 cigarettes/day: -0.095 (-0.363 to 0.172; 0.485)^	Treated, ≥20/day: 208 Control, ≥20/day: 93 Treated, <20/day: 1,641 Control, <20: 516
Intermediate and strict use versus non-use	Current smoker: -0.043 (-0.076 to -0.011; 0.009) Ex/non-smoker: -0.026 (-0.059 to 0.006; 0.116)	Treated, smoker: 7,809 Control, smoker: 8,250 Treated, ex/non smoker: 12,054 Control, ex/non smoker: 8,788	Current smoker: -0.100 (-0.162 to -0.038; 0.002) Ex/non-smoker: -0.043 (-0.085 to -0.002; 0.040)	Treated, smoker: 4,629 Control, smoker: 3,894 Treated, ex/non smoker: 7,037 Control, ex/non smoker: 4,457	Current smoker: -0.058 (-0.239 to 0.122; 0.528)^ Ex/non-smoker: -0.136 (-0.391 to 0.119; 0.296)^	Treated, smoker: 931 Control, smoker: 316 Treated, ex/non smoker: 1,456 Control, ex/non smoker: 293
	≥20 cigarettes/day: -0.056 (-0.116 to 0.004; 0.069) <20 cigarettes/day: -0.031 (-0.055 to -0.007; 0.010)	Treated, ≥20/day: 2,117 Control, ≥20/day: 2,443 Treated, <20/day: 17,746 Control, <20/day: 14,595	≥20 cigarettes/day: -0.092 (-0.183 to 0.001; 0.048) <20 cigarettes/day: -0.062 (-0.102 to -0.022; 0.003)	Treated, ≥20/day: 1,259 Control, ≥20/day: 1,177 Treated, <20/day: 10.407 Control, <20: 7,174	≥20 cigarettes/day: -0.180 (-0.402 to 0.041; 0.111)* <20 cigarettes/day: -0.092 (-0.346 to 0.161; 0.477)^	Treated, ≥20/day: 272 Control, ≥20/day: 93 Treated, <20/day: 2115 Control, <20: 516

Table 6-6 Change in lung function (FEV_1/L) categorised by smoking status with ICS use versus no use

Differences in propensity score matching to method: ^Caliper=0.1, NN=5; *Caliper=0.1, NN=2; #Caliper=0.2, NN=1

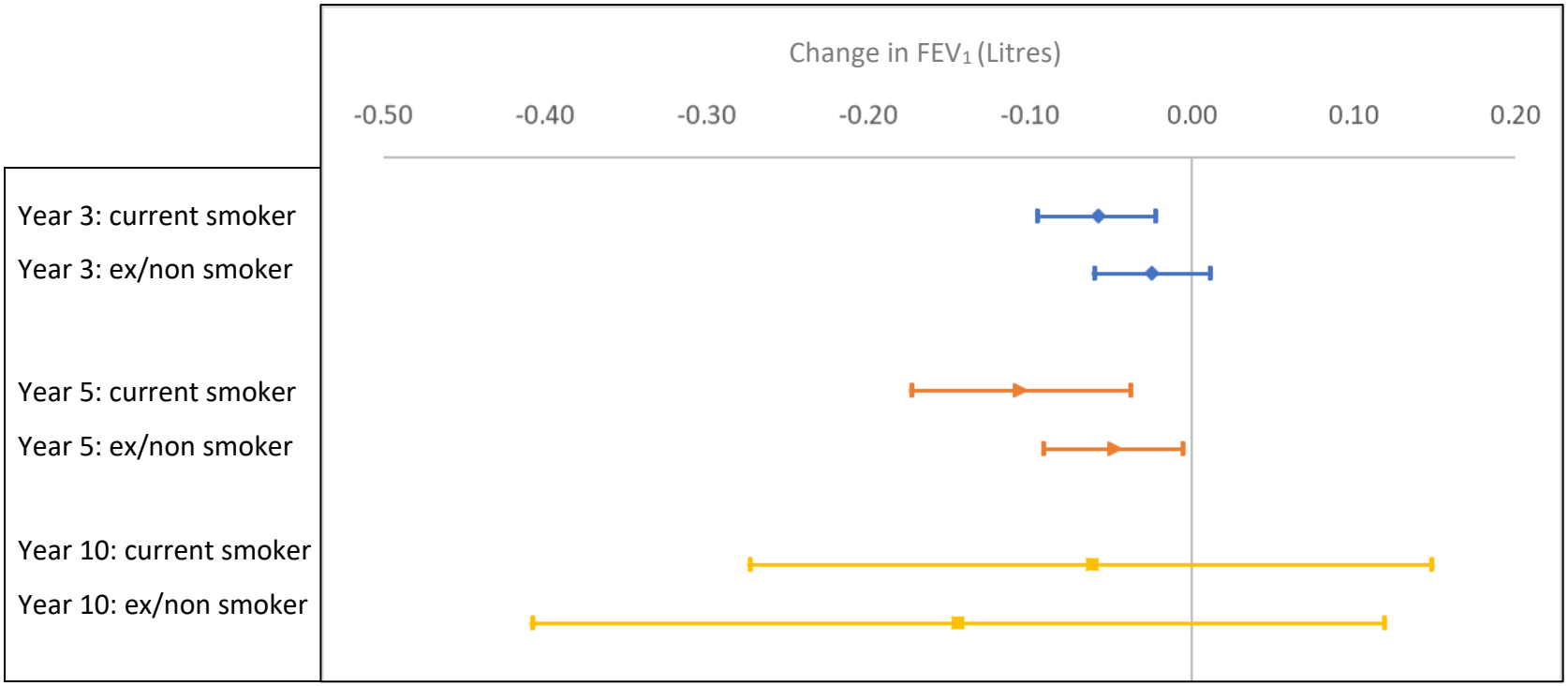

Figure 6-2 Change in FEV_1(Litres) for strict ICS use versus non-ICS use subdivided by smoking status at years three, five and ten

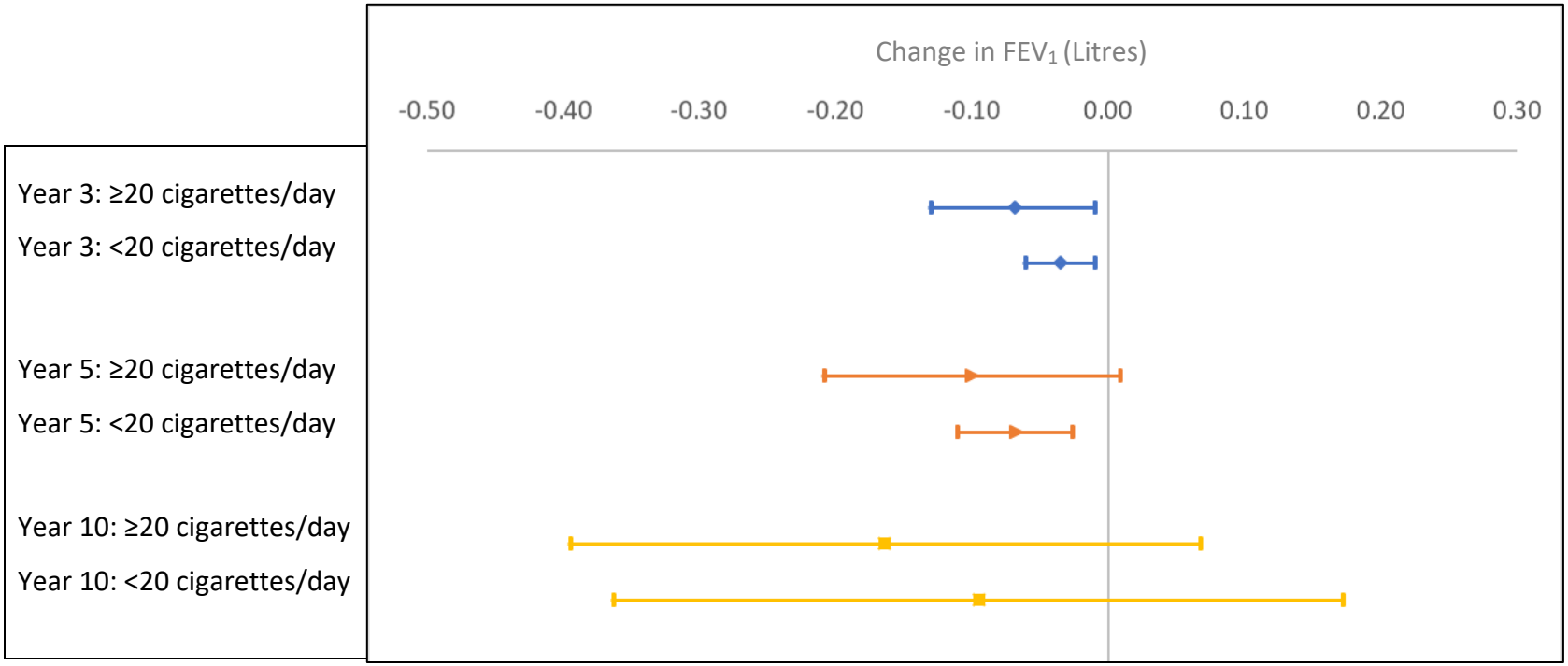

Figure 6-3 Change in FEV_1(Litres) for strict ICS use versus non-ICS use categorised by amount smoked at years three, five and ten

6.4.5 Asthma

When the cohort was split into those with an asthma diagnosis and those without, the results after three and five years showed that those with co-diagnosis of asthma using ICS had a lower decline in lung function than those with no asthma diagnosis using ICS (Table 6-7). This occurred in both the 'strict' ICS group and 'intermediate' ICS use group. At year ten the outcome was unclear due to lack of statistical significance.

The maximal difference in the effect seen was 52ml at year five: in the asthma/strict ICS group the decline in lung function was -39ml (-94 to 15; 0.160) compared to -91ml (-137 to -45; 0.000) in the no asthma/strict ICS group.

As can be seen in Figure 6-4, the 95% confidence intervals for asthma versus no asthma groups overlap, so it is uncertain that there is a true effect of having an asthma diagnosis on lung function over no diagnosis, but the trend to a lower decline in FEV_1 can be seen.

ICS usage	Year 3		Year 5		Year 10	
	FEV_1/L (*95% CI; p*)	Participants	FEV_1/L (*95% CI; p*)	Participants	FEV_1/L (*95% CI; p*)	Participants
Strict use versus non use	Asthma: -0.024[+] (-0.071 to 0.024; 0.332)	Treated with asthma: 10,721 Control with asthma: 4,613	Asthma: -0.039 (-0.094 to 0.015; 0.160)	Treated with asthma: 6,480 Control with asthma: 2,482	Asthma: -0.247 (-0.949 to 0.455; 0.490)*	Treated with asthma: 1,481 Control with asthma: 239
	No Asthma: -0.054 (-0.081 to -0.027; 0.000)	Treated, no asthma: 5,260 Control, no asthma: 12,425	No Asthma: -0.091 (-0.137 to -0.045; 0.000)	Treated, no asthma: 2,608 Control, no asthma: 5,869	No Asthma: -0.100 (-0.278 to 0.078; 0.267)*	Treated, no asthma: 368 Control, no asthma: 370
Intermediate/ strict use versus non use	Asthma: -0.018 (-0.059 to 0.022; 0.374)^	Treated with asthma: 13,224 Control with asthma: 4,613	Asthma: -0.039 (-0.092 to 0.013; 0.146)^	Treated with asthma: 8,222 Control with asthma: 2,482	Asthma: -0.231 (-0.870 to 0.408; 0.479)#	Treated with asthma: 1,893 Control with asthma: 239
	No Asthma: -0.053 (-0.077 to -0.028; 0.000)	Treated, no asthma: 6,639 Control, no asthma: 12,425	No Asthma: -0.083 (-0.125 to -0.041; 0.000)	Treated, no asthma: 3,444 Control, no asthma: 5,869	No Asthma: -0.099 (-0.272 to 0.074; 0.259)*	Treated, no asthma: 494 Control, no asthma: 370

Table 6-7 Change in lung function (FEV_1/L) categorised by asthma diagnosis with ICS use versus no ICS use

Differences in propensity score matching to method: ^Caliper=0.1, NN=5; *Caliper=0.1, NN=2; [#]Caliper=0.2, NN=1; [+]Caliper=0.05, NN=2

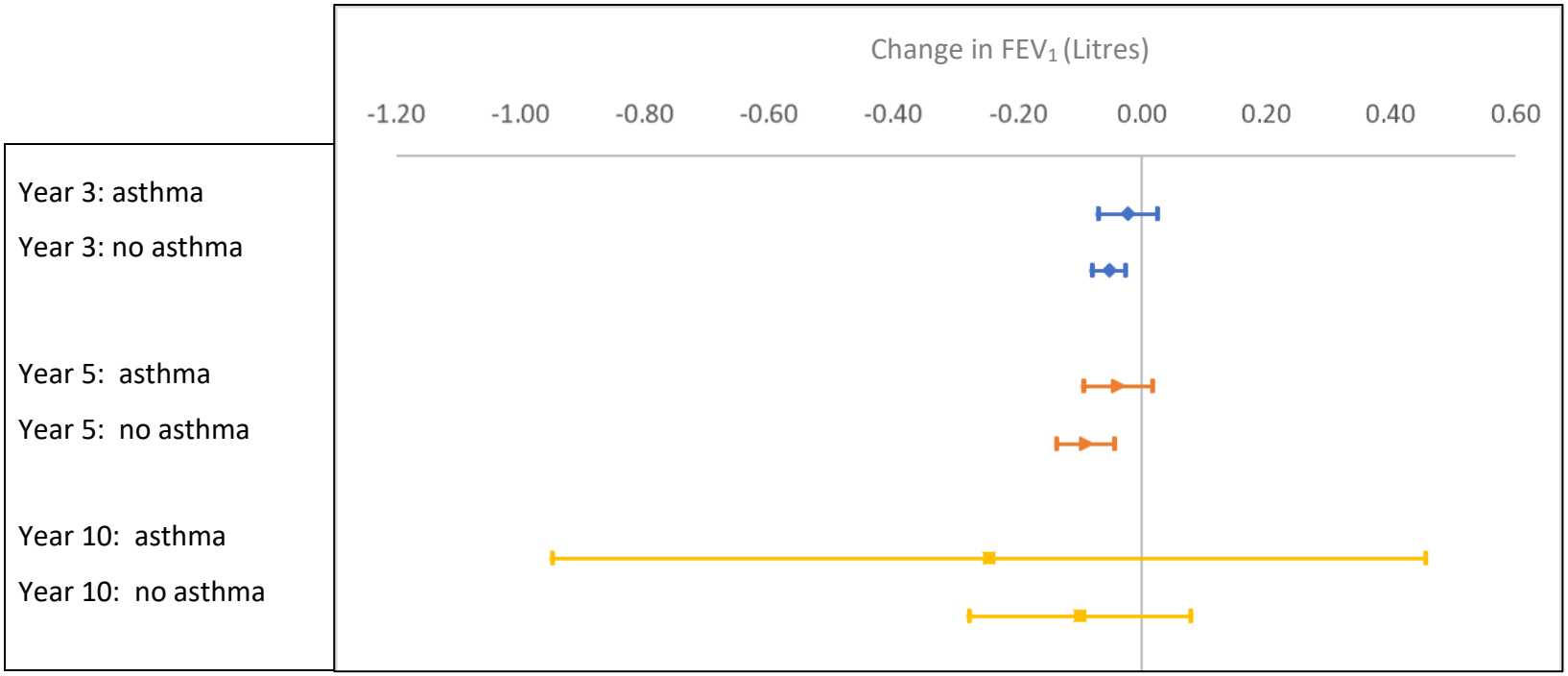

Figure 6-4 Change in FEV_1(L) for strict ICS use versus non-ICS use stratified by baseline asthma diagnosis at years three, five and ten

6.4.6 Eosinophils

The overall change in lung function in this nested cohort (Table 6-8) was similar to that of the whole cohort (Table 6-5).

When patients were categorised as having either a 'high eosinophil' count or 'normal eosinophil' count the effect on lung function showed very little difference at three and five years. After ten years, the effect was that those in the 'high eosinophil' group treated with ICS had a lower decline in lung function compared to the 'normal eosinophil' group (Table 6-9). However, none of these results reached statistical significance and the comparison groups had significantly overlapping 95% confidence intervals, as demonstrated by Figure 6-5.

ICS usage	Year 3		Year 5		Year 10	
	FEV_1/L (*95% CI; p*)	Participants	FEV_1/L (*95% CI; p*)	Participants	FEV_1/L (*95% CI; p*)	Participants
Strict use versus non use	-0.040 (-0.077 to -0.002; 0.037)	Treated: 5,698 Control: 7,165	-0.065 (-0.125 to -0.004; 0.037)	Treated: 4,820 Control: 5,033	-0.184 (-0.504 to 0.136; 0.259)^	Treated: 1,482 Control: 511
Intermediate/strict use versus non use	-0.023 (-0.057 to 0.012; 0.202)	Treated: 7,001 Control: 7,165	-0.057 (-0.119 to 0.006; 0.076)	Treated: 6,147 Control: 5,033	-0.178 (-0.484 to 0.128; 0.253)^	Treated: 1,904 Control: 511

Table 6-8 Change in lung function (FEV_1/L) with ICS use versus no ICS use for the nested eosinophil cohort

^caliper=0.1, NN=5;

ICS usage	Year 3		Year 5		Year 10	
	FEV_1/L (*95% CI; p*)	Participants	FEV_1/L (*95% CI; p*)	Participants	FEV_1/L (*95% CI; p*)	Participants
Strict use versus non use	High eosin: -0.030 (-0.123 to 0.063; 0.525)	Treated, high eosin: 915 Control, high eosin: 991	High eosin: -0.101 (-0.227 to 0.025; 0.114)^	Treated, high eosin: 813 Control, high eosin: 666	High eosin: -0.044 (-0.404 to 0.315; 0.809)*	Treated, high eosin: 284 Control, high eosin: 77
	Normal eosin: -0.036 (-0.081 to 0.008; 0.110)	Treated, norm eosin: 4,783 Control, norm eosin: 6,174	Normal eosin: -0.069 (-0.134 to -0.003; 0.039)	Treated, norm eosin: 4,007 Control, norm eosin: 4,367	Normal eosin: -0.169 (-0.451 to 0.112; 0.238)^	Treated, norm eosin: 1,198 Control, norm eosin: 434
Intermediate/ strict use versus non use	High eosin: -0.022 (-0.107 to 0.064; 0.617)	Treated, high eosin: 1,112 Control, high eosin: 991	High eosin: -0.061 (-0.205 to 0.083; 0.404)^	Treated, high eosin: 1,020 Control, high eosin: 666	High eosin: -0.056 (-0.425 to 0.310; 0.757)*	Treated, high eosin: 351 Control, high eosin: 77
	Normal eosin: -0.023 (-0.065 to 0.019; 0.285)	Treated, norm eosin: 5,889 Control, norm eosin: 6,174	Normal eosin: -0.063 (-0.130 to 0.004; 0.067)	Treated, norm eosin: 5,127 Control, norm eosin: 4,367	Normal eosin: -0.176 (-0.453 to 0.100; 0.211)^	Treated, norm eosin: 1,553 Control, norm eosin: 434

Table 6-9 Change in lung function (FEV_1/L) categorised by eosinophil count with ICS use versus no ICS use

^caliper=0.1, NN=5; *cailper=0.1, NN=2

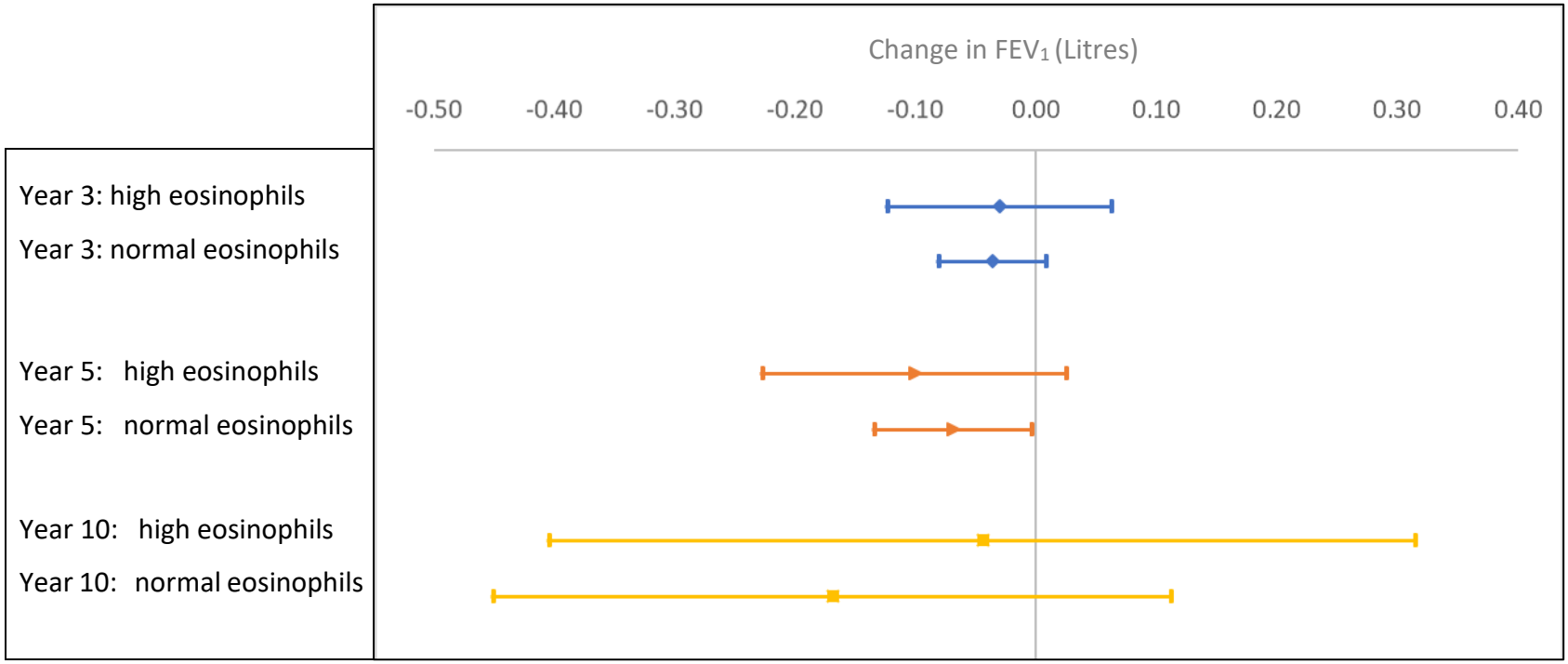

Figure 6-5 Change in FEV_1(L) for strict ICS use versus non-ICS use stratified by baseline eosinophil counts at years three, five and ten

6.5 Discussion

Overall, prescription of ICS was associated with a decline in lung function as measured by FEV_1 compared to no-ICS. Current and heavier smokers had a greater decline in lung function with ICS use than ex- and non-smokers. People with an asthma diagnosis had a lesser decline in lung function than those without an asthma diagnosis, however there was little difference in lung function between people with high and normal blood eosinophil counts.

6.5.1 Demographics – main cohort

In most respects the demographics of each ICS-usage group are similar. They differ most significantly in terms of asthma diagnosis and use of other medicines used. Smoking status, lung function and exacerbations also vary between groups, but to a lesser extent. The significant differences in asthma diagnosis and other COPD medications prescribed would be expected; ICS use (as per the previous iteration of NICE guidance published in 2010) is recommended for people with severe or very severe COPD and it would therefore be expected for them to be on other medications too. In addition, it would be expected that these people would have worse lung function at baseline and more exacerbations too.

In terms of smoking status, more people in the non-ICS group were current smokers than in the intermediate and strict user groups. This could be because their COPD is not severe enough that they have considered stopping smoking to improve their breathing at that point of being diagnosed.

Asthma co-diagnosis and prescription of LABA medication appear to be correlated with ICS use; this was expected as ICS are the first line treatment (along with a LABA) in people with asthma.

To test the appropriateness of propensity score matching, a test such as standardised difference should be carried out. However, this was not possible for these data due to the use of multiple imputation and this limitation is discussed further in section 9.5.

6.5.2 Demographics – eosinophil nested cohort

Overall, the demographics of the eosinophil nested cohort (Table 6-4) are broadly similar to those of the main cohort in terms of baseline lung function, exacerbations, age and sex. Although there are some differences in for example number of deaths, there does not appear to be any pattern to this. This is important as it shows that there is no fundamental difference between the nested cohort and main cohort that would make the results observed not applicable to the wider COPD-population.

6.5.2 Effect of ICS use on COPD outcomes

The finding of increased decline in lung function with ICS use over no use was interesting although not completely unexpected. The results presented here are similar to that of a recent systematic review; ICS use of over one year duration was associated with loss of lung function, at a similar amount to that of people not using ICS (Whittaker et al., 2019a). In addition, this systematic review found the scale of decline in lung function was comparable to the results seen in this chapter; change in FEV_1 varied between -57 ml/year to +85 ml/year for ICS-containing medications in the systematic review compared to -72ml decline in FEV_1 after five years in this chapter.

One aspect noted in this chapter is the heterogeneity of changes in lung function; particularly by year ten, there was a vast difference of -350 to +175ml in the strict ICS use group. This has been seen previously, with the ECLIPSE study demonstrating a between-patient standard deviation of 59 $mL \cdot year^{-1}$ (Vestbo et al., 2011). As reported in randomised controlled trials, it is difficult to predict the lung function response of an individual patient with COPD.

6.5.3 Effect of smoking

The current smoker/strict ICS group had a greater decline in lung function than the current smoker/no ICS group after three and five years; -58ml at year five in the strict ICS group. By year ten there was no clear trend. However, the overlapping confidence intervals of the smoker and ex-/non-smoker groups suggest that there may be no true difference between these groups. A similar trend was seen when categorised by amount smoked into 'heavier' (≥20 cigarettes/day) and 'lighter' (<20 cigarettes/day).

These results are comparable to those in the systematic review in chapter three of this thesis; when patients were categorised by pack-year history and the decline ranged from -22ml to -75ml at up to 36 months (Table 3-2). However, these results were from RCTs and not observational studies. In this thesis it was not possible to categorise patients by pack-years as the length of time a person has smoked for is generally not recorded in CPRD. Instead a proxy of number of cigarettes per day was used. This was set at 20-a-day because as most patient were around 60 years old when they were diagnosed, if we were to assume that they had been smoking or their whole adult life a habit of 20-cigarettes a day would give most patients a pack-year history of over 40.

It is difficult to draw conclusions from these data as although those who are smokers saw a greater decline in lung function while using ICS than ex/non-smokers, this could be entirely due to the effect of smoking on the lungs, rather than any interaction with the ICS medication. For comparison, the ECLIPSE study found current smoking was associated with an additional 21 mL per year decline in FEV_1 (Vestbo et al., 2011). In this study, the effect of smoking on people using ICS was an additional decline in lung function of 58ml after five years. As this decline is lower than demonstrated in the ECLIPSE study, the decline found here could be solely due to the impact of smoking, and in fact the ICS may have had a small beneficial effect on preventing a larger decline.

6.5.4 Asthma

When the cohort was stratified according to asthma co-diagnosis the trend was that those with an asthma diagnosis had a lower decline in lung function at years three and five than those with no diagnosis while using ICS; the difference was 52ml after five years. However, all patients using ICS still had a decline in lung function which is surprising as ICS are the mainstay of treatment for people with asthma and have repeatedly been shown to be beneficial (NICE, 2017a). Several factors may have affected this outcome; for example, uncertainty over the asthma diagnosis and the fact that FEV_1 is not a usual measurement of ICS efficacy in asthma. Uncertainty over an asthma co-diagnosis is caused by the method by which these patients were identified in the CPRD database; more of the people in this COPD cohort had asthma than is generally reported in the literature indicating that many of the people recorded as having asthma may not have had asthma. These people could have had their symptoms miss-classified before a definite diagnosis was made. There is currently no literature

on a validated method to identify people with both COPD and asthma (commonly known as asthma-COPD overlap) in the CPRD dataset. Many researchers have investigated one disease or the other and sought to minimise the inclusion of people with the other disease from their cohort. To further complicate this, there is no well-defined diagnosis of asthma-COPD overlap in clinical practice.

6.5.5 Eosinophils

In the eosinophil nested cohort there was very little difference between groups after three and five years, while a statistically non-significant lower decline in FEV_1 was seen in the 'high eosinophil' group after ten years. After year three the high eosinophil group had a decline in lung function of 6ml less than the normal eosinophil group with strict ICS use; this difference increased to 125ml at year ten. A previous observational study found similar; there was no difference in rate of FEV_1 decline when stratifying by eosinophils, however FEV_1 declined slower with ICS use than with no use (Whittaker et al., 2019b). It is not possible to draw conclusions from these results due to the lack of statistical significance. It is likely that no clear result has been found due to the incidental nature of recording of eosinophil blood results within the dataset; implying that a specific trial to investigate this is needed.

In this chapter, a cut-off to determine a high-eosinophil count was set at 400 cells/µL. This was based on clinical experience and limited evidence (Kerkhof et al., 2017, Oshagbemi et al., 2018). However subsequent to the study in this thesis commencing, a systematic review and meta-analysis concluded that blood eosinophil counts of ≥300 cells/µL was associated with a 39% reduction of exacerbation risk with ICS use (Harries et al., 2020). Furthermore, 'normal' eosinophil counts in this chapter were considered

to be <400 cells/µL, however more usually comparison is made to people with eosinophil counts <150 cells/µL (Kolsum et al., 2017). Therefore, together these methodological differences are likely to have limited the findings in this chapter.

6.5.6 Limitations

The main limitations of this study are in the methodology used and as this method is the same across chapters six to eight, it will be discussed in detail in chapter nine of this thesis.

There are limitations in interpreting the results of this study to make conclusions about the effectiveness of ICS to treat COPD. As mentioned previously, other studies have found similar mixed effects on lung function. It is widely acknowledged that ICS may have limited effect on FEV_1 but may benefit in terms of reducing exacerbations or quality of life. This study adds to the knowledge that there are some sub-groups which gain more or less benefit than others, however the scale of the change in lung function observed is unlikely to be clinically significant and impact upon their severity of COPD.

6.6 Conclusion

Overall, the results demonstrate that ICS use is associated with decline in lung function at all time points; most likely because they have been prescribed to people with more severe disease or more severely progressing disease. However, when analysing the sub-groups, those who are current or heavy smokers (in comparison to non-smokers or lighter smokers) and those with no-asthma co-diagnosis (in comparison to those with an asthma diagnosis) will experience a greater decline in FEV_1 with ICS use.

It was not expected that a clinically significant difference in FEV_1 would be observed, it is therefore important to also investigate the other COPD outcomes of yearly exacerbations and mortality.

7. Prospective cohort study: Exacerbations

7.1 Introduction

In this chapter, the effect of smoking status, asthma co-diagnosis and blood eosinophilia on the effectiveness of ICS use the outcomes of total yearly exacerbations, community-based exacerbations and hospital-based exacerbations will be investigated at the three-, five- and ten-year time points.

7.2 Method

This was described in chapter six. Below outlines the additional methods relevant to this chapter investigating yearly exacerbation rates.

7.2.1 Definition of exacerbation

Total yearly exacerbations were the number of exacerbations treated in community plus exacerbations treated in hospital. The method of defining these exacerbations was explored in full in chapter 4 (section 4.4.5). An exacerbation treated in hospital was defined as the patient having an ICD-10 code for COPD exacerbation recorded as the primary cause of the hospitalisation. An exacerbation in the community was defined as per the validated method of Rothnie *et al* (2016):

1. Both a prescription for OCS and antibiotics on the same day OR
2. Symptom definition (2 or more or cough, breathlessness, sputum) with prescription for either OCS or antibiotics
3. A diagnostic code for an exacerbation of COPD OR
4. A diagnostic code for LRTI

7.3 Results

7.3.1 Demographics

The same cohort was used as in chapter six. The demographics of the whole cohort and nested eosinophil cohort were presented in Table 6-3 and Table 6-4.

7.3.2 Whole cohort

Overall, both adherence levels of ICS usage were associated with an increase in all settings of yearly exacerbations after three and five years; however, results did not show statistical significance after ten years (Table 7-1, Table 7-2 and Table 7-3). Most exacerbations per year were experienced in the community setting, with relatively few hospital-based exacerbations.

At year three there was a small increase in the total yearly exacerbations (YE) in both groups of ICS use versus non-users; strict ICS use had an extra 0.095 YE (95% CI=0.037 to 0.154, p=0.001) and intermediate/strict use had 0.082 YE (0.027 to 0.137, 0.003). At year five the number of yearly exacerbations had increased further in each ICS group: 0.199 YE (0.073 to 0.325, 0.002) and 0.181 YE (0.064 to 0.298, 0.002) respectively.

When subdivided into exacerbations occurring in the community and those requiring hospitalisation, the same pattern was seen; at years three and five the number exacerbations occurring in each setting was higher in the ICS groups versus the non-ICS group.

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non-use	0.095 (0.037 to 0.154; 0.001)	Treated: 15,981 Control: 17,038	0.199 (0.073 to 0.325; 0.002)	Treated: 9,088 Control: 8,351	-0.020 (-0.150 to 0.111; 0.766)	Treated: 1,849 Control: 609
Intermediate and strict use versus non-use	0.082 (0.027 to 0.137; 0.003)	Treated: 19,863 Control: 17,038	0.181 (0.064 to 0.298; 0.002)	Treated: 11,666 Control: 8,351	0.027 (-0.083 to 0.138; 0.626)^	Treated: 2,387 Control: 609

Table 7-1 Change in total yearly exacerbations, whole cohort

Change in propensity score matching from methods: ^caliper=0.05, NN=2

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict user versus non-user	0.088 (0.034 to 0.143; 0.002)	Treated: 15,981 Control: 17,038	0.154 (0.023 to 0.285; 0.022)	Treated: 9,088 Control: 8,351	-0.091 (-0.219 to 0.038; 0.165)	Treated: 1,849 Control: 609
Intermediate and strict use versus non-use	0.076 (0.024 to 0.127; 0.004)	Treated: 19,863 Control: 17,038	0.135 (0.013 to 0.257; 0.030)	Treated: 11,666 Control: 8,351	-0.043 (-0.149 to 0.063; 0.422)^	Treated: 2,387 Control: 609

Table 7-2 Change in community yearly exacerbations, whole cohort

Change in propensity score matching from methods: ^caliper=0.05, NN=2

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non-use	0.007 (-0.005 to 0.019; 0.259)	Treated: 15,981 Control: 17,038	0.045 (0.013 to 0.078; 0.006)	Treated: 9,088 Control: 8,351	0.071 (0.041 to 0.101; 0.000)	Treated: 1,849 Control: 609
Intermediate/strict use versus non-use	0.006 (-0.004 to 0.016; 0.220)	Treated: 19,863 Control: 17,038	0.046 (0.017 to 0.076; 0.002)	Treated: 11,666 Control: 8,351	0.071 (0.044 to 0.097; 0.000)^	Treated: 2,387 Control: 609

Table 7-3 Change in hospital yearly exacerbations, whole cohort

Change in propensity score matching from methods: ^caliper=0.05, NN=2

7.3.3 Smoking sub-groups

7.3.3.1 Smoking status at baseline

Current smokers had a larger increase in total yearly exacerbations when prescribed ICS than non/ex- smokers at years five and ten (Table 7-4); at year five this increase was 0.207 YE (95% CI=0.126 to 0.287; p=0.000) in the current smokers/strict ICS group versus 0.133 YE (-0.035 to 0.300; 0.121) in the ex/non-smokers/strict ICS group (Figure 7-1). This gives an overall effect from smoking of an additional 0.074 YE when using ICS. The pattern seen in the intermediate ICS group was similar. However, after three years current smokers with strict ICS use conversely had a lower increase in exacerbations than ex- and non-smokers: 0.082 YE (0.008 to 0.157; 0.030) versus 0.092 YE (0.028 to 0.156; 0.005).

When broken down by location of exacerbation, the same trend was seen in both the community and hospital. At year five in the community (Table 7-5) there was an increase of 0.156 YE (0.078 to 0.234; 0.000) in the current smoker/strict ICS group versus 0.117 YE (-0.050 to 0.285; 0.169) in the ex&non-smoker/strict ICS group. At year five in hospital (Table 7-6) there was an increase of 0.051 YE (0.031 to 0.071; 0.000) in the current smokers/strict ICS group versus 0.015 YE (0.004 to 0.027; 0.009) in the ex&non-smoker/strict ICS group.

7.3.3.2 Amount smoked per day at baseline

When grouped by amount smoked, mixed results were observed when comparing those who smoke 20 or more cigarettes a day to those who smoke <20/day; with large 95% confidence intervals and lack of statistical significance it is not possible to draw any firm conclusions. For example, increased total yearly exacerbations at year five in

the heavy smoker/strict ICS group was 0.180 (0.042 to 0.318; 0.010) versus 0.204 (0.068 to 0.340; 0.003) in the lighter smoker group (Table 7-4). Whereas at year ten the heavy smoker/strict ICS group had an increase of 0.020 YE (-0.217 to 0.257; 0.869) versus a decrease of -0.027 YE (-0.159 to 0.105; 0.690) in the lighter smoker group.

When broken down by location of exacerbation an interesting trend was observed; in general the trend was that heavier smokers/ICS users had a higher rise in community exacerbations than the lighter smokers, but a lower rise in hospital exacerbations. For example at year five in the community the strict ICS use group, heavier smokers had an increase of 0.171 YE (0.036 to 0.306; 0.013) versus 0.155 YE (0.012 to 0.298; 0.033) for lighter smokers (Table 7-5). Whereas this was 0.009 YE (-0.031 to 0.048; 0.670) versus 0.049 YE (0.014 to 0.084; 0.006) in hospital (Table 7-6). Similar trends were seen in the intermediate/strict ICS use group. This suggests that the lower increase in yearly exacerbations experienced by the heavy smoker group is due to less hospital-based exacerbations.

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non use	Current smoker: 0.082 (0.008 to 0.157; 0.030) Ex/never smoker: 0.092 (0.028 to 0.156; 0.005)	Treated, smoker: 6,299 Control, smoker: 8,250 Treated, ex/non smoker: 9,682 Control, ex/non smoker: 8,788	Current smoker: 0.207 (0.126 to 0.287; 0.000) Ex/never smoker: 0.133 (-0.035 to 0.300; 0.121)	Treated, smoker: 3,602 Control, smoker: 3,894 Treated, ex/non smoker: 5,486 Control, ex/non smoker: 4,457	Current smoker: 0.056 (-0.138 to 0.249; 0.574)^ Ex/never smoker: -0.088 (-0.302 to 0.125; 0.418)^	Treated, smoker: 724 Control, smoker: 316 Treated, ex/non smoker: 1,125 Control, ex/non smoker: 293
	Smoke ≥20/day: 0.072 (-0.004 to 0.148; 0.064) Smoke <20/day: 0.099 (0.031 to 0.166; 0.004)	Treated, ≥20/day: 1,692 Control, ≥20/day: 2,443 Treated, <20/day: 14,289 Control, <20/day: 14,595	Smoke ≥20/day: 0.180 (0.042 to 0.318; 0.010) Smoke <20/day: 0.204 (0.068 to 0.340; 0.003)	Treated, ≥20/day: 979 Control, ≥20/day: 1,177 Treated, <20/day: 8,109 Control, <20/day: 7,174	Smoke ≥20/day: 0.020 (-0.217 to 0.257; 0.869)* Smoke <20/day: -0.027 (-0.159 to 0.105; 0.690)^	Treated, ≥20/day: 208 Control, ≥20/day: 93 Treated, <20/day: 1,641 Control, <20: 516
Intermediate and strict use versus non use	Current smoker: 0.091 (0.015 to 0.167; 0.019) Ex/never smoker: 0.075 (0.017 to 0.133; 0.011)	Treated, smoker: 7,809 Control, smoker: 8,250 Treated, ex/non smoker: 12,054 Control, ex/non smoker: 8,788	Current smoker: 0.193 (0.121 to 0.265; 0.000) Ex/never smoker: 0.118 (-0.042 to 0.278; 0.149)	Treated, smoker: 4,629 Control, smoker: 3,894 Treated, ex/non smoker: 7,037 Control, ex/non smoker: 4,457	Current smoker: 0.067 (-0.126 to 0.259; 0.499)^ Ex/never smoker: -0.080 (-0.286 to 0.126; 0.446)^	Treated, smoker: 931 Control, smoker: 316 Treated, ex/non smoker: 1,456 Control, ex/non smoker: 293
	Smoke ≥20/day: 0.070 (0.000 to 0.140; 0.051) Smoke <20/day: 0.081 (0.029 to 0.133; 0.002)	Treated, ≥20/day: 2,117 Control, ≥20/day: 2,443 Treated, <20/day: 17,746 Control, <20/day: 14,595	Smoke ≥20/day: 0.150 (0.020 to 0.280; 0.024) Smoke <20/day: 0.184 (0.058 to 0.310; 0.004)	Treated, ≥20/day: 1,259 Control, ≥20/day: 1,177 Treated, <20/day: 10.407 Control, <20/day: 7,174	Smoke ≥20/day: 0.047 (-0.194 to 0.288; 0.705)* Smoke <20/day: -0.033 (-0.161 to 0.095; 0.612)	Treated, ≥20/day: 272 Control, ≥20/day: 93 Treated, <20/day: 2115 Control, <20: 516

Table 7-4 Change in total yearly exacerbations by smoking status

Change in propensity score matching from methods: ^caliper=0.05, NN=2; *caliper=0.1, NN=2

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non use	Current smoker: 0.071 (0.010 to 0.131; 0.021) Ex/never smoker: 0.091 (0.027 to 0.154; 0.005)	Treated, smoker: 6,299 Control, smoker: 8,250 Treated, ex/non smoker: 9,682 Control, ex/non smoker: 8,788	Current smoker: 0.156 (0.078 to 0.234; 0.000) Ex/never smoker: 0.117 (-0.050 to 0.285; 0.169)	Treated, smoker: 3,602 Control, smoker: 3,894 Treated, ex/non smoker: 5,486 Control, ex/non smoker: 4,457	Current smoker: -0.25 (-0.212 to 0.162; 0.792)^ Ex/never smoker: -0.151 (-0.331 to 0.028; 0.097)^	Treated, smoker: 724 Control, smoker: 316 Treated, ex/non smoker: 1,125 Control, ex/non smoker: 293
	Smoke ≥20/day: 0.073 (0.001 to 0.146; 0.048) Smoke <20/day: 0.090 (0.028 to 0.153; 0.005)	Treated, ≥20/day: 1,692 Control, ≥20/day: 2,443 Treated, <20/day: 14,289 Control, <20/day: 14,595	Smoke ≥20/day: 0.171 (0.036 to 0.306; 0.013) Smoke <20/day: 0.155 (0.012 to 0.298; 0.033)	Treated, ≥20/day: 979 Control, ≥20/day: 1,177 Treated, <20/day: 8,109 Control, <20: 7,174	Smoke ≥20/day: -0.075 (-0.254 to 0.104; 0.413)* Smoke <20/day: -0.099 (-0.229 to 0.031; 0.136)^	Treated, ≥20/day: 208 Control, ≥20/day: 93 Treated, <20/day: 1,641 Control, <20: 516
Intermediate and strict use versus non use	Current smoker: 0.077 (0.015 to 0.139; 0.015) Ex/never smoker: 0.074 (0.017 to 0.131; 0.011)	Treated, smoker: 7,809 Control, smoker: 8,250 Treated, ex/non smoker: 12,054 Control, ex/non smoker: 8,788	Current smoker: 0.138 (0.076 to 0.200; 0.000) Ex/never smoker: 0.099 (-0.061 to 0.259; 0.224)	Treated, smoker: 4,629 Control, smoker: 3,894 Treated, ex/non smoker: 7,037 Control, ex/non smoker: 4,457	Current smoker: -0.023 (-0.021 to 0.162; 0.810)^ Ex/never smoker: -0.141 (-0.312 to 0.030; 0.106)^	Treated, smoker: 931 Control, smoker: 316 Treated, ex/non smoker: 1,456 Control, ex/non smoker: 293
	Smoke ≥20/day: 0.073 (0.006 to 0.139; 0.032) Smoke <20/day: 0.075 (0.025 to 0.124; 0.003)	Treated, ≥20/day: 2,117 Control, ≥20/day: 2,443 Treated, <20/day: 17,746 Control, <20/day: 14,595	Smoke ≥20/day: 0.138 (-0.018 to 0.260; 0.025) Smoke <20/day: 0.133 (0.001 to 0.266; 0.049)	Treated, ≥20/day: 1,259 Control, ≥20/day: 1,177 Treated, <20/day: 10.407 Control, <20: 7,174	Smoke ≥20/day: -0.030 (-0.240 to 0.179; 0.778)* Smoke <20/day: -0.103 (-0.226 to 0.021; 0.102)^	Treated, ≥20/day: 272 Control, ≥20/day: 93 Treated, <20/day: 2115 Control, <20: 516

Table 7-5 Change in community yearly exacerbations by smoking status

Change in propensity score matching from methods: ^caliper=0.05, NN=2; *caliper=0.1, NN=2

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non use	Current smoker: 0.012 (-0.016 to 0.040; 0.419)	Treated, smoker: 6,299 Control, smoker: 8,250	Current smoker: 0.051 (0.031 to 0.071; 0.000)	Treated, smoker: 3,602 Control, smoker: 3,894	Current smoker: 0.081 (0.035 to 0.126; 0.001)^	Treated, smoker: 724 Control, smoker: 316
	Ex/never smoker: 0.001 (-0.007 to 0.010; 0.756)	Treated, ex/non smoker: 9,682 Control, ex/non smoker: 8,788	Ex/never smoker: 0.015 (0.004 to 0.027; 0.009)	Treated, ex/non smoker: 5,486 Control, ex/non smoker: 4,457	Ex/never smoker: 0.063 (-0.054 to 0.180; 0.289)^	Treated, ex/non smoker: 1,125 Control, ex/non smoker: 293
	Smoke ≥20/day: -0.001 (-0.028 to 0.025; 0.924)	Treated, ≥20/day: 1,692 Control, ≥20/day: 2,443	Smoke ≥20/day: 0.009 (-0.031 to 0.048; 0.670)	Treated, ≥20/day: 979 Control, ≥20/day: 1,177	Smoke ≥20/day: 0.095 (-0.023 to 0.213; 0.115)*	Treated, ≥20/day: 208 Control, ≥20/day: 93
	Smoke <20/day: 0.008 (-0.005 to 0.021; 0.201)	Treated, <20/day: 14,289 Control, <20/day: 14,595	Smoke <20/day: 0.049 (0.014 to 0.084; 0.006)	Treated, <20/day: 8,109 Control, <20: 7,174	Smoke <20/day: 0.072 (0.041 to 0.103; 0.000)^	Treated, <20/day: 1,641 Control, <20: 516
Intermediate and strict use versus non use	Current smoker: 0.014 (-0.012 to 0.041; 0.295)	Treated, smoker: 7,809 Control, smoker: 8,250	Current smoker: 0.055 (0.021 to 0.089; 0.001)	Treated, smoker: 4,629 Control, smoker: 3,894	Current smoker: 0.089 (0.040 to 0.138; 0.000)^	Treated, smoker: 931 Control, smoker: 316
	Ex/never smoker: 0.001 (-0.007 to 0.001; 0.861)	Treated, ex/non smoker: 12,054 Control, ex/non smoker: 8,788	Ex/never smoker: 0.019 (0.008 to 0.029; 0.001)	Treated, ex/non smoker: 7,037 Control, ex/non smoker: 4,457	Ex/never smoker: 0.061 (-0.054 to 0.176; 0.299)^	Treated, ex/non smoker: 1,456 Control, ex/non smoker: 293
	Smoke ≥20/day: -0.003 (-0.021 to 0.016; 0.772)	Treated, ≥20/day: 2,117 Control, ≥20/day: 2,443	Smoke ≥20/day: 0.011 (-0.021 to 0.044; 0.490)	Treated, ≥20/day: 1,259 Control, ≥20/day: 1,177	Smoke ≥20/day: 0.077 (-0.011 to 0.164; 0.088)*	Treated, ≥20/day: 272 Control, ≥20/day: 93
	Smoke <20/day: 0.007 (-0.003 to 0.016; 0.179)	Treated, <20/day: 17,746 Control, <20/day: 14,595	Smoke <20/day: 0.050 (0.018 to 0.083; 0.002)	Treated, <20/day: 10.407 Control, <20: 7,174	Smoke <20/day: 0.070 (0.038 to 0.101; 0.000)^	Treated, <20/day: 2115 Control, <20: 516

Table 7-6 Change in yearly hospital exacerbations by smoking status group

Change in propensity score matching from methods: ^caliper=0.05, NN=2; *caliper=0.1, NN=2

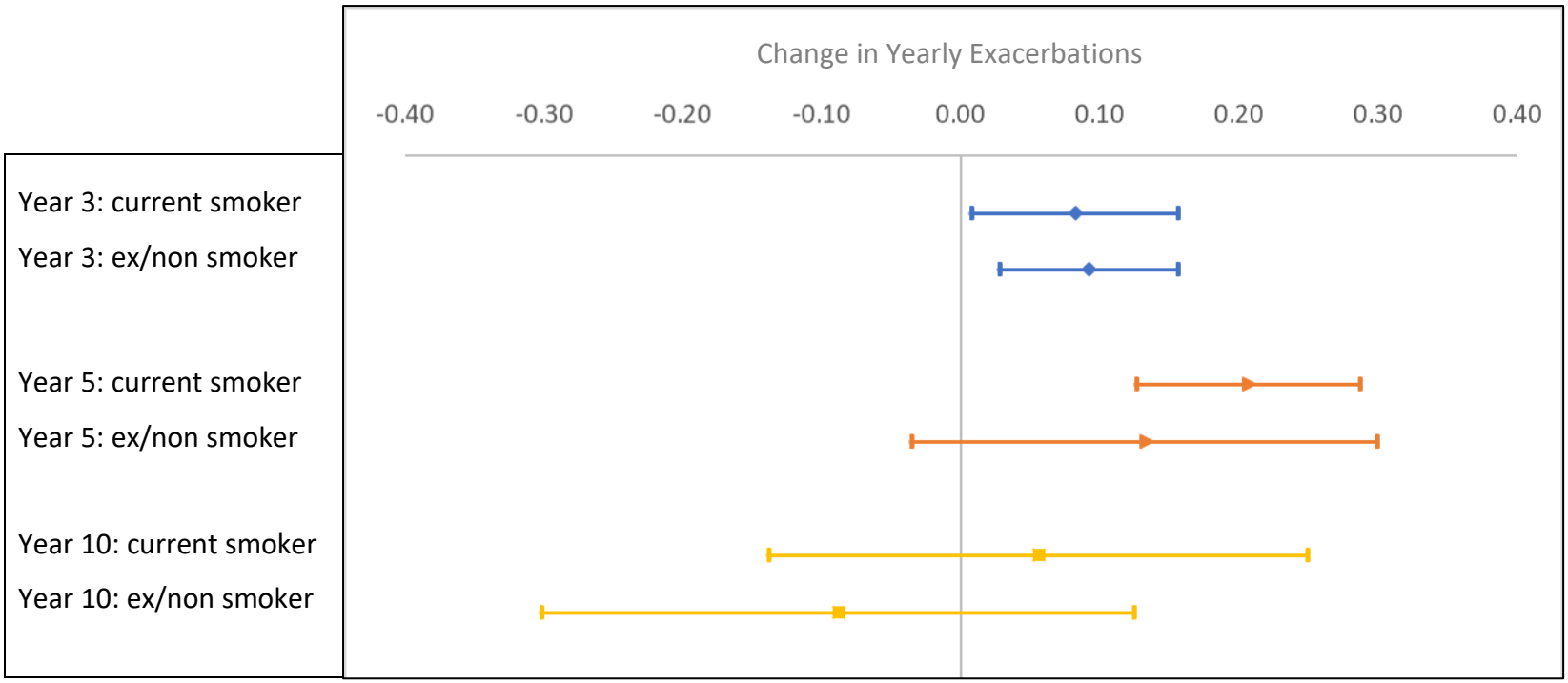

Figure 7-1 Change in total exacerbations/year with strict ICS use versus no-ICS use by smoking status sub-group at years three, five and ten

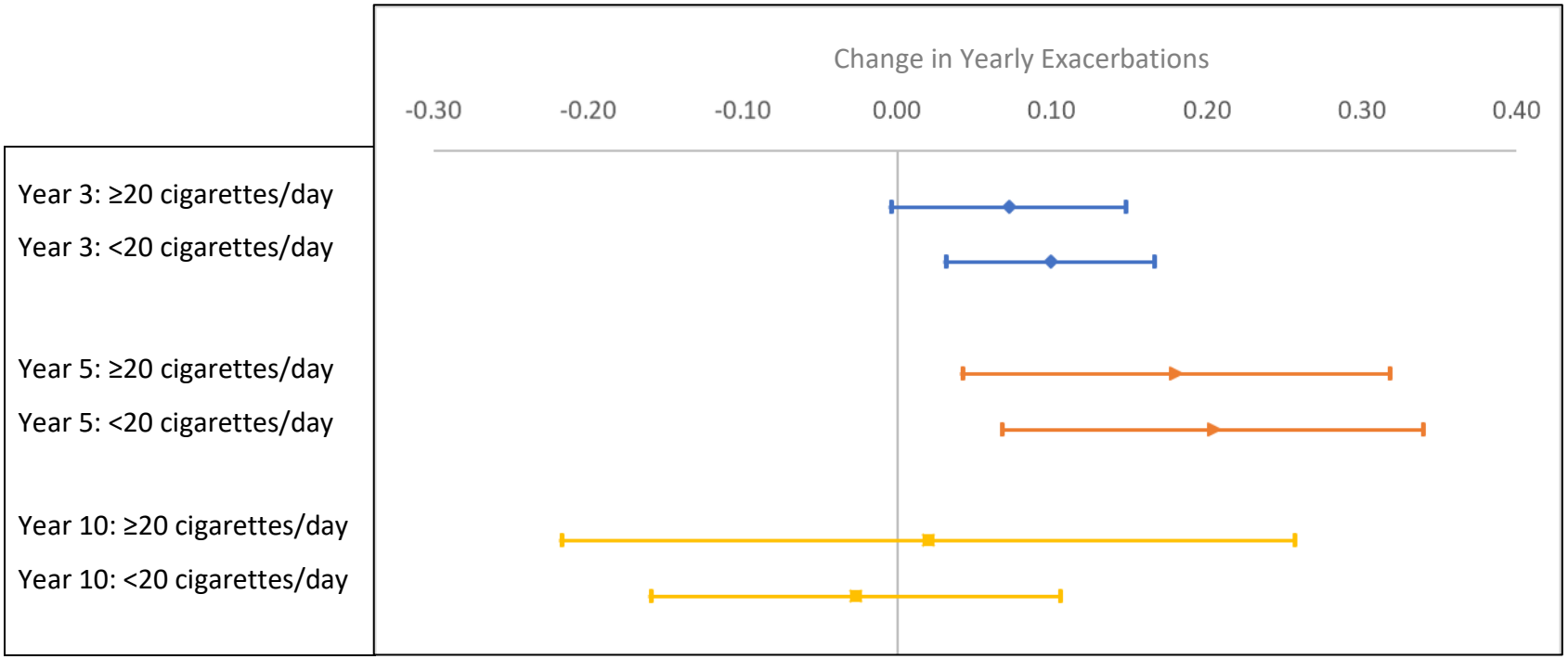

Figure 7-2 Change in total exacerbations/year with strict ICS use versus no-ICS use by amount smoked sub-group at years three, five and ten

7.3.3 Asthma diagnosis sub-groups

After three years, there was no real difference in increase in total yearly exacerbation rates between people co-diagnosed with asthma and those without when using ICS: 0.098 YE (95% CI=0.008 to 0.188; p=0.032) in the strict ICS/asthma group versus 0.093 YE (0.036 to 0.150; 0.001) in the no asthma/ICS group (Table 7-7). After five years the asthma/strict ICS group experienced a greater increase in yearly exacerbations than the no asthma/strict ICS group; 0.274 (0.063 to 0.485; 0.011) versus 0.117 (0.033 to 0.200; 0.006). This gives an overall effect due to asthma diagnosis of 0.157 more yearly exacerbations with ICS use over no asthma diagnosis. The same trend was seen in the intermediate/strict ICS use group (Table 7-7) and when exacerbations were divided into community or hospital-based (Table 7-8 and Table 7-9).

At year ten the opposite effect was seen; people with asthma/strict ICS use had a small decrease in yearly exacerbations than those without asthma; -0.019 YE (-0.138 to 0.100; 0.755) versus an increase of 0.271 YE (0.084 to 0.458; 0.004) in the no-asthma group. Giving an overall effect due to asthma diagnosis of -0.290 YE with ICS use over no-diagnosis. Although the effect in the asthma group is not statistically significant, when viewed in Figure 7-3, it is clear to see the magnitude of difference in the effect of ICS on these two groups; people with asthma gain more benefit in using ICS than those without asthma after ten years.

When the exacerbations were sub-divided into community-based and hospital-based at year ten, the decrease in yearly exacerbations described above is only seen in the community; -0.103 YE (-0.217 to 0.011; 0.077) in the asthma/strict ICS group versus 0.232 YE (0.053 to 0.410; 0.011) in the no asthma group (Table 7-8). The opposite is

true of hospital yearly exacerbations; 0.084 (0.045 to 0.123; 0.000) in the asthma/strict ICS group versus 0.039 (-0.004 to 0.083; 0.078) in the no asthma group (Table 7-9).

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non use	Asthma: 0.098 (0.008 to 0.188; 0.032)^	Treated with asthma: 10,721 Control with asthma: 4,613	Asthma: 0.274 (0.063 to 0.485; 0.011)	Treated with asthma: 6,480 Control with asthma: 2,482	Asthma: -0.019 (-0.138 to 0.100; 0.755)*	Treated with asthma: 1,481 Control with asthma: 239
	No asthma: 0.093 (0.036 to 0.150; 0.001)	Treated, no asthma: 5,260 Control, no asthma: 12,425	No Asthma: 0.117 (0.033 to 0.200; 0.006)	Treated, no asthma: 2,608 Control, no asthma: 5,869	No Asthma: 0.271 (0.084 to 0.458; 0.004)*	Treated, no asthma: 368 Control, no asthma: 370
Intermediate and strict use versus non use	Asthma: 0.082 (0.004 to 0.161; 0.040)^	Treated with asthma: 13,224 Control with asthma: 4,613	Asthma: 0.237 (0.046 to 0.428; 0.015)^	Treated with asthma: 8,222 Control with asthma: 2,482	Asthma: -0.022 (-0.152 to 0.108; 0.742)$^{+}$	Treated with asthma: 1,893 Control with asthma: 239
	No asthma: 0.098 (0.047 to 0.148; 0.000)	Treated, no asthma: 6,6425 Control, no asthma: 12,425	No Asthma: 0.103 (0.031 to 0.175; 0.005)	Treated, no asthma: 3,444 Control, no asthma: 5,869	No Asthma: 0.103 (-0.088 to 0.295; 0.290)^	Treated, no asthma: 494 Control, no asthma: 370

Table 7-7 Change in total yearly exacerbations by asthma diagnosis

Changes to propensity score matching in method: ^caliper=0.1, NN=5; *caliper=0.1,NN=2; $^{+}$Caliper=0.2, NN=2

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non use	Asthma: 0.087 (0.004 to 0.170; 0.040)^	Treated with asthma: 10,721 Control with asthma: 4,613	Asthma: 0.202 (-0.019 to 0.424; 0.074)	Treated with asthma: 6,480 Control with asthma: 2,482	Asthma: -0.103 (-0.217 to 0.011; 0.077)*	Treated with asthma: 1,481 Control with asthma: 239
	No asthma: 0.089 (0.036 to 0.142; 0.001)	Treated, no asthma: 5,260 Control, no asthma: 12,425	No Asthma: 0.102 (0.022 to 0.182; 0.013	Treated, no asthma: 2,608 Control, no asthma: 5,869	No Asthma: 0.232 (0.053 to 0.410; 0.011)*	Treated, no asthma: 368 Control, no asthma: 370
Intermediate and strict use versus non use	Asthma: 0.082 (-0.002 to 0.149; 0.055)^	Treated with asthma: 13,224 Control with asthma: 4,613	Asthma: 0.169 (-0.032 to 0.369; 0.099)^	Treated with asthma: 8,222 Control with asthma: 2,482	Asthma: -0.101 (-0.227 to 0.024; 0.114)+	Treated with asthma: 1,893 Control with asthma: 239
	No asthma: 0.093 (0.046 to 0.140; 0.000)	Treated, no asthma: 6,6425 Control, no asthma: 12,425	No Asthma: 0.085 (0.017 to 0.154; 0.015)	Treated, no asthma: 3,444 Control, no asthma: 5,869	No Asthma: 0.051 (-0.129 to 0.231; 0.579)^	Treated, no asthma: 494 Control, no asthma: 370

Table 7-8 Change in community yearly exacerbations by asthma diagnosis

Changes to propensity score matching in method: ^caliper=0.1, NN=5; *caliper=0.1,NN=2; +Caliper=0.2, NN=2

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non use	Asthma: 0.011 (-0.008 to 0.031; 0.257)^	Treated with asthma: 10,721 Control with asthma: 4,613	Asthma: 0.072 (0.015 to 0.128; 0.013)	Treated with asthma: 6,480 Control with asthma: 2,482	Asthma: 0.084 (0.045 to 0.123; 0.000)*	Treated with asthma: 1,481 Control with asthma: 239
	No asthma: 0.004 (-0.001 to 0.017; 0.561)	Treated, no asthma: 5,260 Control, no asthma: 12,425	No Asthma: 0.014 (-0.008 to 0.037; 0.213)	Treated, no asthma: 2,608 Control, no asthma: 5,869	No Asthma: 0.039 (-0.004 to 0.083; 0.078)*	Treated, no asthma: 368 Control, no asthma: 370
Intermediate and strict use versus non use	Asthma: 0.009 (-0.005 to 0.022; 0.217)^	Treated with asthma: 13,224 Control with asthma: 4,613	Asthma: 0.068 (0.017 to 0.119; 0.009)^	Treated with asthma: 8,222 Control with asthma: 2,482	Asthma: 0.080 (0.047 to 0.112; 0.000)+	Treated with asthma: 1,893 Control with asthma: 239
	No asthma: 0.005 (-0.007 to 0.016; 0.416)	Treated, no asthma: 6,6425 Control, no asthma: 12,425	No Asthma: 0.018 (0.001 to 0.034; 0.042)	Treated, no asthma: 3,444 Control, no asthma: 5,869	No Asthma: 0.052 (0.002 to 0.102; 0.041)^	Treated, no asthma: 494 Control, no asthma: 370

Table 7-9 Change in hospital yearly exacerbations by asthma diagnosis

Changes to propensity score matching in method: ^caliper=0.1, NN=5; *caliper=0.1,NN=2; +Caliper=0.2, NN=2

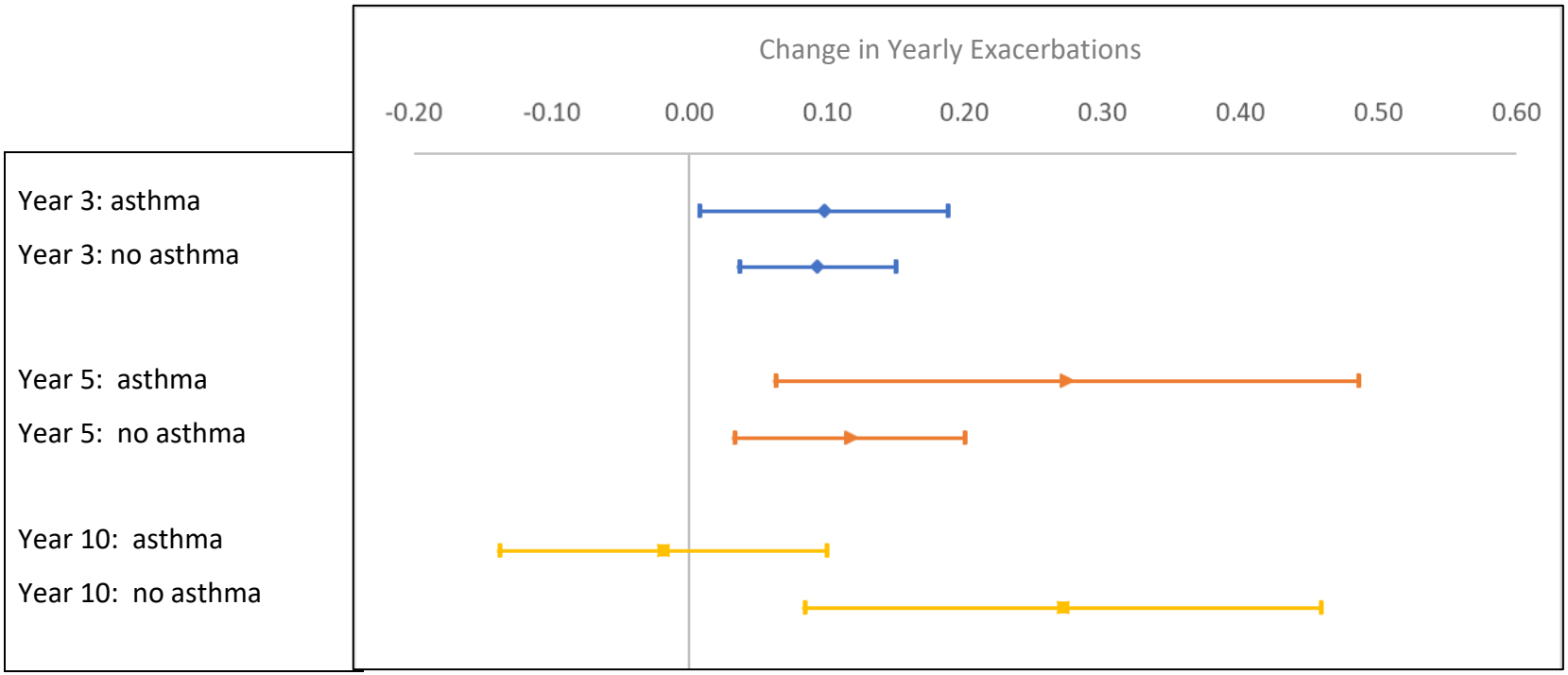

Figure 7-3 Change in total exacerbations/year with strict ICS use versus no-ICS use by asthma diagnosis sub-group at years three, five and ten

7.3.4 Eosinophils

7.3.4.1 Eosinophil nested cohort exacerbations compared to whole cohort

Overall the patients in the nested eosinophil cohort had a similar trend in yearly exacerbations to the whole cohort; there were more yearly exacerbations in the ICS use group versus non-use. However, the magnitude of the difference was greater than for the whole cohort; the nested eosinophil cohort experienced more total yearly exacerbations, community exacerbations and hospital exacerbations (Table 7-10, Table 7-11 and Table 7-12).

7.3.4.2 Eosinophil sub-groups

When patients were categorised as having either high blood eosinophil counts or normal blood eosinophil counts, there was a greater increase in yearly exacerbations at three years in the high eosinophil/strict ICS group; 0.294 YE (95% CI=0.018 to 0.570; p=0.037) versus 0.117 YE (0.062 to 0.172; 0.000) in the normal eosinophil/strict ICS group (Table 7-13). At years five and ten the trend was reversed: 0.144 YE (-0.036 to 0.323; 0.116) in the high eosinophil/strict ICS group versus 0.201 YE (0.097 to 0.305; 0.000) in the normal eosinophil/strict ICS group at year five; -0.048 YE (-0.447 to 0.350; 0.811) in the high eosinophil/strict ICS group versus 0.046 YE (-0.101 to 0.193; 0.542) in the normal eosinophil/strict ICS group at year ten. This equates to a 28% reduction in yearly exacerbations at year five in the high-eosinophil group. These results are displayed in Figure 7-4.

The same trend was seen for both intermediate/strict ICS use and when exacerbations were categorised as either community-based or hospital-based (Table 7-14 and Table 7-15).

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non use	0.123 (0.058 to 0.189; 0.000)	Treated: 5,698 Control: 7,165	0.208 (0.109 to 0.306; 0.000)	Treated: 4,820 Control: 5,033	0.027 (-0.081 to 0.134; 0.628)	Treated: 1,482 Control: 511
Intermediate and strict use versus non use	0.129 (0.074 to 0.183; 0.000)	Treated: 7,001 Control: 7,165	0.189 (0.102 to 0.276; 0.000)	Treated: 6,147 Control: 5,033	0.020^ (-0.085 to 0.125; 0.710)	Treated: 1,904 Control: 511

Table 7-10 Change in total yearly exacerbations, eosinophil nested cohort
Change in propensity score matching from methods: ^caliper=0.05

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non use	0.113 (0.053 to 0.173; 0.000)	Treated: 5,698 Control: 7,165	0.174 (0.052 to 0.300; 0.005)	Treated: 4,820 Control: 5,033	-0.047 (-0.152 to 0.057; 0.375)	Treated: 1,482 Control: 511
Intermediate and strict use versus non use	0.116 (0.065 to 0.168; 0.000)	Treated: 7,001 Control: 7,165	0.149 (0.034 to 0.264; 0.011)	Treated: 6,147 Control: 5,033	-0.059^ (-0.156 to 0.045; 0.276)	Treated: 1,904 Control: 511

Table 7-11 Change in community yearly exacerbations, eosinophil nested cohort
Change in propensity score matching from methods: ^caliper=0.05, NN=2

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non use	0.011 (-0.005 to 0.026; 0.178)	Treated: 5,698 Control: 7,165	0.034 (-0.017 to 0.084; 0.196)	Treated: 4,820 Control: 5,033	0.074 (0.039 to 0.109; 0.000)	Treated: 1,482 Control: 511
Intermediate and strict use versus non use	0.013 (0.000 to 0.026; 0.059)	Treated: 7,001 Control: 7,165	0.040 (0.003 to 0.077; 0.034)	Treated: 6,147 Control: 5,033	0.076^ (0.041 to 0.110; 0.000)	Treated: 1,904 Control: 511

Table 7-12 Change in hospital yearly exacerbations, eosinophil nested cohort
Change in propensity score matching from methods: ^caliper=0.05, NN=2

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non use	High eosin: 0.294 (0.018 to 0.570; 0.037)	Treated, high eosin: 915 Control, high eosin: 991	High eosin: 0.144 (-0.036 to 0.323; 0.116)^	Treated, high eosin: 813 Control, high eosin: 666	High eosin: -0.048 (-0.447 to 0.350; 0.811)*	Treated, high eosin: 284 Control, high eosin: 77
	Normal eosin: 0.117 (0.062 to 0.172; 0.000)	Treated, norm eosin: 4,783 Control, norm eosin: 6,174	Normal eosin: 0.201 (0.097 to 0.305; 0.000)	Treated, norm eosin: 4,007 Control, norm eosin: 4,367	Normal eosin: 0.046 (-0.101 to 0.193; 0.542)	Treated, norm eosin: 1,198 Control, norm eosin: 434
Intermediate and strict use versus non use	High eosin: 0.172 (-0.080 to 0.425; 0.181)	Treated, high eosin: 1,112 Control, high eosin: 991	High eosin: 0.134 (-0.161 to 0.429; 0.372)^	Treated, high eosin: 1,020 Control, high eosin: 666	High eosin: -0.055 (-0.445 to 0.335; 0.783)*	Treated, high eosin: 351 Control, high eosin: 77
	Normal eosin: 0.133 (0.083 to 0.182; 0.000)	Treated, norm eosin: 5,889 Control, norm eosin: 6,174	Normal eosin: 0.194 (0.106 to 0.281 0.000)	Treated, norm eosin: 5,127 Control, norm eosin: 4,367	Normal eosin: -0.014 (-0.158 to 0.131; 0.851)^	Treated, norm eosin: 1,553 Control, norm eosin: 434

Table 7-13 Change in total yearly exacerbations, categorised by eosinophil group

Change in propensity score matching from methods: ^caliper=0.05, NN=2; *caliper=0.1, NN=2

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non use	High eosin: 0.254 (0.008 to 0.499; 0.043) Normal eosin: 0.101 (0.053 to 0.150; 0.000)	Treated, high eosin: 915 Control, high eosin: 991 Treated, norm eosin: 4,783 Control, norm eosin: 6,174	High eosin: 0.144 (-0.022 to 0.310; 0.089)^ Normal eosin: 0.166 (0.038 to 0.293; 0.011)	Treated, high eosin: 813 Control, high eosin: 666 Treated, norm eosin: 4,007 Control, norm eosin: 4,367	High eosin: -0.111 (-0.503 to 0.281; 0.580)* Normal eosin: -0.030 (-0.174 to 0.114; 0.684)	Treated, high eosin: 284 Control, high eosin: 77 Treated, norm eosin: 1,198 Control, norm eosin: 434
Intermediate and strict use versus non use	High eosin: 0.152 (-0.068 to 0.373; 0.176) Normal eosin: 0.112 (0.069 to 0.156; 0.000)	Treated, high eosin: 1,112 Control, high eosin: 991 Treated, norm eosin: 5,889 Control, norm eosin: 6,174	High eosin: 0.124 (-0.098 to 0.346; 0.274)^ Normal eosin: 0.152 (0.035 to 0.268; 0.011)	Treated, high eosin: 1,020 Control, high eosin: 666 Treated, norm eosin: 5,127 Control, norm eosin: 4,367	High eosin: -0.116 (-0.504 to 0.272; 0.559)* Normal eosin: -0.089 (-0.229 to 0.050; 0.210)^	Treated, high eosin: 351 Control, high eosin: 77 Treated, norm eosin: 1,553 Control, norm eosin: 434

Table 7-14 Change in community yearly exacerbations, categorised by eosinophil group
Change in propensity score matching from methods: ^caliper=0.05, NN=2; *caliper=0.1, NN=2

ICS usage	Year 3		Year 5		Year 10	
	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants	Exacerbations/yr (*95% CI; p*)	Participants
Strict use versus non use	High eosin: 0.040 (-0.006 to 0.086; 0.086) Normal eosin: 0.016 (-0.010 to 0.041; 0.227)	Treated, high eosin: 915 Control, high eosin: 991 Treated, norm eosin: 4,783 Control, norm eosin: 6,174	High eosin: -0.001 (-0.037 to 0.036; 0.977)^ Normal eosin: 0.036 (-0.021 to 0.092; 0.215)	Treated, high eosin: 813 Control, high eosin: 666 Treated, norm eosin: 4,007 Control, norm eosin: 4,367	High eosin: 0.062 (0.007 to 0.118; 0.028) Normal eosin: 0.076 (0.037 to 0.114; 0.000)	Treated, high eosin: 284 Control, high eosin: 77 Treated, norm eosin: 1,198 Control, norm eosin: 434
Intermediate and strict use versus non use	High eosin: 0.020 (-0.031 to 0.071; 0.441) Normal eosin: 0.020 (-0.004 to 0.044; 0.095)	Treated, high eosin: 1,112 Control, high eosin: 991 Treated, norm eosin: 5,889 Control, norm eosin: 6,174	High eosin: 0.011 (-0.079 to 0.100; 0.816)^ Normal eosin: 0.042 (0.004 to 0.080; 0.032)	Treated, high eosin: 1,020 Control, high eosin: 666 Treated, norm eosin: 5,127 Control, norm eosin: 4,367	High eosin: 0.061 (0.016 to 0.106; 0.008)* Normal eosin: 0.076 (0.038 to 0.113; 0.000)	Treated, high eosin: 351 Control, high eosin: 77 Treated, norm eosin: 1,553 Control, norm eosin: 434

Table 7-15 Change in hospital yearly exacerbations, categorised by eosinophil group
Change in propensity score matching from methods ^caliper=0.05, NN=2; *caliper=0.1, NN=2

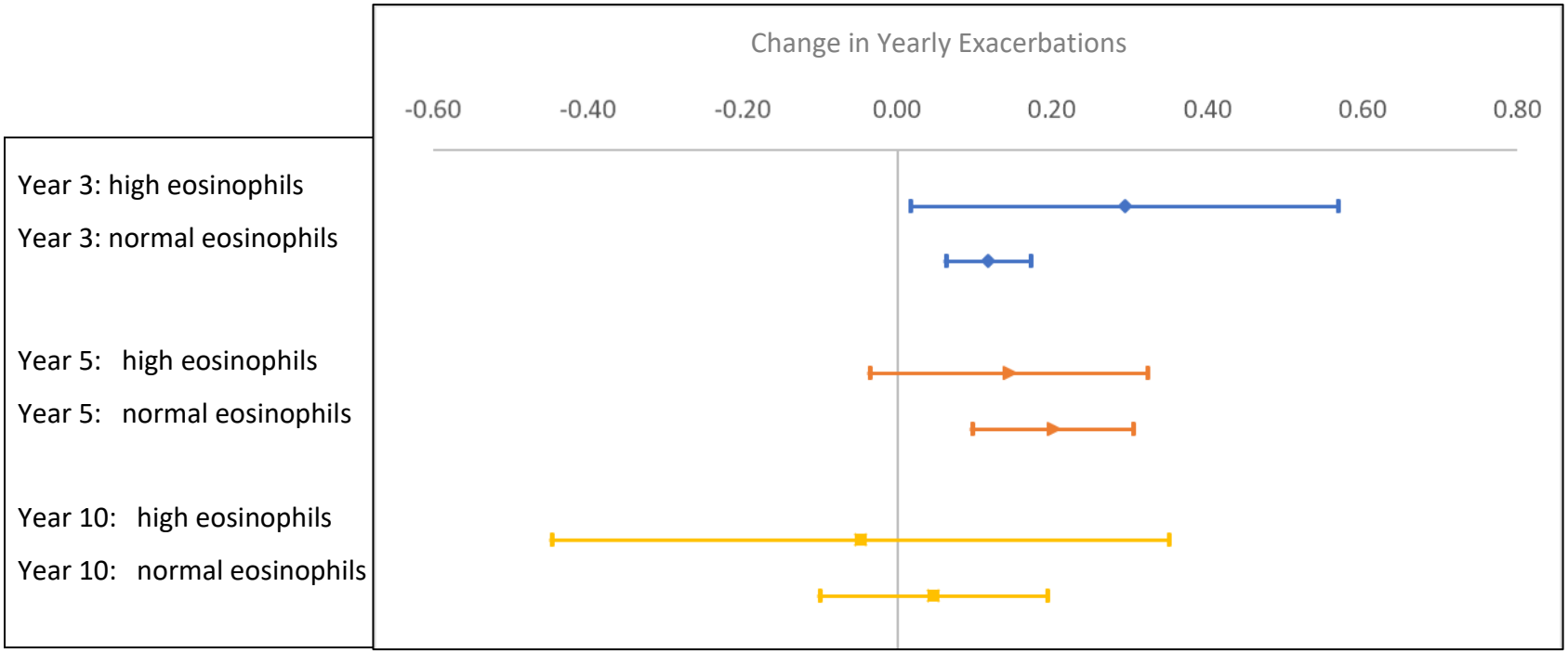

Figure 7-4 Change in total Exacerbations/year with strict ICS use versus no-ICS use by blood eosinophil sub-group at years three, five and ten

7.4 Discussion

It was found throughout this chapter that ICS use was associated with an increase in yearly exacerbations. After five years this increase in yearly exacerbations was greater in current smokers versus non- and ex-smokers and in those with normal eosinophils counts versus high eosinophil counts. Those with an asthma co-diagnosis had more yearly exacerbations with ICS use at year five than those without an asthma co-diagnosis, but this trend was reversed at year ten.

7.4.1 Exacerbations in the whole cohort

Although a surprising finding that yearly exacerbation rates increased with ICS use, this had actually been reported before in a similar study using data from CPRD (Oshagbemi et al., 2018). The authors of this previous study found that current use of ICS was associated with a higher frequency of exacerbations (HR of 1.15; 95% CI 1.09-1.21) compared to never-use; they postulate this is because of disease severity being a confounding factor, or the people being prescribed ICS having the 'frequent exacerbator' phenotype. Additionally at least two other studies in COPD patients also reported an increased risk of COPD exacerbation in patients exposed to any ICS compared to patients not exposed to ICS; one a case-controlled study (de Melo et al., 2004, Morjaria et al., 2017) and the other an RCT (Morjaria et al., 2017). Furthermore, a recent Cochrane review by Horita et al. (2017) found that LAMA plus LABA inhaler combination to be more effective in reducing exacerbations than LABA plus ICS; OR 0.82 (95% CI 0.70 to 0.96, p= 0.01). Since ICS are prescribed in order to prevent these events, confounding by disease severity may explain this.

The frequency of exacerbations increased in all settings after years three and five, hospital-based exacerbations contributed to a relatively low number of the total exacerbations. After ten years, hospital exacerbations had increased, however community-based may have decreased, but was not statistically significant. This was expected as hospital-based exacerbations are used as a proxy measure for more severe exacerbations and community for mild or moderate exacerbations. The aim of dividing the setting of exacerbation was to assess if there was any difference of effect of ICS on severity of exacerbation, but it is difficult to draw any firm conclusions from these data due to the low number of hospital-based exacerbations contributing to lack of statistical significance. It is possible that extended use of ICS leads to a reduction in community exacerbations but does not appear to have any effect on hospital or severe exacerbations.

Both 'strict' ICS adherence and 'intermediate' ICS adherence were studied in this chapter; however as can be seen from all results tables, the effect size was very similar between the two groups and therefore just the effect of 'strict' ICS use is discussed further.

7.4.2 Exacerbations in the nested cohort

The same trend in yearly exacerbations was seen in the nested eosinophil cohort as that of the main cohort. This suggests that blood eosinophil counts are not an important predictor of exacerbations.

7.4.3 Smoking status sub-groups

Overall the total number of yearly exacerbations increased more after five and ten years in current smokers who used ICS versus ex- and non-smokers with ICS use. These exacerbations mostly occurred in the community setting, but the trends seen were similar in both the hospital and community exacerbations. Additionally, similar results were seen in both categories of ICS use; strict and strict/intermediate use. This was as expected; a known risk factor for an exacerbation of COPD is smoking and smoking cessation is associated with a reduced risk of an exacerbation (Au et al., 2009).

When categorised by amount smoked, no clear conclusions could be drawn due to lack of statistical significance and overlapping 95% confidence intervals. On closer examination of these data, lighter smokers (<20 cigarettes/day) had a larger increase in hospital-based yearly exacerbations of COPD than heavier smokers (≥20 cigarettes/day), but this may be a statistical anomaly due to low numbers of hospital-based exacerbations recorded.

The systematic review in chapter three of this thesis identified that there were more yearly exacerbations in ICS users who were current or heavier smokers than those who were ex-smokers or lighter smokers; an increase in RR of 0.09 to 0.21 at up to 52-weeks duration. However, a lack of data and methodological limitations meant this warranted further investigation. The results presented in this chapter also demonstrate that ICS have no beneficial effect in current smokers over ex- and non-smokers in preventing exacerbations; after five years the effect of smoking was an extra 0.074 yearly exacerbations with ICS use. As the study presented in this chapter was of a significantly

longer duration than those of the systematic review, it can be concluded that the effect of smoking on increasing yearly exacerbation rates is maintained in the long-term.

7.4.4 Asthma diagnosis sub-groups

The effect of ICS in people with an asthma co-diagnosis versus those without is interesting; for both total and community-based yearly exacerbations there appears to be no difference in the groups at year three, increased yearly exacerbations in the asthma group at year five, and by year ten the trend is reversed with the asthma group experiencing fewer yearly exacerbations than the no-asthma group treated with ICS, although the data at year ten is not statistically significant. Section 2.2.4 of this thesis found that there was very limited literature on the effect ICS have in asthma-COPD overlap, with one large cohort study also finding that LABA/ICS therapy reduced the risk of exacerbation in the long-term (Su et al., 2018), so the lack of definitive conclusion is not surprising.

Although the total yearly exacerbations at year ten were reduced in the asthma/ICS group, the hospital-based exacerbations were higher than in the no-asthma group at all time-points. This is intuitive as people with asthma-COPD overlap have been shown to have more severe disease (Menezes et al., 2014) or to be more severely affected by an exacerbation and thus require hospitalisation.

These results suggest that people with a co-diagnosis of asthma are may be more likely to respond to ICS in terms of mild or moderate exacerbations treated in the community than those without, but in the long term only.

7.4.5 Blood eosinophil sub-groups

The trend seen for people with high blood eosinophils/ICS use is to have a lower increase in yearly exacerbation rates than those with normal blood eosinophils at years five and ten. However, there are large, overlapping 95% confidence intervals which suggests that there may be no significant effect. A similar study (Oshagbemi et al., 2018) also demonstrated that stratification of ICS use by absolute or relative blood eosinophil counts did not result in significant differences in risk of COPD exacerbations or hospitalisations/accident and emergency visits. Furthermore, the systematic review discussed in section 2.1.4 of this thesis by Harries et al. (2020) found a lack of association between ICS and moderate/severe exacerbations in four of the five observational studies. The one study in this systematic review that did find an association was also conducted using CPRD data; it reported results of 21% fewer exacerbations when blood eosinophils ≥4% and 24% fewer exacerbations when blood eosinophils ≥300 cells/microL (Suissa et al., 2018). This is comparable to the 28% reduction in yearly exacerbations found at year five in the high eosinophil group reported in this thesis.

7.4.6 Strengths and Limitations

7.4.6.1 Methods

The limitations around the methods used in this study, including propensity score matching and use of the CPRD dataset will be discussed in chapter nine.

7.4.6.2 Use and definition of exacerbations

Exacerbations of COPD are a good indicator of both severity of the disease and quality of life and are used in all studies of patient-orientated outcomes. However, the number of exacerbations an individual experiences per year is low, with many people not experiencing a single exacerbation per year and fluctuations from one year to the next often occurring. Furthermore, as COPD is a chronic, progressive disease, it would be expected that yearly exacerbations would tend to increase with time, thereby making it a variable measure of efficacy of therapy.

The method for definition of both community and hospital exacerbations were discussed in chapter four (section 4.6.1). There are weaknesses with these methods in determining outcomes, as it is likely that the data captured here under-represents the true number of exacerbations experienced. Hospital exacerbations were only recorded if they were the primary cause of the admission, thereby missing some that occurred during other hospital admissions. Community exacerbations were recorded as a combination of factors, however amongst those was the need for antibiotics and OCS on the same day; this may have missed some exacerbations where one or the other was started a day or two apart, as can often happen in real-life situations.

The flaws with the definition of asthma within CPRD are discussed in chapter nine (section 9.5). One possible confounding factor is blood eosinophilia which is associated with both asthma and increased exacerbation rates. As demonstrated in this chapter, people with high eosinophil counts tended to have a lower increase in yearly exacerbation rates than those with normal counts and it would have been expected that those with asthma would demonstrate similar results. The fact that an asthma diagnosis seemed to have the opposite effect suggests that the method by which an asthma diagnosis was recorded may be inaccurate.

7.5 Conclusion

Overall ICS use is associated with increased yearly exacerbation rates compared to non-use. However, this may be due to the inherent nature of the people prescribed these medications being 'frequent exacerbators' or having more severe COPD.

No real effect was seen in any of the sub-groups at year three. At years five and ten current smokers had a greater increase in yearly exacerbations than ex- and non-smokers with ICS use. The asthma co-diagnosis group and the high blood eosinophil group showed no clear trend in response to ICS; there was possibly a decrease in yearly exacerbations at the ten-year time point in both groups but lacked statistical significance.

Finally, there was only a small difference in effect size on yearly exacerbations when ICS were taken with 'strict' adherence in comparison to 'intermediate' adherence on all results; suggesting that any reasonable usage of ICS would produce the effects presented in this chapter.

8. Prospective cohort study: Mortality

8.1 Introduction

In this chapter, the effect of smoking status, asthma co-diagnosis and blood eosinophilia on the effectiveness of ICS use the outcomes of: all-cause and respiratory-cause mortality will be investigated at the three-, five- and ten-year time points.

8.2 Methods

This was described in chapter six. Below outlines the additional methods relevant to this chapter investigating mortality.

8.2.1 Definition of ICS use

For the outcome of all-cause death and respiratory-cause death, the usage of ICS was defined as the usage in year one only (Table 8-1). This was because many patients would not have the full three, five or ten years of ICS due to death.

8.2.2 Definition of death

Deaths were measured as probability of all-cause death and respiratory-cause death after three, five and ten years. Respiratory cause death was defined as per ICD-10 codes for mortality (from ONS data), as per Table 8-2. It is important to note that the outcome of death reported here is the relative probability of death and if this increased or decreased with ICS use in each of the sub-groups, not absolute probability of death.

Category of ICS use	Definition
Strict ICS user	Over 80% persistence (≤20% CMG) with a prescription in each quarter of the year. OR adherence of: DDD ≥292, or ≥233mg beclometasone equivalence/year
Intermediate ICS user	Over 50% persistence (≤50% CMG) with a prescription in at least 3 of the 4 quarters. OR adherence of: DDD ≥182, or ≥146mg beclometasone equivalence/year
Wider ICS user	Over 10% persistence (≤90% CMG) in at least one quarter of the year. OR adherence of: DDD >28, or >23mg beclometasone equivalence/year
Non-ICS user	Less than 10% persistence (≥90% CMG) in no more than one quarter. OR adherence of: DDD ≤28, or ≤23mg beclometasone equivalence/year

Table 8-1 Definitions of ICS use during each one year period from entry date
Based on the method of Svendson et al (2012) for opiate usage.

ICD-10	Definition
J09	Influenza due to certain identified influenza virus
J10-11	Influenza
J12-18	Pneumonia
J40-44	Bronchitis, emphysema and other chronic obstructive pulmonary disease
J45-46	Asthma

Table 8-2 ICD-10 Respiratory-cause death classification
Taken from ONS user guide to mortality statistics (ONS, 2022)

8.2.3 Data analysis

Whereas a logistic model was used for the outcomes of lung function and exacerbations, a probability model was used for the outcome of deaths due to this being a binary outcome. Propensity score matching was undertaken and then a probabilistic model was fitted to the data using the *teffect* command. An example of the command used in Stata v15 is in Figure 8-1.

```
By asthma1, sort: teffects psmatch (respdeathyr3) (ICSyr3 pc_pscore, probit), caliper(0.05) nn(5)
```

Figure 8-1 Stata command for probabilistic model using propensity score matching to investigate mortality

8.3 Results

8.3.1 Demographics

The same cohort was used as in chapter six. The demographics of the whole cohort and nested eosinophil cohort were presented in Table 6-3 and Table 6-4.

The cumulative number of all-cause deaths in the cohort were 13,601 (21.7%) after three years and 45,701 (73.0%) after ten years. The cumulative number of respiratory-cause deaths were 3,114 (5.0%) after three years and 6,975 (11.1%) after ten years.

For all results reported, a probability of death of zero (or 95% confidence intervals overlapping zero) mean that there is no change in the probability of death with ICS use; this is the relative risk. A probability of below zero with ICS use means that ICS have reduced the relative risk of dying at that time point and conversely a probability above zero means the relative risk of death has increased in that group. Of course, in the comparison of some groups (e.g. current smokers versus non/ex-smokers) the absolute risk of death would be expected to be higher in the current smoker group than the non/ex-smoker group, but it is the relative risk reduction with ICS use that is being compared.

8.3.2 All-cause deaths

Use of ICS (strict and intermediate usage) resulted in a reduction in probability of all-cause death at all time points for in the range of 2.3-5.7% for the whole cohort. The reduction in probability of death had declined by year ten; -0.051 (95% CI = -0.069 to -

0.033; p= 0.000) at year three to -0.023 (-0.039 to -0.007; 0.005) at year ten with strict ICS use. See Table 8-3.

8.3.3 Respiratory-cause deaths

ICS users (strict and intermediate use) had an increased probability of respiratory-cause death in all time frames compared to non-use; from 0.008 (-0.001 to 0.017; 0.096) at year three to 0.033 (0.017 to 0.049; 0.000) at year ten in the 'strict' ICS use group; this was unlike all-cause deaths. See Table 8-4.

ICS usage	Year 3		Year 5		Year 10	
	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants
Strict versus non-use	-0.050 (-0.072 to -0.029; 0.000)	Treated: 15,814 Control: 28,108	-0.040 (-0.065 to -0.016; 0.001)	Treated: 14,938 Control: 26,415	-0.023 (-0.039 to -0.007; 0.005)	Treated: 13,474 Control: 24,057
Intermediate/strict versus non-use	-0.051 (-0.069 to -0.033; 0.000)	Treated: 20,136 Control: 28,108	-0.057 (-0.077 to -0.038; 0.000)	Treated: 19,016 Control: 26,415	-0.031 (-0.044 to -0.018; 0.000)	Treated: 17,168 Control: 24,057

Table 8-3 Change in probability of all-cause deaths in whole cohort with ICS use versus no use

ICS usage	Year 3		Year 5		Year 10	
	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants
Strict versus non-use	0.008 (-0.001 to 0.017; 0.096)	Treated: 15,814 Control: 28,108	0.022 (0.009 to 0.034; 0.001)	Treated: 14,938 Control: 26,415	0.033 (0.017 to 0.049; 0.000)	Treated: 13,474 Control: 24,057
Intermediate/strict versus non-use	0.009 (0.001 to 0.016; 0.026)	Treated: 20,136 Control: 28,108	0.019 (0.008 to 0.030; 0.001)	Treated: 19,016 Control: 26,415	0.027 (0.014 to 0.040; 0.000)	Treated: 17,168 Control: 24,057

Table 8-4 Change in probability of respiratory-cause deaths in whole cohort with ICS use versus no use

8.3.4 Smoking

8.3.4.1 All-cause deaths

Current smokers using ICS consistently had a higher probability of all-cause death than current smokers not using ICS (Table 8-5 and Figure 8-2). These results did not always achieve statistical significance though. After five years there was an increased probability of death in the strict ICS/smoking group of 0.030 (95% CI=0.007 to 0.053; p=0.010) over current smoking/no ICS group. Furthermore, ex- and non-smokers using ICS saw the opposite effect; a decline in the probability of death with use of ICS over non-use at all time points, for example year five: -0.038 (-0.063 to -0.013; 0.003). This equates to smokers having a 6.8% increase in mortality with ICS use over ex- and non-smokers.

There was a mixed picture when categorised by amount smoked (Table 8-5 and Figure 8-3); with some instances of heavy smokers using ICS having a lower probability of all-cause death than non-ICS users. For example, after three years the heavy smoker/ICS use had a decreased probability of death over non-ICS use: -0.057 (-0.131 to 0.017; 0.131) and this was greater than the decrease in probability of death seen in the ex- and non-smoking group with ICS use: -0.051 (-0.073 to -0.029; 0.000). However, there were very low numbers of patients in the heavy smoking plus ICS sub-group and wide 95% confidence interval, spanning both increased and decreased probability of death.

8.3.4.2 Respiratory-cause deaths

When categorised by current smoking status, interesting results were observed: after five years the current smoker/strict ICS patient had a higher probability of respiratory-cause death than non-ICS patients (Table 8-6 and Figure 8-4); 0.023 (0.003 to 0.042;

0.024), which was expectedly higher than the corresponding ex- and non-smoker/ICS use group; 0.020 (0.002 to 0.038; 0.028). By ten years this trend was reversed: the current smoker/strict ICS use group's probability of death was 0.023 (-0.001 to 0.046; 0.056) greater than non-ICS use and ex- and non-smoker/strict ICS use was 0.040 (0.019 to 0.062; 0.000) greater than non-ICS use.

When categorised by amount smoked, probability of respiratory-cause death up to year five did not reach statistical significance (Table 8-6 and Figure 8-5). However, at year ten heavy smokers (≥20 cigarettes/day) with strict ICS use had a higher probability of respiratory death than heavy smokers with no ICS use; 0.067 (0.015 to 0.119; 0.011). In addition, this increase in probability of death was greater than in the corresponding lighter-smoking group/strict ICS use group; 0.028 (0.011 to 0.045; 0.001).

ICS usage	Year 3		Year 5		Year 10	
	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants
Strict versus non-use	Current smoker: 0.003 (-0.008 to 0.015; 0.577)	Treated, smoker: 4,033 Control, smoker: 8,869	Current smoker: 0.030 (0.007 to 0.053; 0.010)	Treated, smoker: 2,496 Control, smoker: 4,990	Current smoker: 0.056 (-0.062 to 0.175; 0.352)*	Treated, smoker: 362 Control, smoker: 615
	Ex/never smoker: -0.056 (-0.083 to -0.029; 0.000)	Treated, ex/non smoker: 11,781 Control, ex/non smoker: 19,239	Ex/never smoker: -0.038 (-0.063 to -0.013; 0.003)	Treated, ex/non smoker: 12,442 Control, ex/non smoker: 21,425	Ex/never smoker: -0.021 (-0.039 to -0.002; 0.027)	Treated, ex/non smoker: 13,112 Control, ex/non smoker: 23,442
	Smoked >20/day: -0.057 (-0.131 to 0.017; 0.131)	Treated, >20/day: 968 Control, >20/day: 2,566	Smoked >20/day: -0.028 (-0.103 to 0.046; 0.456)^	Treated, >20/day: 796 Control, >20/day: 2,120	Smoked >20/day: -0.003 (-0.023 to 0.017; 0.769)*	Treated, >20/day: 672 Control, >20/day: 1,858
	<20/day: -0.051 (-0.073 to -0.029; 0.000)	Treated, <20/day: 14,846 Control, <20/day: 25,542	<20/day: -0.041 (-0.066 to -0.015; 0.002)	Treated, <20/day: 14,142 Control, <20/day: 24,295	<20/day: -0.021 (-0.041 to -0.001; 0.035)	Treated, <20/day: 12,802 Control, <20/day: 22,199
Intermediate and strict versus non-use	Current smoker: 0.002 (-0.008 to 0.011; 0.721)	Treated, smoker: 5,203 Control, smoker: 8,869	Current smoker: 0.017 (0.001 to 0.033; 0.039)	Treated, smoker: 3,238 Control, smoker: 4,990	Current smoker: 0.017 (-0.053 to 0.088; 0.630)*	Treated, smoker: 480 Control, smoker: 615
	Ex/never smoker: -0.060 (-0.083 to -0.036; 0.000)	Treated, ex/non smoker: 14,933 Control, ex/non smoker: 19,239	Ex/never smoker: -0.058 (-0.079 to -0.036; 0.000)	Treated, ex/non smoker: 15,778 Control, ex/non smoker: 21,425	Ex/never smoker: -0.026 (-0.042 to -0.011; 0.001)	Treated, ex/non smoker: 16,688 Control, ex/non smoker: 23,442
	Smoked >20/day: -0.055 (-0.113 to 0.003; 0.061)	Treated, >20/day: 1,240 Control, >20/day: 2,566	Smoked >20/day: -0.050 (-0.117 to 0.016; 0.134)^	Treated, >20/day: 1,010 Control, >20/day: 2,120	Smoked >20/day: -0.027 (-0.063 to 0.008; 0.133)*	Treated, >20/day: 847 Control, >20/day: 1,858
	<20/day: -0.052 (-0.070 to -0.033; 0.000)	Treated, <20/day: 18,896 Control, <20/day: 25,542	<20/day: -0.059 (-0.080 to -0.038; 0.000)	Treated, <20/day: 18,006 Control, <20/day: 24,295	<20/day: -0.031 (-0.049 to -0.014; 0.000)	Treated, <20/day: 16,321 Control, <20/day: 22,199

Table 8-5 Change in probability of all-cause deaths categorised by smoking status with ICS use versus no use

Changes to propensity score matching to methods: *Caliper=0.1, nn<5

ICS usage	Year 3		Year 5		Year 10	
	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants
Strict versus non-use	Current smoker: 0.004 (-0.007 to 0.016; 0.463) Ex/never smoker: 0.013 (0.000 to 0.026; 0.042)	Treated, smoker: 5,742 Control, smoker: 13,793 Treated, ex/non smoker: 10,072 Control, ex/non smoker: 14,315	Current smoker: 0.023 (0.003 to 0.042; 0.024) Ex/never smoker: 0.020 (0.002 to 0.038; 0.028)	Treated, smoker: 5,457 Control, smoker: 13,068 Treated, ex/non smoker: 9,481 Control, ex/non smoker: 13,347	Current smoker: 0.023 (-0.001 to 0.046; 0.056) Ex/never smoker: 0.040 (0.019 to 0.062; 0.000)	Treated, smoker: 4,968 Control, smoker: 12,018 Treated, ex/non smoker: 8,506 Control, ex/non smoker: 12,039
	Smoked ≥20/day: 0.036 (0.000 to 0.073; 0.051) Smoked<20/day: 0.006 (-0.004 to 0.015; 0.233)	Treated, ≥20/day: 1,454 Control, ≥20/day: 3,968 Treated, <20/day: 14,360 Control, <20/day: 24,140	Smoked ≥20/day: 0.049 (0.001 to 0.096; 0.044) Smoked<20/day: 0.018 (0.005 to 0.031; 0.007)	Treated, ≥20/day: 1,383 Control, ≥20/day: 3,763 Treated, <20/day: 13,555 Control, <20/day: 22,652	Smoked ≥20/day: 0.067 (0.015 to 0.119; 0.011) Smoked<20/day: 0.028 (0.011 to 0.045; 0.001)	Treated, ≥20/day: 1,265 Control, ≥20/day: 3,476 Treated, <20/day: 12,209 Control, <20/day: 20,581
Intermediate and strict versus non-use	Current smoker: 0.005 (-0.006 to 0.016; 0.334) Ex/never smoker: 0.012 (0.001 to 0.022; 0.030)	Treated, smoker: 7,365 Control, smoker: 13,793 Treated, ex/non smoker: 12,771 Control, ex/non smoker: 14,315	Current smoker: 0.018 (0.003 to 0.034; 0.020) Ex/never smoker: 0.020 (0.006 to 0.034; 0.006)	Treated, smoker: 6,988 Control, smoker: 13,068 Treated, ex/non smoker: 12,028 Control, ex/non smoker: 13,347	Current smoker: 0.021 (0.002 to 0.041; 0.033) Ex/never smoker: 0.035 (0.016 to 0.054; 0.000)	Treated, smoker: 6,338 Control, smoker: 12,018 Treated, ex/non smoker: 10,830 Control, ex/non smoker: 12,039
	Smoked ≥20/day: 0.023 (-0.001 to 0.047; 0.059) Smoked<20/day: 0.007 (-0.001 to 0.015; 0.106)	Treated, ≥20/day: 1,883 Control, ≥20/day: 3,968 Treated, <20/day: 18,253 Control, <20/day: 24,140	Smoked ≥20/day: 0.021 (-0.009 to 0.051; 0.166) Smoked<20/day: 0.019 (0.008 to 0.029; 0.001)	Treated, ≥20/day: 1,789 Control, ≥20/day: 3,763 Treated, <20/day: 17,227 Control, <20/day: 22,652	Smoked ≥20/day: 0.039 (0.003 to 0.074; 0.033) Smoked<20/day: 0.026 (0.012 to 0.040; 0.000)	Treated, ≥20/day: 1,631 Control, ≥20/day: 3,476 Treated, <20/day: 15,537 Control, <20/day: 20,581

Table 8-6 Change in probability of respiratory-cause deaths categorised by smoking status with ICS use versus no use

Changes to propensity score matching to methods: +Caliper =0.15, nn=2, ^Caliper=0.1, *Caliper=0.1, nn<5

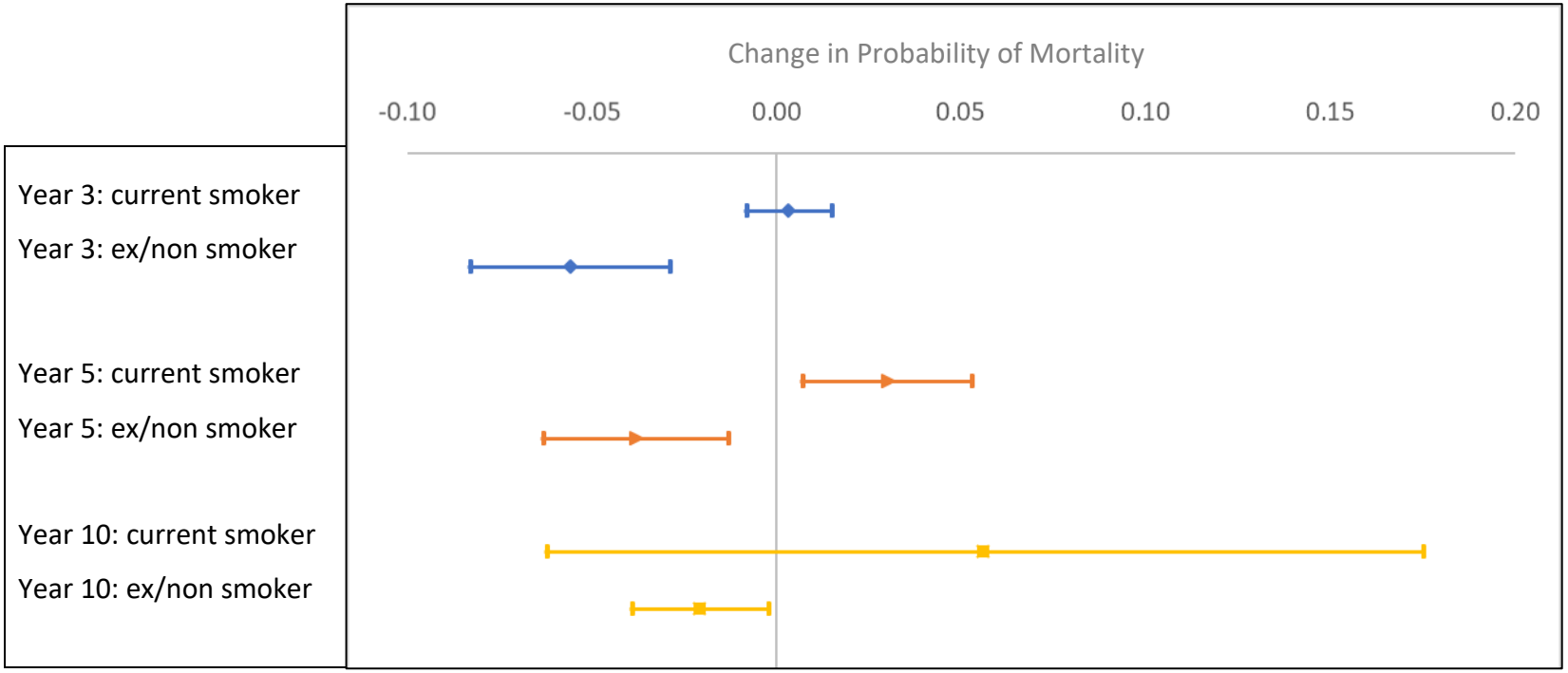

Figure 8-2 Change in probability of all-cause death at years 3,5 and 10 in people with COPD who were 'strict' users of ICS versus non-use, categorised by smoking status

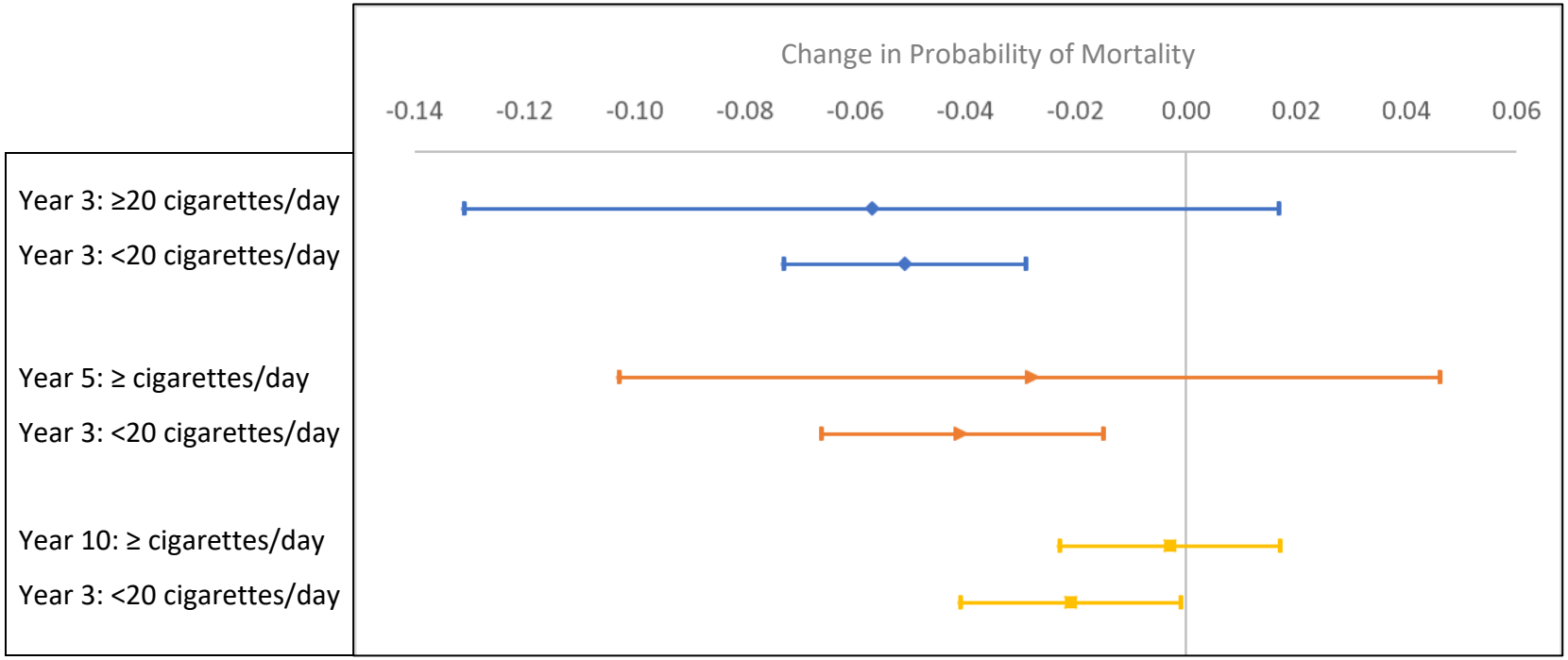

Figure 8-3 Change in probability of all-cause death at years 3,5 and 10 in people with COPD who were 'strict' users of ICS versus non-use, categorised by amounted smoked

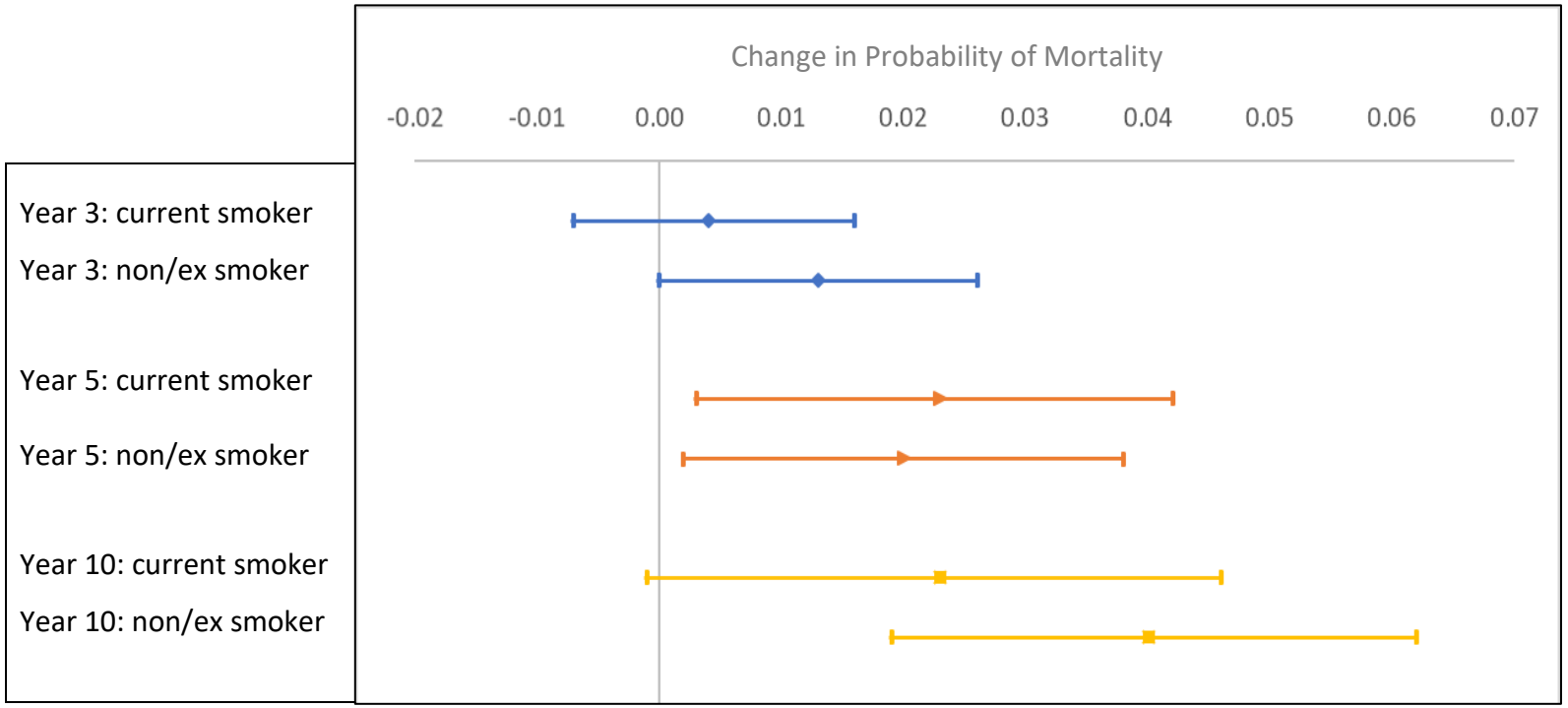

Figure 8-4 Change in probability of respiratory-cause death at years 3,5 and 10 in people with COPD who were 'strict' users of ICS versus non-use, categorised by smoking status

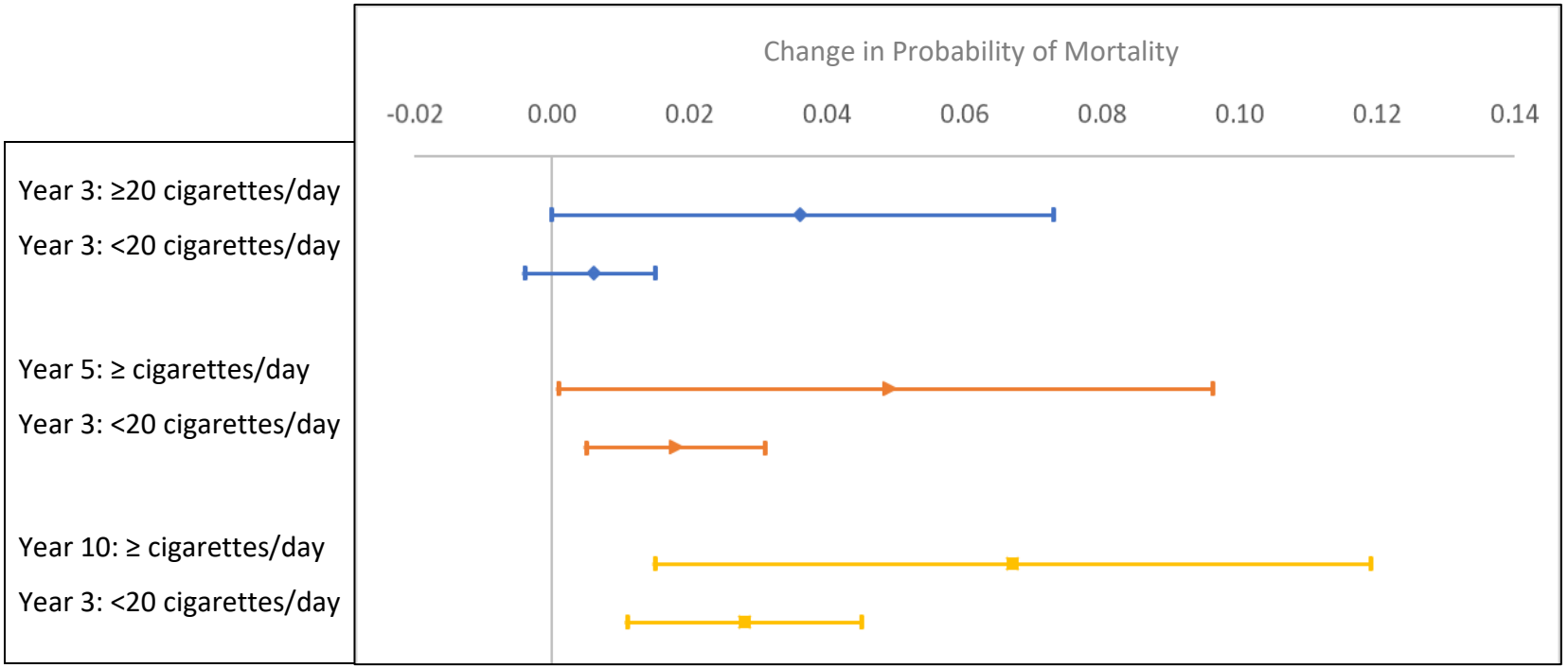

Figure 8-5 Change in probability of respiratory-cause death at years 3,5 and 10 in people with COPD who were 'strict' users of ICS versus non-use, categorised by amounted smoked

8.3.5 Asthma

8.3.5.1 All-cause deaths

When the patients were categorised by asthma diagnosis, all patients with asthma using ICS had a lower probability of all-cause death compared to those not using ICS (Table 8-7 and Figure 8-6). This benefit seemed to peak after five years with the asthma/strict ICS use group having a lower probability of all-cause death than the asthma/no ICS group: -0.092 (95% CI=-0.122 to -0.062; p=0.000). Interestingly, the group of patients who did not have asthma also saw a benefit of using ICS; after five years the benefit in the strict ICS group was -0.010 (-0.040 to 0.020; 0.506) over non-use of ICS. Overall this result shows that an asthma diagnosis is associated with a reduction in mortality of 8.2% with ICS use over no asthma diagnosis. The benefit seen by those without asthma using ICS was consistently lower than those with asthma using ICS, however many of these results did not reach statistical significance.

8.3.5.2 Respiratory-cause deaths

For the respiratory-cause death outcome, many of the results did not reach statistical significance (Table 8-8 and Figure 8-7). The general trend was that ICS use increased the probability of respiratory death, but this increase was lower in the asthma group using ICS versus the no-asthma group. For example, after ten years in the 'strict' ICS/ asthma group increased probability of death was 0.011 (-0.009 to 0.031; 0.293) versus 0.045 (0.021 to 0.069; 0.000) in the strict ICS/no asthma.

ICS usage	Year 3		Year 5		Year 10	
	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants
Strict use versus non use	Asthma: -0.068 (-0.099 to -0.037; 0.000) No asthma: -0.04 (-0.065 to -0.015; 0.002)	Treated with asthma: 11,616 Control with asthma: 7,403 Treated, no asthma: 4,198 Control, no asthma: 20,705	Asthma: -0.092 (-0.122 to -0.062; 0.000) No asthma: -0.010 (-0.040 to 0.020; 0.506)	Treated with asthma: 11,071 Control with asthma: 7,058 Treated, no asthma: 3,867 Control, no asthma: 19,357	Asthma: -0.052 (-0.071 to -0.032; 0.000) No asthma: -0.012 (-0.026 to 0.002; 0.105)	Treated with asthma: 10,044 Control with asthma: 6,443 Treated, no asthma: 3,430 Control, no asthma: 17,614
Intermediate or strict use versus non use	Asthma: -0.063 (-0.090 to -0.036; 0.000)^ No asthma: -0.046 (-0.066 to -0.026; 0.000)	Treated with asthma: 14,399 Control with asthma: 7,403 Treated, no asthma: 5,737 Control, no asthma: 20,705	Asthma: -0.092 (-0.118 to -0.065; 0.000)^ No asthma: -0.037 (-0.060 to -0.015; 0.001)	Treated with asthma: 13,724 Control with asthma: 7,058 Treated, no asthma: 5,292 Control, no asthma: 19,357	Asthma: -0.055 (-0.073 to -0.036; 0.000)^ No asthma: -0.022 (-0.035 to -0.009; 0.001)	Treated with asthma: 12,477 Control with asthma: 6,443 Treated, no asthma: 4,691 Control, no asthma: 17,614

Table 8-7 Change in probability of all-cause deaths in categorised by asthma status with ICS use versus no use

Changes to propensity score matching to methods: ^Caliper=0.1, NN=5

ICS usage	Year 3		Year 5		Year 10	
	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants
Strict use versus non use	Asthma: 0.003 (-0.005 to 0.012; 0.435) No asthma: 0.011 (-0.003 to 0.025; 0.134)	Treated with asthma: 11,616 Control with asthma: 7,403 Treated, no asthma: 4,198 Control, no asthma: 20,705	Asthma: 0.002 (-0.014 to 0.018; 0.804) No asthma: 0.035 (0.016 to 0.055; 0.000)	Treated with asthma: 11,071 Control with asthma: 7,058 Treated, no asthma: 3,867 Control, no asthma: 19,357	Asthma: 0.011 (-0.009 to 0.031; 0.293) No asthma: 0.045 (0.021 to 0.069; 0.000)	Treated with asthma: 10,044 Control with asthma: 6,443 Treated, no asthma: 3,430 Control, no asthma: 17,614
Intermediate or strict use versus non use	Asthma: 0.002 (-0.006 to 0.011; 0.571)^ No asthma: 0.013 (0.002 to 0.025; 0.025)	Treated with asthma: 14,399 Control with asthma: 7,403 Treated, no asthma: 5,737 Control, no asthma: 20,705	Asthma: 0.005 (-0.010 to 0.020; 0.543)^ No asthma: 0.030 (0.014 to 0.045; 0.000)	Treated with asthma: 13,724 Control with asthma: 7,058 Treated, no asthma: 5,292 Control, no asthma: 19,357	Asthma: 0.012 (-0.007 to 0.032; 0.221)^ No asthma: 0.038 (0.019 to 0.057; 0.000)	Treated with asthma: 12,477 Control with asthma: 6,443 Treated, no asthma: 4,691 Control, no asthma: 17,614

Table 8-8 Change in probability of respiratory-cause deaths categorised by asthma status with ICS use versus no use

Changes to propensity score matching to methods: ^Caliper=0.1, NN=5

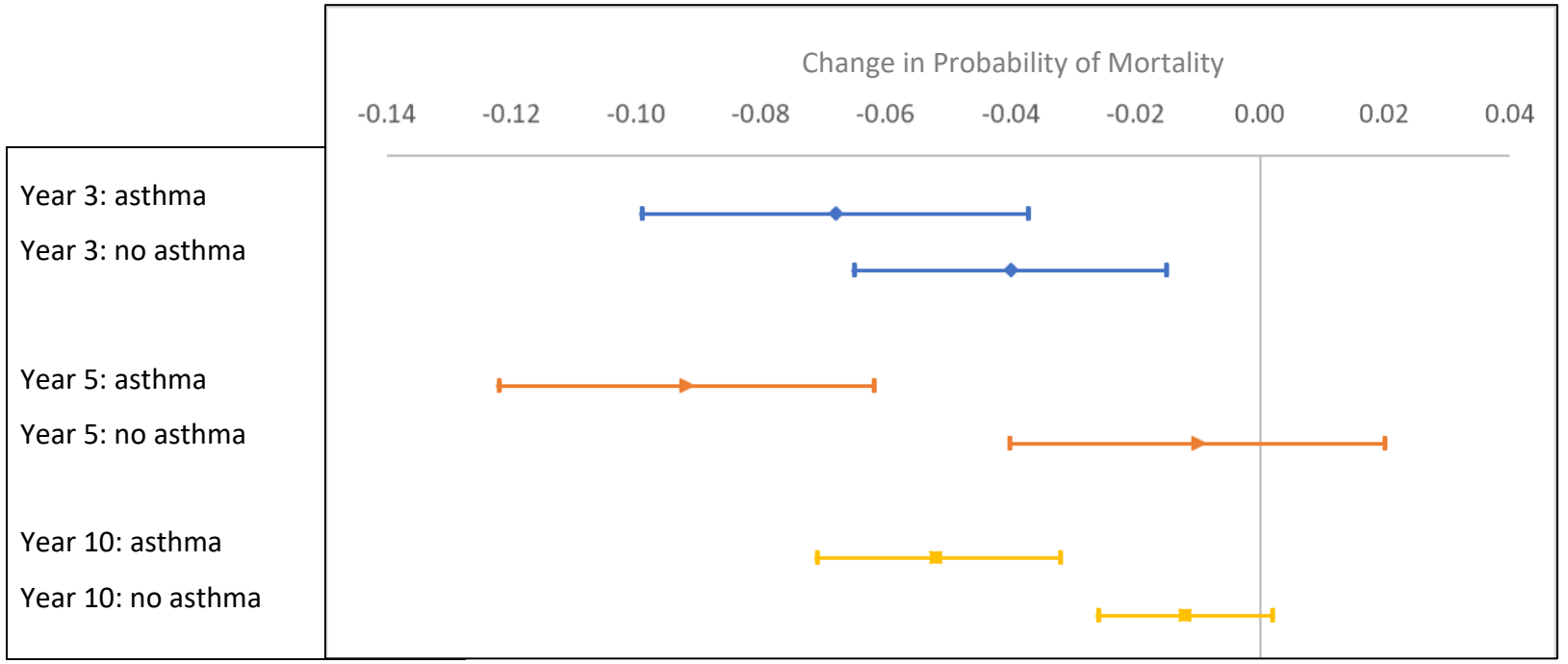

Figure 8-6 Change in probability of all-cause death at years 3,5 and 10 in people with COPD who were 'strict' users of ICS versus non-use, categorised by asthma diagnosis

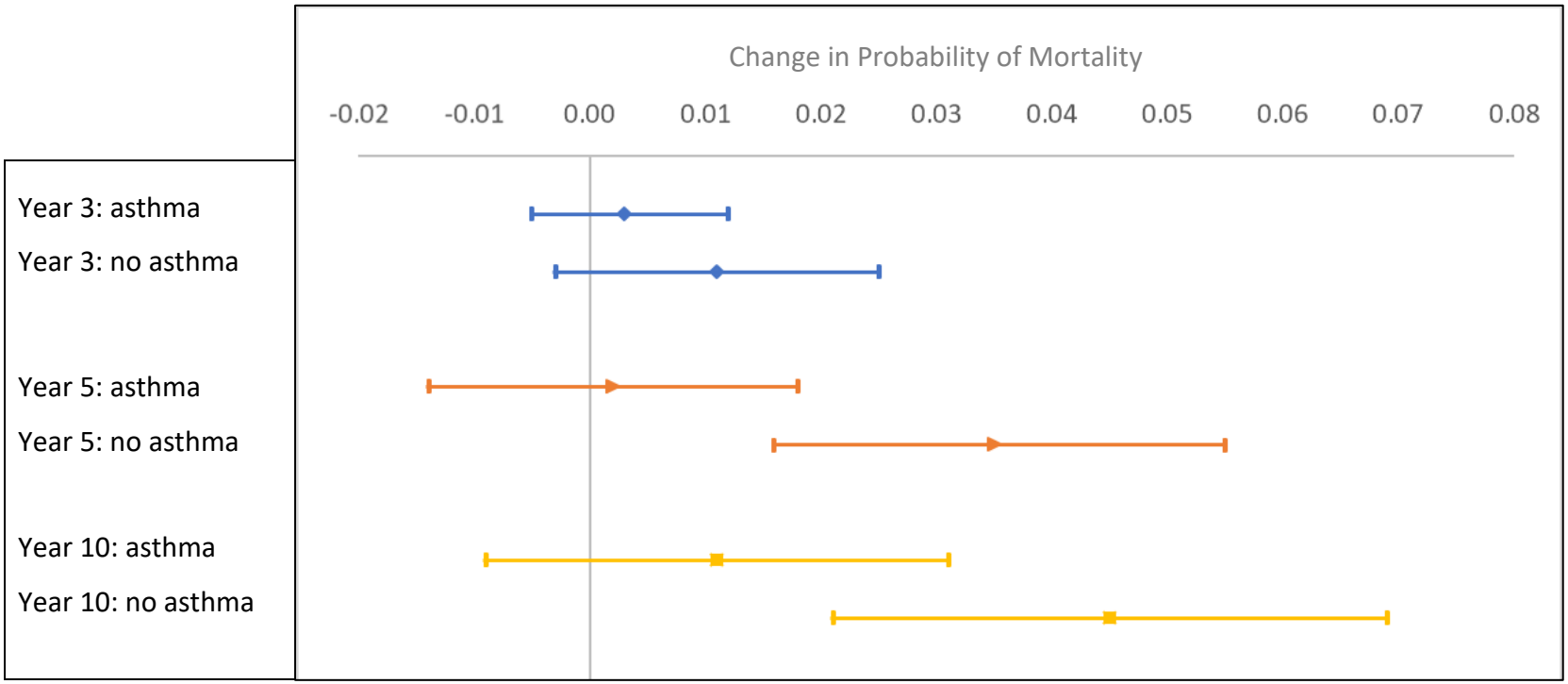

Figure 8-7 Change in probability of respiratory-cause death at years 3,5 and 10 in people with COPD who were 'strict' users of ICS versus non-use, categorised by asthma diagnosis

8.3.6 Eosinophil nested cohort

In the nested eosinophil cohort, the probability of all-cause death was similar to that of the whole cohort; a reduction in chance of death of up to 6% was seen with ICS use (Table 8-9). When the outcome of respiratory-death was observed, the same pattern of results was seen to the main cohort; an increased risk of respiratory death with ICS use versus no ICS use, of up to 1.5% (Table 8-10).

8.3.6.1 All-cause deaths

For all-cause deaths (Table 8-11 and Figure 8-8) there was a clear trend at years five and ten for people with high blood eosinophil counts, treated with ICS to have a lower probability of death than those with high eosinophil counts and not treated with ICS: -0.135 (-0.231 to -0.039; 0.006) after five years and -0.045 (-0.075 to -0.015; 0.004) after ten years. At these two time points, people with high eosinophils using ICS also had a lower probability of death than people with normal eosinophils using ICS; normal eosinophils/ICS versus no ICS: -0.035 (-0.071 to 0.000; 0.052) after five years and -0.041 (-0.066 to -0.017; 0.001) after ten years. Overall, at year five, the effect of high blood eosinophils was a decline in mortality of 10% with ICS use compared to those with normal blood eosinophil counts.

8.3.6.2 Respiratory-cause deaths

When categorised as having either high eosinophil counts or normal eosinophil counts, there was no discernible trend as no results met statistical significance for respiratory-cause deaths (Table 8-12 and Figure 8-9).

ICS usage	Year 3		Year 5		Year 10	
	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants
Strict use versus non-use	-0.050 (-0.082 to -0.019; 0.001)	Treated: 5,236 Control: 10,589	-0.043 (-0.076 to -0.010; 0.010)	Treated: 6,883 Control: 13,005	-0.039 (-0.061 to -0.016; 0.001)	Treated: 7,421 Control: 13,107
Intermediate or strict use versus non-use	-0.047 (-0.076 to -0.019; 0.001)	Treated: 6,596 Control: 10,589	-0.060 (-0.088 to -0.031; 0.000)	Treated: 8,754 Control: 13,005	-0.053 (-0.075 to -0.031; 0.000)	Treated: 9,491 Control: 13,107

Table 8-9 Change in probability of all-cause deaths with ICS use versus no use, nested eosinophil cohort

ICS usage	Year 3		Year 5		Year 10	
	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants
Strict use versus non use	-0.003 (-0.019 to 0.013; 0.730)	Treated: 5,236 Control: 10,589	0.004 (-0.015 to 0.023; 0.678)	Treated: 6,883 Control: 13,005	0.015 (-0.009 to 0.039; 0.227)	Treated: 7,421 Control: 13,107
Intermediate or strict use versus non use	0.002 (-0.012 to 0.017; 0.744)	Treated: 6,596 Control: 10,589	0.001 (-0.015 to 0.016; 0.941)	Treated: 8,754 Control: 13,005	0.008 (-0.012 to 0.027; 0.429)	Treated: 9,491 Control: 13,107

Table 8-10 Change in probability of respiratory-cause deaths with ICS use versus no use, nested eosinophil cohort

ICS usage	Year 3		Year 5		Year 10	
	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants
Strict use versus non use	High eosin: -0.012 (-0.075 to 0.051; 0.708)^	Treated, high eos: 869 Control, high eos: 1,463	High eosin: -0.135 (-0.231 to -0.039; 0.006)	Treated, high eos: 1,162 Control, high eos: 1,733	High eosin: -0.045 (-0.075 to -0.015; 0.004)	Treated, high eos: 1,302 Control, high eos: 1,732
	Normal eosin: -0.053 (-0.087 to -0.018; 0.003)	Treated, norm eos: 4,367 Control, norm eos: 9,126	Normal eosin: -0.035 (-0.071 to 0.000; 0.052)	Treated, norm eos: 5,721 Control, norm eos: 11,272	Normal eosin: -0.041 (-0.066 to -0.017; 0.001)	Treated, norm eos: 6,119 Control, norm eos: 11,375
Intermediate or strict use versus non use	High eosin: -0.024 (-0.078 to 0.031; 0.397)	Treated, high eos: 1,095 Control, high eos: 1,463	High eosin: -0.121 (-0.203 to -0.038; 0.0040	Treated, high eos: 1,456 Control, high eos: 1,733	High eosin: -0.067 (-0.100 to -0.034; 0.000)	Treated, high eos: 1,637 Control, high eos: 1,732
	Normal eosin: -0.051 (-0.083 to -0.019; 0.002)	Treated, norm eos: 5,501 Control, norm eos: 9,126	Normal eosin: -0.054 (-0.082 to -0.026; 0.000)	Treated, norm eos: 7,298 Control, norm eos: 11,272	Normal eosin: -0.052 (-0.076 to -0.028; 0.000)	Treated, norm eos: 7,854 Control, norm eos: 11,375

Table 8-11 Change in probability of all-cause deaths categorised by eosinophil groups with ICS use versus no use

Changes to propensity score matching to methods: ^Caliper=0.1, NN=5

ICS usage	Year 3		Year 5		Year 10	
	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants	Death probability (*95% CI; p*)	Participants
Strict use versus non use	^High eosin: 0.022 (-0.025 to 0.069; 0.352) Normal eosin: -0.003 (-0.021 to 0.014; 0.707)	Treated, high eos: 869 Control, high eos: 1,463 Treated, norm eos: 4,367 Control, norm eos: 9,126	High eosin: -0.002 (-0.088 to 0.083; 0.956) Normal eosin: 0.004 (-0.015 to 0.024; 0.652)	Treated, high eos: 1,162 Control, high eos: 1,733 Treated, norm eos: 5,721 Control, norm eos: 11,272	High eosin: -0.009 (-0.118 to 0.100; 0.869) Normal eosin: 0.020 (-0.004 to 0.044; 0.096)	Treated, high eos: 1,302 Control, high eos: 1,732 Treated, norm eos: 6,119 Control, norm eos: 11,375
Intermediate or strict use versus non use	High eosin: 0.022 (-0.012 to 0.056; 0.205) Normal eosin: 0.000 (-0.016 to 0.016; 0.967)	Treated, high eos: 1,095 Control, high eos: 1,463 Treated, norm eos: 5,501 Control, norm eos: 9,126	High eosin: -0.012 (-0.084 to 0.060; 0.745) Normal eosin: 0.005 (-0.011 to 0.020; 0.552)	Treated, high eos: 1,456 Control, high eos: 1,733 Treated, norm eos: 7,298 Control, norm eos: 11,272	High eosin: -0.034 (-0.126 to 0.059; 0.477)] Normal eosin: 0.015 (-0.003 to 0.034; 0.110)	Treated, high eos: 1,637 Control, high eos: 1,732 Treated, norm eos: 7,854 Control, norm eos: 11,375

Table 8-12 Change in probability of respiratory-cause deaths categorised by eosinophil groups with ICS use versus no use
Changes to propensity score matching to methods: ^Caliper=0.1, NN=5

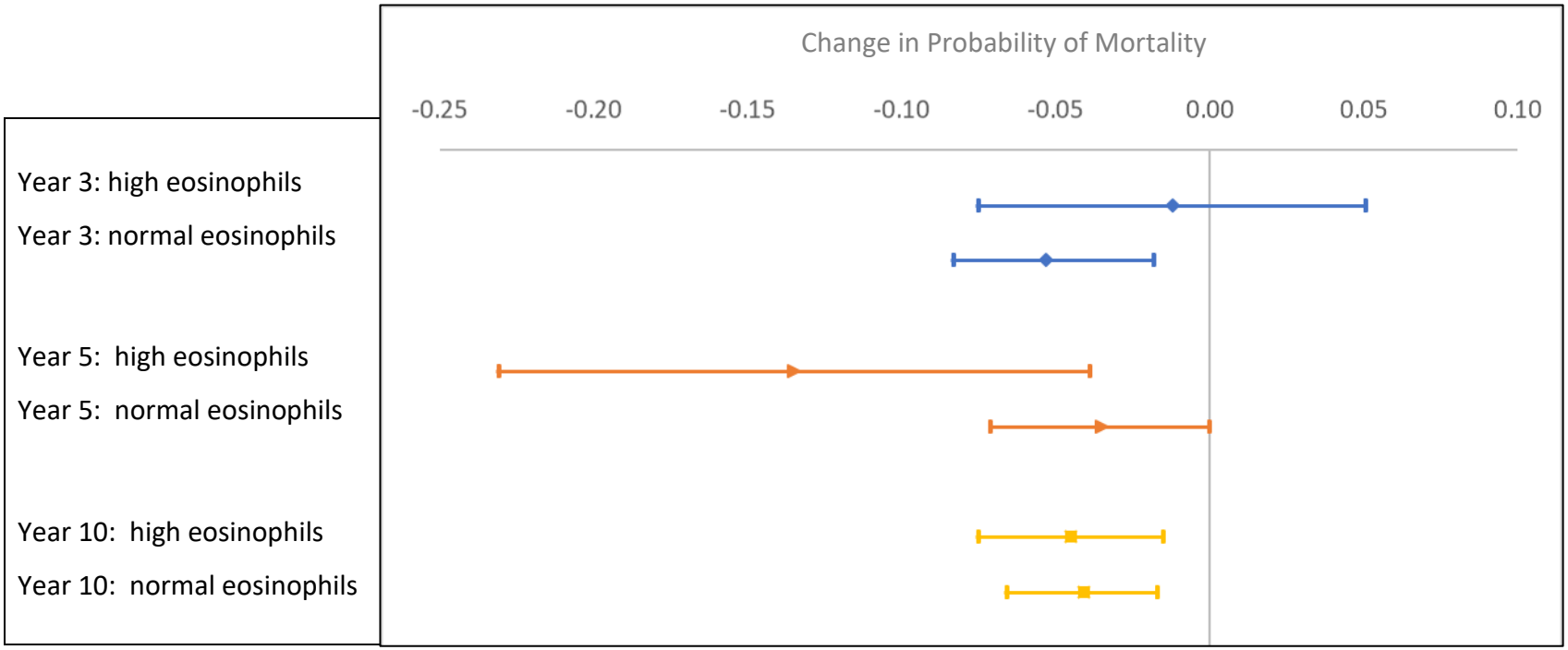

Figure 8-8 Change in probability of all-cause death at years 3,5 and 10 in people with COPD who were 'strict' users of ICS versus non-use, categorised by blood eosinophil level

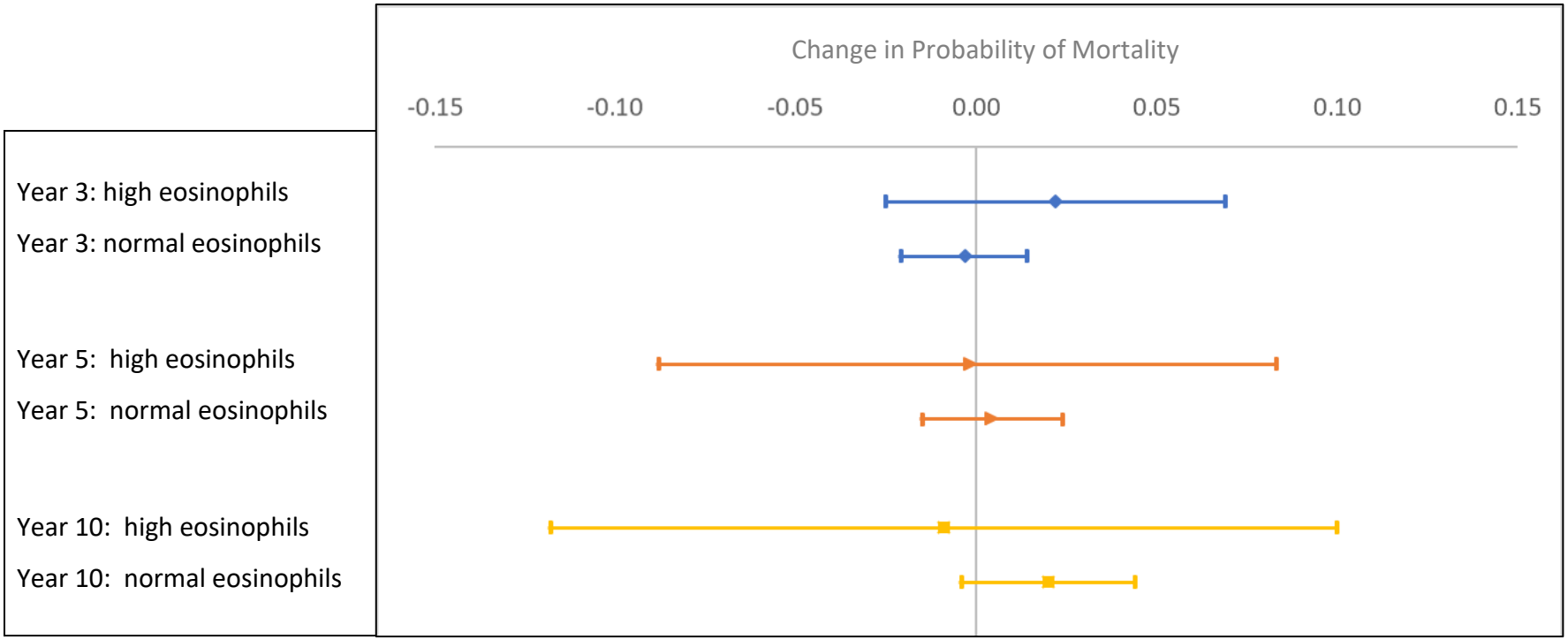

Figure 8-9 Change in probability of respiratory-cause death at years 3,5 and 10 in people with COPD who were 'strict' users of ICS versus non-use, categorised by blood eosinophil level

8.4 Discussion

ICS use was associated with a decrease in probability of all-cause death at all time points but a small increase in respiratory-cause death. Current smokers had a greater probability of all-cause death than ex- and non-smokers at all time points, however when categorised by amount smoked there was no clear result. People with an asthma co-diagnosis also had a lower probability of all-cause deaths than those with no asthma diagnosis at all time points. People with high blood eosinophil counts had lower probability of death than those with normal counts after five and ten years. When each of the sub-groups was analysed for respiratory-cause deaths, there was no statistical significance found.

8.4.1 Overall trend in probability of deaths with ICS use

When observing the deaths for the whole cohort, ICS use was associated with a lower probability of all-cause deaths at all time points (however the reduced probability diminished with time). This outcome has been demonstrated previously in a meta-analysis (Chen et al., 2022). Conversely in this study, ICS use was associated with higher probability of respiratory-cause deaths at all time points and the probability increased with time. This is an interesting finding as it was expected that the trend in respiratory deaths would mimic that of all-cause deaths.

It is worth considering in more depth why this effect was seen; it is probable that the answer lies in the way deaths are recorded within the ONS death data and how that was utilised in this study. A person will have the primary cause of death recorded in the ONS data, plus underlying or contributing causes of death. These causes are coded

using the ICD-10 system. This study only included the primary cause of death rather than including contributing causes of death too. The rationale for this was that often people with COPD will have multiple morbidities, particularly diabetes, cardio-vascular disease and cancers which also have relatively high probabilities of death and therefore there was the potential to mis-identify people with primarily respiratory-cause deaths.

However, for those in this study that had a respiratory-cause recorded as their primary cause of death, it is possible that they had more severe-respiratory disease, more likely to be on maximal COPD treatment, including ICS, and have a clearer respiratory diagnosis as their cause of death, possibly as a result of hospitalisation. Rather than more non-specific causes which may be recorded if their death was in the community; such as cardiovascular disease, stroke and old age.

Furthermore respiratory-cause deaths included pneumonia, which has been shown to be linked to use of inhaled steroids (Kew and Seniukovich, 2014), thus potentially adding a confounding factor that was not previously considered. However, it should be noted that this Cochrane review did not find that the increase in pneumonia with ICS affected mortality.

Further work is needed in this area to better understand the recording of respiratory-cause deaths as both the primary and contributing causes and the suitability of this to be used as a primary endpoint in the future. As such, this discussion focusses mostly on the all-cause death endpoint.

8.4.1.1 Strict and intermediate definitions of ICS use

As discussed in previous chapters, the use of both the 'strict' and 'intermediate' definitions of ICS use were analysed. Overall, there was not much difference between the results obtained between these two groups on the outcome of deaths. Mostly the 'intermediate' ICS use group showed the same trend in outcome as the 'strict' group, but often did not reach statistical significance. This suggests that the results reported here can be widely generalised to most people using ICS for COPD as the intermediate group includes people who have prescriptions that are sufficient for around half of the year, however any benefit seen for ICS is clearer with increased use and adherence.

8.4.1.2 Nested eosinophil cohort

The trends seen in both all-cause and respiratory-cause death with ICS use versus no ICS use in the nested eosinophil cohort were like the parent cohort; ICS use decreased the probability of all-cause death over no-use. As discussed in previous chapters, it is reassuring that the nested cohort is not fundamentality different to the whole cohort and therefore the findings can be generalised to the wider-COPD population.

8.4.2 Effect of smoking

8.4.2.1 Smoking status

Current smokers using ICS had a higher probability of all-cause death than the current smoker/no-ICS groups, however it only reached statistical significance after five years. The increased probability of death after five years was 3% in the strict ICS group and 1.7% in the intermediate ICS group. As stated above, ICS reduced the probability of death overall, however in smokers this was not observed. Furthermore, ex- and non-smokers given ICS did benefit, with a decrease in probability of death in the region of 2.1-6.0% across all time points and levels of ICS use.

Although it would be expected that smokers would have a higher probability of death than non-smokers, adding an ICS in fact increased this probability slightly. In section 2.3.2 the proposed mechanism for the lack of effect of ICS in smokers was discussed, and the limited evidence to date of the impact on outcomes such as lung function and exacerbation rates was discussed in the systematic review (Sonnex et al., 2020), however this is the first time that the effect on mortality has been studied. Most published work on the area of effect of smoking on outcomes with ICS in COPD have not assessed mortality as an outcome, likely because randomised controlled trials are ineffective at studying such an outcome due to the limited time period of the trial.

The results presented here are important as they demonstrate that due consideration should be given to prescribing ICS to current smokers as there is a lack of benefit that is seen in other patient groups.

8.4.2.2 Amount smoked

The results seen when sub-groups were divided into heavy smokers (≥20 cigarettes/day) and lighter smokers (<20 cigarettes/day) were less clear. All groups saw a benefit from using ICS over no-ICS use in terms of lower all-cause mortality, however statistical significance was not reached in the heavy smoker sub-group, likely because of the low number of patients. In general, a larger decrease in probability of death with ICS use was observed in the lighter smoker group than the heavy smoker group, but no conclusions can be drawn from this. As discussed in previous chapters, under reporting of number of cigarettes smoked per day and lack of data for many patients have contributed to this.

8.4.3 Effect of asthma

After five and ten years those co-diagnosed with asthma using ICS had the largest reduction in mortality; larger than those with asthma and not using ICS and those without asthma on ICS. The largest effect size was after five years; asthma/ICS use had a 9.2% decrease in mortality versus 1% for no asthma/ICS use. This suggests that treating people with a COPD/asthma co-diagnosis, or overlap syndrome, with ICS is beneficial in lowering the probability of deaths versus those without an asthma co-diagnosis.

This result was expected as there is a wealth of evidence on the benefit of ICS to people with asthma (GINA, 2020). However, there is limited evidence on COPD/asthma co-diagnosis outcomes, and none could be found specifically on mortality with ICS in COPD/asthma overlap. Therefore, the research presented in this thesis is important to add to the knowledge on outcomes with ICS and confirms that ICS should be prescribed

to people with COPD/asthma co-diagnosis (or features of asthma) as there is a reduction in mortality.

8.4.4 Effect of eosinophils

Targeting ICS use to people with high blood-eosinophil counts showed a trend in reduction in probability of death from all causes and respiratory causes. After five and ten years there was a decrease in the probability of all-cause death for people with high eosinophil counts using ICS above those with high eosinophils not using ICS of 13.5% and 4.5% respectively. In addition, the high eosinophil/ICS group had a greater reduction in mortality than the normal eosinophil/ICS group, however the 95% confidence intervals were overlapping so it is possible there may be no true difference. This could be because the data held in CPRD on blood eosinophil counts is not sufficiently rich for this kind of investigation and therefore the number of patients in the nested eosinophil cohort was low and eosinophils were not recorded for the purpose of research. It was expected that the use of ICS in people with COPD and high eosinophil counts would reduce mortality as a very similar study reported this previously, and found a similar reduction in all-cause mortality of 12-24% (Oshagbemi et al., 2018). The method by which ICS use was categorised varied between the study in this thesis and Oshagbemi *et al*; with the latter categorising by 'current use' versus 'never use'.

8.4.5 Strengths and limitations

8.4.5.1 Methods

The limitations around the methods used in this study, including propensity score matching and use of the CPRD dataset will be discussed in chapter nine. The strength of this study is in the use of longitudinal data to enable long-term data trends, such as mortality to be studied. As such there has previously been very limited research published on the outcome of mortality with ICS use and this chapter adds to this knowledge in terms of the smoking and asthma sub-groups.

8.4.5.2 Use and definition of mortality

An interesting finding in this chapter is that ICS use was associated with an increase in respiratory-cause mortality but a decrease in all-cause mortality. It is likely that this is due to people having a respiratory-cause of death also having more severe-respiratory disease and be more likely to be on maximal COPD treatment, including ICS. In addition, only the primary cause of death was used in this study; including contributing causes may have been more likely to pick up people who died with less severe lung disease.

8.5 Conclusion

Prescribing ICS to current smokers has been shown to increase the probability of all-cause death in comparison to not prescribing them. Furthermore, non-smokers prescribed ICS have a decreased probability of all-cause death compared to non-smokers not prescribed ICS.

People with an asthma co-diagnosis and high blood eosinophil counts were also more likely to see benefit from the prescription of ICS in terms of all-cause death over those with no asthma or normal eosinophil counts.

The observations on respiratory-cause death were unclear and possibly caused by lack of sensitivity in the methodology.

9. Discussion

The aim of this thesis was to investigate variables that may predict if inhaled corticosteroids are more, or less effective at treating COPD, in terms of the outcomes of lung function, exacerbations and deaths by using data from a large healthcare database. The hypothesis was that smoking may make ICS less effective, whereas targeting ICS to people with a co-diagnosis of asthma or high blood eosinophils would be more beneficial. A secondary aim of this thesis was to investigate the suitability of a large UK healthcare database, CPRD, in undertaking this research.

9.1 Systematic review

It was identified from the literature review in chapter two that a systematic review of the effect of smoking on outcomes with ICS treatment in COPD had not previously been published. Chapter three of this thesis undertook this systematic review. There were eight studies included which studied the outcomes of either yearly exacerbations or lung function with ICS usage and stratified participants by smoking (either by smoking status or pack-year history). All studies reported more yearly exacerbations when ICS were given to heavy or current smokers versus ex-smokers or lighter smokers; (RR= 0.81 to 0.99 for current/heavy smokers versus 0.92 to 1.29 for ex-smokers/lighter smokers on ICS). Taking the lower end of this range equates to smoking causing 0.148 exacerbations per year more with ICS use.

For the outcome of lung function the results were mixed; when categorised by smoking status no clear difference was observed between current and ex/non-smokers using ICS. However, when categorised by pack-year history, a decline in FEV_1 of 22ml/year to 75ml/year was seen in the heavier smokers using ICS versus lighter-smokers. This was the first time that all of the relevant literature on the effect of smoking on ICS outcomes had been synthesised together, however the low number of participants and lack of adequate design of the studies investigating the lung function outcome suggested that this was an area still needing further research.

9.2 Suitability of CPRD dataset

Chapter four of this thesis explored the availability and completeness of data held within the CPRD dataset and its linkages. Overall the CPRD dataset was a good source of data for investigating the outcomes of COPD as key information, such as lung function, exacerbations, medicines prescribed and smoking status, were well recorded.

A cohort of people with COPD within the CPRD dataset was developed and linked to the HES dataset; 62,642 cases were identified and over 75% had at least three years of data available. The characteristics of the cohort developed here were comparable to similar studies (Quint et al., 2014, Mullerova et al., 2012, Whittaker et al., 2019b, Oshagbemi et al., 2018).

Some limitations were found including; missing data in the recording of lung function each year and a high number of patients with no blood eosinophil count recorded. To account for this, multiple imputation of the missing lung function data in year one was

performed successfully. Additionally, it was decided that a nested cohort of patients with at least one eosinophil count would be used to investigate this variable.

9.3 Variables affecting outcomes with ICS treatment in COPD

The literature review and systematic review established that there were several key variables that may affect outcomes with ICS use in COPD, which required further study. The key variables identified were smoking status, asthma co-diagnosis and blood eosinophilia. Furthermore, some variables were identified as being potentially confounders; socio-economic status (as measured by index of multiple deprivation) and co-morbidities (as measured by Charlson score). Chapter five of this thesis explored a random effects panel data model to make predictions about the magnitude of impact of these and other variables on outcomes from COPD.

Increased doses of ICS were associated with decreased lung function, this was unexpected but may be due to them being prescribed for people with more severe disease, or more severely progressing disease and has been seen in other work (Whittaker et al., 2019a).

An interesting finding from the result of chapter five (section 5.5.1) was that a person smoking 20 cigarettes per day would expect their lung function, as measured by FEV_1 percentage, to decline by 1.5 percentage points after three years (0.076% per cigarette daily). The loss of lung function per cigarette/day has not been reported in the literature previously.

Smoking status and asthma were established as variables that required further investigation on how they impact the outcomes with ICS therapy. Although blood eosinophil counts did not have a significant impact on the panel data model, it was identified that this may be due to the methodology of a panel data model and that a further observational study would be beneficial. Other factors, such as Charlson score and the multiple deprivation index were investigated due to the likelihood of them being confounding factors and as such in subsequent analysis, treatment and control cases were matched on these variables.

9.4 Main findings

9.4.1 Effect of ICS on COPD outcomes

Chapters six to eight of this thesis used the cohort identified in chapter four to undertake a prospective cohort study to investigate the impact of smoking status, asthma co-diagnosis and blood eosinophil counts on outcomes with ICS use.

Within this cohort, people with high adherence to ICS therapy were matched to those with no use of ICS at the three, five and ten-year time points. Demographics of the ICS and no-ICS cohorts were similar in terms of lung function and exacerbations, however there were differences in the number of people within the cohort who had a co-diagnosis of asthma; the ICS use group had significantly higher number of asthma co-diagnoses.

Throughout this thesis two different levels of ICS adherence were used; “strict” and “intermediate” which translated to people who had approximately ≥80% and ≥50%

adherence respectively. In most cases, similar results were seen; suggesting that any reasonable adherence to ICS (≥50%) is likely to have the same effect. However, the intermediate usage group often had wide 95% confidence intervals, which limits the clinical interpretation and therefore it is the 'strict' usage group results that have mostly been discussed.

Strict ICS use was associated with an increase in yearly exacerbations of up to 0.199 and decline in lung function of up to 72ml after five years in comparison to no use. However, ICS use was associated with a decrease in all-cause mortality; -5.7% versus no-ICS use after five years. The increase in yearly exacerbations and decline of lung function were not expected findings, however this has been seen in a recent systematic reviews (Whittaker et al., 2019a) and similar study using CPRD data (Oshagbemi et al., 2018). These papers suggest that many of the people prescribed ICS have more severe COPD, are more likely to exacerbate or have more rapidly declining COPD for reasons currently unknown. In addition, as discussed in section 1.4 of this thesis, a previous iteration of the national clinical guidelines in 2010 suggested that ICS be reserved for people with severe or very severe COPD. Coupled with difficulties stopping ICS once started, have probably resulted in far too many people taking ICS with no real benefit, who may already have had quite severe disease.

9.4.2 Effect of smoking status

The effect of smoking was an additional 58ml decline in lung function (FEV_1) after five years with strict ICS use over ex- and non-smokers. This is comparable to the decline in lung function found in the systematic review in chapter three (section 3.3) of 22-75ml/year. These results show that smokers using ICS have the greatest decline in lung

function over all other groups. However, smoking is a known to cause a decline in lung function, so it is difficult to draw conclusions regarding the specific effect of smoking on ICS efficacy from these results. The conclusion that can be drawn is that lung function will decline at the most rapid rate while smoking and using ICS; this could be attributable to the severity of disease, smoke damage to the lungs, interaction between the smoke inhaled and ICS as discussed in the literature review (Section 2.3), or perhaps a complex combination of all three. A similar trend was seen for the amount smoked with heavier smokers using ICS having worse lung function outcomes compared to lighter or non-smokers using; possibly suggesting that it is in fact the effect of smoking interaction with the ICS causing a greater decline.

On the outcome of exacerbations after five years, the effect of smoking was an extra 0.074 yearly exacerbations with strict ICS use in comparison to ex- and non-smokers. These results are again comparable to those found in the systematic review of chapter 3 (section 3.3) where smoking was associated with an additional RR of 0.09 to 0.21 with ICS use after up to 52 weeks over ex- and non-smokers. In the non-smoker/ICS group, the 95% confidence intervals spanned a range that include a beneficial effect of using ICS in reducing yearly exacerbations; it is generally accepted in the literature that ICS reduce yearly exacerbation rates (Oba et al., 2018).

It was established for the first time in this thesis that ICS use in current smokers led to a higher probability of all-cause mortality than no ICS use of 3%. Use of ICS in non-smokers had a beneficial effect of decreasing the probability of mortality over non-use of -3.8%. Therefore, the overall effect of smoking was a 6.8% increase in mortality with

ICS use. This indicates that for non-smokers, ICS use is associated with a reduction in mortality, but an increase in smokers.

Overall, the effect of using ICS while smoking shows no benefit, however much of the detrimental effect seen on lung function, exacerbation rates and mortality may be due to the damage smoking does to the lungs, or because ICS may have been prescribed to people with more severe disease. For those who are not smokers, there is a clear benefit to using ICS in reduced mortality; the effect on other outcomes is not so clear, there may be a reduction in yearly exacerbation rates and a small, reduced decline in lung function.

9.4.3 Effect of asthma co-diagnosis

In terms of lung function, asthma was associated with a smaller decline in FEV_1 of up to 52ml after five years with strict ICS use than no-asthma, however the 95% confidence intervals were significantly overlapping suggesting that there may be no overall benefit to using ICS with an asthma diagnosis.

When the outcome of exacerbations was studied, mixed results were seen. After five years an asthma diagnosis was associated with an increase of 0.157 yearly exacerbations with ICS use over no asthma diagnosis. However, by ten years, the trend had reversed; the asthma group was associated with 0.290 yearly exacerbations less with ICS use than those with no asthma diagnosis.

In terms of the all-cause mortality outcome, all patients using ICS benefited, however those with an asthma co-diagnosis had a larger benefit than those without; a reduction of 8.2% in mortality with ICS use after five years.

From the literature review in section 2.2 it was identified that there was very little published data on the effect of ICS use in people with COPD plus asthma; only one small study on lung function was found (Lee et al., 2016) which demonstrated that ICS/LABA increased FEV_1 in people with asthma-COPD overlap in comparison to COPD alone. For yearly exacerbation rates, one study found similar outcomes to this thesis after ten years, but another found benefit as soon as one year, with both studies demonstrating that patients with asthma-COPD overlap using ICS were less likely to experience exacerbations (Su et al., 2018, Jo et al., 2020). Effect on mortality had not previously been studied.

Overall, people with an asthma co-diagnosis may benefit more than those with no asthma co-diagnosis from using ICS in terms of mortality and exacerbations. However, reduction in exacerbations was only seen at the ten-year time point. It would have been expected that people with COPD and asthma would benefit more significantly from ICS use due to the known nature of asthma and evidence base for ICS use, particularly reduction of yearly exacerbations at all time points. However, from the literature review in section 2.2 only a few studies were identified, whereas the study presented here is much larger and uses real-world data. It is possible that those with asthma and COPD in this study have more severe disease, with more frequent exacerbations (and subsequent worsening of lung function) than the general COPD population. The most likely reason for the lack of significant difference seen between the asthma and no-asthma group is in the definition of 'asthma' used in the methodology; a very broad definition was used, which may have resulted in many patients being included who did not have asthmatic features. The literature review in

chapter two of this thesis identified that up to 40% of people with COPD may have an asthma co-diagnosis, however it was found to be significantly higher in the strict ICS use group in this thesis. This limitation is discussed further on in this chapter.

9.4.4 Effect of blood eosinophil counts

In terms of lung function, there was no difference seen between the high blood eosinophil group and the normal eosinophil group in terms of ICS use; all were associated with a small decline in lung function.

However, when the outcome of total yearly exacerbations was observed after five years, ICS use in the high eosinophil group was associated with a smaller increase in total yearly exacerbations than in the normal eosinophil group; 0.144 yearly exacerbations versus 0.201 yearly exacerbations. However, the overlapping confidence intervals limit the wider interpretation of this result.

For all-cause mortality after five years, ICS use in the high eosinophil group was associated with a greater decline in mortality than ICS use in the normal eosinophil group: -10%.

It was expected from the literature review (section 2.1) that the targeting ICS to people with high blood eosinophil counts using observational data would probably not produce a beneficial effect on exacerbation rates, lung function or mortality. Although several RCTs did demonstrate benefit on FEV_1 and exacerbation rates, the studies and systematic review using observational data and/or the CPRD dataset (Harries et al., 2020) did not show it to be beneficial. The outcome of the systematic review into the observational studies was that four of the five studies demonstrated no reduction in

moderate or severe exacerbation rates, but one showed a 21-24% reduction when ICS were targeted to people with blood eosinophils of >300 cells/microL or 4%, however only one-year follow up was included (Suissa et al., 2018).

A very similar study by Oshagbemi (2018) also showed a decline in mortality when targeting ICS to people with moderate to very high eosinophil counts in a similar region to this thesis; 12-24% compared to 10%. The limitation of using blood eosinophil counts is that it was not well recorded in the CPRD dataset, meaning that many patients had to be excluded from this nested cohort study. There is the possibility of some bias in that people who had blood eosinophil counts recorded were already undergoing closer monitoring for COPD (or other medical conditions) and were therefore more likely to have their COPD well managed.

The method by which ICS use was categorised in this thesis is different to these previously published observational studies into the effect of targeting ICS to specific eosinophil counts, hence although the study in this thesis is similar, the data have been included. All methods of defining ICS use have their limitations, for example in many of the observational studies only one year of follow up with ICS use was undertaken, or current use was compared to never-use. The limitations specific to this thesis are included in section 9.5.

9.5 Strengths and weaknesses

9.5.1 Methodology

Both the strengths and weaknesses of this thesis can be found in the methodology used. The use of real-world prescribing data from the CPRD dataset and its linkage to hospital data and mortality statistics give a richness to the study and is representative of the UK population. The size of the dataset and years of follow up allows epidemiological studies to be carried out with statistical confidence. The limitations of using CPRD for research are well documented and mostly related to the data not being recorded primarily for research; including missing or miss-inputted data and lack of definitive diagnoses meaning that surrogate markers need to be used. (Herrett et al., 2015b)

Specific limitations of the prospective cohort methodology used in this thesis include patients lost to follow up, censoring of data and missing data.

Censoring of data occurs as either right-censoring (when an event, for example an exacerbation or death may have occurred after the last time a person was observed), or left-censoring (when the event occurred before the patient was enrolled in the study). Right-censoring is most likely to have occurred in this study as patients were lost to follow-up and/or the study was ended before events occurred; patients will transfer out of the dataset over time, due to moving area and re-registering with a different GP. This can lead to bias in the results, as fewer events such as exacerbations and deaths are recorded than actually occurred. It is unlikely that left-censoring will have contributed much to the bias in this study as only patient with a new diagnosis of

COPD within the timeframe of the study were included. However, a patient who transferred out of the database due to changing GP may then be re-registered in the dataset as a new patient and therefore all events that occurred previously are lost, lead to double counting and left-censoring.

Propensity score matching cannot account for unmeasured confounders; it can only control for observed variables and only to the extent that they are accurately measured therefore some residual confounding is possible. Propensity score matching based on OCS use and theophylline use could not be undertaken due to the low numbers of patients who use these medications; however it would be assumed that these would have an effect on the propensity score. In addition, matching was done at baseline however as this data is real-world, the factors that were matched at baseline could substantially vary over the study period; such as smoking status.

Linear regression was used for propensity score matching as the true propensity score is generally unknown, so it needs to be estimated. This means that a test, such as a standardised difference, should be carried out to check the balance of covariates between the treated and untreated. Ideally the standardised difference should be less than 10%. However, due to the multiple imputation methods used in this study, it was not possible to check the balance of matching in Stata by this method and therefore a visual inspection of the data was undertaken.

Using nearest neighbour matching has strengths and weaknesses; all treated cases find a match however, some of these matches may be poor because for some treated case the nearest neighbour may have a very different propensity score, and, nevertheless, would contribute to the estimation of the treatment effect independently of this

difference. This was minimised by using a caliper. In some cases, the planned method of propensity score matching (caliper 0.05 and NN 5) could not be completed as there were insufficient matches. In these cases, the caliper was widened and/or the NN reduced to achieve matching. In these cases, this implies that the two cohorts were not very similar to each other. Widening the caliper means that the cases are not as closely matched and reducing the NN weakens the results – often giving statistically insignificant results.

9.5.2 Use of CPRD

There are some limitations in terms of the data held within CPRD, which were already discussed in the methods chapter. Throughout this thesis, the outcomes from COPD of lung function, exacerbations and mortality were used. There is no consensus on the best outcomes measures to use, these are all reasonable outcome measures frequently used in COPD research, however, it was not possible to use other measures such as dyspnoea and SGRQ because of lack of recording in the CPRD dataset. This limits knowledge on the effect of ICS on more patient-oriented outcomes such as their daily symptoms and breathlessness.

Smoking

Investigating the impact of smoking was done with relatively high confidence because of a Quality and Outcomes Framework target that meant it is well recorded in the dataset, however it is likely that 'amount smoked' would be an under-representation of the true number of cigarettes smoked due to it being reliant on self-reporting and the lack of inclusion of other tobacco products. Blood eosinophil counts were not well recorded in the dataset; most likely because it is a specific test that would need to be

requested and then recorded, it is not a routine measurement taken in people with COPD. This was dealt with by using a nested cohort for those with at least one recording of blood eosinophils.

Outcome measures

The recording of lung function within the dataset is a further limitation. For example, the lung function recording relies on the spirometry procedure being correctly performed at the GP surgery. This can be a complex procedure requiring significant training to perform and interpret correctly. There were several obviously incorrect results documented; i.e. FEV_1 results that were either far too high or low to be clinically possible. These were of course cleaned up in the processing of the data, but it leaves a question over how accurate other lung function results were, even if they appeared to be in the correct range. Furthermore, a recent study looked at the different methods by which decline in lung function in the CPRD dataset can be captured (Whittaker et al., 2021). Reassuringly, it found that FEV_1 decline was similar no matter how many measurements, or time interval between measurements was defined; these were factors not considered at the start of this thesis.

As mentioned above, a lack of definitive methods for defining diagnoses and other variables within CPRD limits its use. Validated methods were used for defining a diagnosis of COPD and exacerbations, so there was high confidence in the accuracy of these, however no such methods existed for some aspects of this study. The two primary areas where this caused difficulties were in determining adherence to ICS use and defining a co-diagnosis of asthma.

Definition of ICS use

As identified in the literature review of observational studies into ICS efficacy (section 2.1.4), previous methods of defining ICS use in the CPRD dataset had limitations because they did not account for the exposure of a person to the medication, with most only requiring that patients had recently received at least one prescription for ICS-containing medication. In this thesis a different approach was taken. ICS use could not be recorded prospectively from the patient's date of entry to the study as when the data was scrutinised, it was clear that patients stopped and started ICS throughout their enrolment. Instead, the patient's total exposure to ICS over their time in the study was determined by developing a marker for adherence over the time period. This method was used instead of, for example the person 'leaving' the study if their ICS use status changed. This was because of the wide variability in ICS use from year to year that was found; this would have resulted in many people leaving the study or only completing one or two years. By defining the person on their use of ICS across all years meant that it replicated what would be seen in practice and enabled this study to look at the long term (ten years) use of medications. However, the number of participants who could be defined as a 'strict' user or 'non' user at year ten was significantly lower than those available in the whole cohort. Furthermore, a patient holding prescriptions for ICS was used as a proxy for adherence to the medication, which has limitations as there is no guarantee the patient had this dispensed by a pharmacy, had the intention to use the inhaler or even used it correctly if the intention was there. In the literature of similar observational studies using CPRD data, particularly into the effect of eosinophil levels, there is no consensus of method by which to define ICS use. The

method used in this thesis presents a novel way to define ICS use over an extended period, accounting for wide inter-person variation in doses and exposure.

Definition of asthma

From the literature review (section 2.2), it was thought that people with COPD and features of asthma may benefit from ICS more than those with no features of asthma. However, not only does no validated method of defining a cohort with asthma-COPD overlap within CPRD exist, this diagnosis is not well-defined clinically, or even well recognised outside of specialist respiratory medicine; for example many GPs may not be aware of this syndrome, or if aware not confident in diagnosing it. Therefore, it was decided that any patient with a diagnosis of COPD and a medcode for asthma would be included in this asthma co-diagnosis cohort. This is a very wide definition and could include people with an initial misdiagnosis or mis-coding in CPRD, as well as those with true features of asthma. This limits the applicability of the results found for the asthma co-diagnosis group in outcomes with ICS use. Recently a protocol for a systematic review to identify patients with asthma-COPD overlap in healthcare databases was published (Amegadzie et al., 2019), however the publication of the findings is still awaited.

9.6 Clinical implications

One of the key questions this thesis set out to add to the knowledge on was posed in the most recent update of the NICE guidance for management of COPD:

"What features predict inhaled corticosteroid responsiveness most accurately in people with COPD?" (NICE, 2020b)

This thesis has identified and explored several possible features to predict the responsiveness of COPD to ICS; smoking status, blood eosinophils and asthma co-diagnosis. It adds to the knowledge base of other research in the area, however as identified in chapters two and three of this thesis, most of the previous clinical research had not identified smoking, asthma or eosinophils as a primary variable for investigation, but rather as a post-hoc subgroup analysis. Furthermore, except for blood eosinophils, no real-world data had previously been explored for its impact on outcomes with ICS in COPD.

The research presented here is useful to prescribers as it includes the real-world use of inhaled corticosteroids, which as identified in chapter four, are often used sub-optimally with many patients having adherence of around 50%. Prescribers can make their own judgement on the likely efficacy of ICS for the individual patient in front of them, given multiple factors such as adherence to ICS, smoking status and asthmatic features. Specific recommendations for practice are as follows:

1. Non-smokers benefit from ICS use in terms of reduced mortality and possibly reduced exacerbations. However, smokers will have a decline in lung function, high yearly exacerbation rates and increased mortality with or without ICS treatment
2. Patients with a co-diagnosis of asthma may benefit from ICS use in terms of reduced mortality and exacerbations but only with long term use (>10 years)
3. Patients known to have eosinophil counts of above 400 cells/microlitre will benefit from receiving ICS in terms of reduced mortality and possibly reduced yearly exacerbations.

4. ICS use does not have any effect on lung function but seems to decrease mortality in all recipients, but only when taken with high adherence

For patients, a co-diagnosis of asthma or high blood eosinophil levels are not factors they can exert any control over, however it may add further weight to their decision to quit smoking in order to improve their lung health and gain more benefit from prescribed inhaled corticosteroids.

Two aspects that have not been directly considered in this thesis but are relevant to prescribers and policy makers are adverse effects from ICS use and their cost-effectiveness. The adverse effects of ICS are well documented and discussed previously in this thesis; ICS are associated with significantly more adverse effects than bronchodilator therapy (Horita et al., 2017). Furthermore, once established on ICS therapy, even if not demonstrating clinical benefit, prescribers are reluctant to withdraw therapy due to perceived increased likelihood to exacerbate and clinically deteriorate; selecting patients to discontinue ICS treatment needs to be carefully considered (Chalmers et al., 2020). Therefore, consideration of which patients prescribers should initiate ICS with is needed; this thesis adds further knowledge in this area.

In terms of cost-effectiveness, no analysis has been carried out in this thesis. However, it is well established that inhaled therapies are frequently in the top ten drug expenditure in England each year. In 2021/22, three ICS medications were in the top ten; beclomethasone dipropionate, budesonide and fluticasone propionate with a total cost of £534,000,000 (NHSBA, 2022). Although many of the prescriptions of these three ICS may be appropriate for people with asthma, there is likely to be a significant

number of prescriptions for people with COPD too. As has been established in this thesis, a large proportion of people with COPD are prescribed ICS and only specific groups are likely to see any benefit. Furthermore, the benefit seen by the non-smokers and those with an asthma co-diagnosis is limited to a small reduction in mortality only, therefore the quality-adjusted life years gained from ICS therapy is likely to be limited in size; making the cost of hundreds of millions of pounds a year spent on these medications high. Therefore, given the finite healthcare budget available, it is important that policy makers consider if patients are likely to be in a group that may benefit from ICS.

9.7 Unanswered questions and future research

In chapter five of this thesis it was identified that the key variables for further investigation; smoking status, asthma and eosinophils, only contributed in part to the effect of ICS on COPD outcomes. A significant part of the panel-data model presented was not accounted for by these and other selected variables. This provides an opportunity for further research into other features that may predict ICS responsiveness. For example, the use of long-term oxygen, specific other co-morbidities (such as cardiovascular disease) and environmental factors such as a person's occupational exposure to toxins.

Chapters six to eight explored the effect of an asthma co-diagnosis on COPD outcomes, however a key limitation of this study was the method used to identify the COPD and asthma co-diagnosis cohort. As no validated method for identifying this patient cohort within CPRD currently exists, this provides an opportunity for further research. A validated method for identifying asthma-COPD overlap could be developed in a similar

way to the method developed for identifying the COPD cohort by Quint *et al* (2014). Once developed, this method could be utilised for further research into the efficacy of ICS (and other medications) on outcomes for those with asthma-COPD overlap syndrome.

Following on from the clinical implications of this research, the next step would be to conduct a cost-utility analysis by calculating the quality-adjusted life years gained with ICS use in COPD.

9.8 Conclusions

ICS have proven in this thesis to be of limited value in treating COPD when used by real-world patients with varying adherence. Prescribers should target them to people who can commit to high adherence, have blood eosinophilia, an asthma co-diagnosis and who are non-smokers. This targeting may produce a small benefit in terms of decreased probability of mortality and possibly exacerbations in the long term. However, on the outcome of lung function no effect was seen.

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Appendices

Appendix 1 Systematic review search strategy

Final search strategies in databases. Date of last search of all databases: 30th January 2020

1. Final search strategies for randomized controlled trials in Embase

SN	Searches
1	(chronic adj obstructive adj pulmonary adj disease).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2	chronic obstructive pulmonary disease.mp. or exp chronic obstructive lung disease/
3	COPD.mp. or exp chronic obstructive lung disease/
4	exp corticosteroid/ or exp chronic obstructive lung disease/ or chronic obstructive airway disease.mp. or exp beclometasone/ or exp obstructive airway disease/
5	(chronic adj obstructive adj airway adj disease).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6	chronic obstructive lung disease.mp. or exp chronic obstructive lung disease/
7	(chronic adj obstructive adj lung adj disease).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	budesonide.mp. or exp budesonide plus formoterol/ or exp budesonide/ or exp budesonide plus salmeterol/ or exp budesonide plus formoterol fumarate/
10	beclometasone dipropionate.mp. or exp beclometasone dipropionate/
11	beclometasone.mp. or exp beclometasone dipropionate/ or exp beclometasone/ or exp beclometasone dipropionate plus salbutamol/ or exp beclometasone dipropionate plus formoterol fumarate/
12	ciclesonide.mp. or exp ciclesonide/
13	fluticasone.mp. or exp fluticasone propionate plus salmeterol/ or exp fluticasone/ or exp fluticasone propionate/ or exp fluticasone propionate plus salmeterol xinafoate/ or exp fluticasone propionate plus formoterol fumarate/
14	fluticasone propionate.mp. or exp fluticasone propionate/
15	mometasone.mp. or exp mometasone furoate/
16	mometasone furoate.mp. or exp mometasone furoate/

SN	Searches
17	(inhaled adj corticosteroid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
18	(inhaled adj glucocorticoid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
19	(inhaled adj steroid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
20	(inhaled adj glucocorticoid).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
21	ICS.mp.
22	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	exp smoking/ or smoking.mp
24	cigarette smoking.mp. or exp smoking/
25	(smoker and non-smoker).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
26	23 or 24 or 25
27	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
28	RETRACTED ARTICLE/
29	(random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
30	exp controlled clinical trial/ or randomized control trial.mp.
31	27 or 28 or 29 or 30
32	8 and 22
33	8 and 22 and 26
34	8 and 22 and 26 and 31
35	Limit 34 to (full text and human and English language and yr=''2000-current'')

2. Search strategies for randomized controlled trial in Medline

SN	Searches
1	(chronic adj obstructive adj pulmonary adj disease).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
2	chronic obstructive pulmonary disease.mp. or *Pulmonary Disease, Chronic Obstructive/
3	COPD.mp. or *Pulmonary Disease, Chronic Obstructive/
4	chronic obstructive lung disease.mp. or *Pulmonary Disease, Chronic Obstructive/
5	(chronic adj obstructive adj lung adj disease).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6	chronic obstructive airway disease.mp. or *Pulmonary Disease, Chronic Obstructive/
7	(chronic adj obstructive adj airway adj disease).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	budesonide.mp. or exp Budesonide/
10	*Anti-Inflammatory Agents/ or *Metered Dose Inhalers/ or *Beclomethasone/ or beclometasone dipropionate.mp. or *Glucocorticoids/
11	beclometasone.mp. or *Beclomethasone/
12	*Anti-Inflammatory Agents/ or *Double-Blind Method/ or ciclesonide.mp. or *Administration, Inhalation/
13	*Pulmonary Disease, Chronic Obstructive/ or *Anti-Inflammatory Agents/ or *Bronchodilator Agents/ or fluticasone.mp.
14	*Pulmonary Disease, Chronic Obstructive/ or *Bronchodilator Agents/ or *Administration, Inhalation/ or fluticasone propionate.mp. or *Anti-Inflammatory Agents/
15	*Anti-Inflammatory Agents/ or mometasone.mp.
16	*Glucocorticoids/ or *Anti-Inflammatory Agents/ or mometasone furoate.mp. or *Receptors, Glucocorticoid/
17	(inhaled adj corticosteroid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
18	(inhaled adj glucocorticoid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
19	(inhaled adj steroid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

SN	Searches
20	(inhaled adj glucocorticosteroid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
21	ICS.mp.
22	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	exp Smoking/ or smoking.mp.
24	cigarette smoking.mp. or exp Smoking/
25	(smoker and non-smoker).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
26	23 or 24 or 25
27	"randomized controlled trial".pt.
28	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
29	(retraction of publication or retracted publication).pt.
30	randomized control trial.mp.
31	27 or 28 or 29 or 30
32	8 and 22
33	8 and 22 and 26
34	8 and 22 and 26 and 31
35	limit 34 to (english language and ovid full text available and full text and humans and yr="2000 - current" and journal article)

3. Final search strategies for randomized controlled trials in Pubmed

Trial	Searches
1	Search chronic obstructive pulmonary disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
2	Search COPD Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
3	Search chronic obstructive lung disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/01; Humans
4	Search chronic obstructive airway disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
5	(((chronic obstructive pulmonary disease[Title/Abstract]) OR COPD[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]) OR chronic obstructive airway disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
6	Search budesonide[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans

Trial	Searches
7	Search fluticasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
8	Search fluticasone propionate[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
9	Search beclometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
10	Search beclometasone dipropionate[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
11	Search inhaled corticosteroid Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
12	Search inhaled steroid Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Human
13	Search inhaled glucocorticoid Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
14	Search inhaled glucocorticosteroid Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
15	Search ciclesonide[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
16	Search mometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
17	((((((((((budesonide[Title/Abstract]) OR fluticasone[Title/Abstract]) OR fluticasone propionate[Title/Abstract]) OR beclometasone[Title/Abstract]) OR beclometasone dipropionate[Title/Abstract]) OR inhaled corticosteroid[Title/Abstract]) OR inhaled steroid[Title/Abstract]) OR inhaled glucocorticoid[Title/Abstract]) OR inhaled glucocorticosteroid[Title/Abstract]) OR ICS[Title/Abstract]) OR ciclesonide[Title/Abstract]) OR mometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
18	Search smoking[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
19	Search cigarette smoking[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
20	Search smoker[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
21	Search non-smoker[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2014/01/30; Humans
22	(((smoking[Title/Abstract]) OR cigarette smoking[Title/Abstract]) OR smoker[Title/Abstract]) OR non-smoker[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
23	Search randomized controlled trial Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
24	Search controlled clinical trial Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans

Trial	Searches
25	Search controlled trial Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
26	(((randomized clinical trial AND ((Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp]) AND full text[sb] AND ("2000/01/01"[PDat] : "2020/01/30"[PDat]) AND Humans[Mesh])) OR (controlled clinical trial AND ((Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp]) AND full text[sb] AND ("2000/01/01"[PDat] : "2020/01/30"[PDat]) AND Humans[Mesh])) OR (controlled trial AND ((Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp]) AND full text[sb] AND ("2000/01/01"[PDat] : "2020/01/30"[PDat]) AND Humans[Mesh])) Filters: Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
27	((((((chronic obstructive pulmonary disease[Title/Abstract]) OR COPD[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]) OR chronic obstructive airway disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans))) AND ((((((((((((budesonide[Title/Abstract]) OR fluticasone[Title/Abstract]) OR fluticasone propionate[Title/Abstract]) OR beclometasone[Title/Abstract]OR beclometasone dipropionate[Title/Abstract]) OR inhaled corticosteroid[Title/Abstract]) OR inhaled steroid[Title/Abstract]) OR inhaled glucocorticoid[Title/Abstract]) OR inhaled glucocorticosteroid[Title/Abstract]) OR ICS[Title/Abstract]) OR ciclesonide[Title/Abstract]) OR mometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans))
28	Search ((((((((((chronic obstructive pulmonary disease[Title/Abstract]) OR COPD[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]) OR chronic obstructive airway disease Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans))) AND ((((((((((((budesonide[Title/Abstract]) OR fluticasone[Title/Abstract]) OR fluticasone propionate[Title/Abstract]) OR beclometasone[Title/Abstract]) OR beclometasone dipropionate[Title/Abstract]) OR inhaled corticosteroid[Title/Abstract]) OR inhaled steroid[Title/Abstract]) OR inhaled glucocorticoid[Title/Abstract]) OR inhaled glucocorticosteroid[Title/Abstract]) OR ICS[Title/Abstract]) OR ciclesonide[Title/Abstract]) OR mometasone[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans)))) AND ((Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp]) AND full text[sb] AND ("2000/01/01"[PDat] : "2020/01/30"[PDat]) AND Humans[Mesh])))) AND ((((((smoking[Title/Abstract]) OR cigarette smoking[Title/Abstract]) OR smoker[Title/Abstract]) OR non-smoker[Title/Abstract] Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans)) AND ((Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp]) AND full text[sb] AND ("2000/01/01"[PDat] :

Trial	Searches
	"2020/01/30"[PDat]) AND Humans[Mesh])) Filters: Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans
29	(((((((chronic obstructive pulmonary disease[Title/Abstract]) OR COPD[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]) OR chronic obstructive airway disease) AND full text[sb] AND ("2000/01/01"[PDat] : "2020/01/30"[PDat]) AND Humans[Mesh])) AND ((((((((((((budesonide[Title/Abstract]) OR fluticasone[Title/Abstract]) OR fluticasone propionate[Title/Abstract]) OR beclometasone[Title/Abstract]) OR beclometasone dipropionate[Title/Abstract]) OR inhaled corticosteroid[Title/Abstract]) OR inhaled steroid[Title/Abstract]) OR inhaled glucocorticoid[Title/Abstract]) OR inhaled glucocorticosteroid[Title/Abstract]) OR ICS[Title/Abstract]) OR ciclesonide[Title/Abstract]) OR mometasone[Title/Abstract]) AND full text[sb] AND ("2000/01/01"[PDat] : "2020/01/30"[PDat]) AND Humans[Mesh])) AND (((((smoking[Title/Abstract]) OR cigarette smoking[Title/Abstract]) OR smoker[Title/Abstract]) OR non-smoker[Title/Abstract]) AND full text[sb] AND ("2000/01/01"[PDat] : "2020/01/30"[PDat]) AND Humans[Mesh])) AND (((randomized controlled trial) AND controlled trial) AND controlled clinical trial AND full text[sb] AND ("2000/01/01"[PDat] : "2000/01/30"[PDat]) AND Humans[Mesh]) Filters: Full text available; Publication date from 2000/01/01 to 2020/01/30; Humans

4. Final search strategies for randomized controlled trials in Cochrane Library

Trial	Searches
1	"COPD":ti,ab,kw (Word variations have been searched)
2	"chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched)
3	"chronic obstructive airway disease":ti,ab,kw (Word variations have been searched)
4	"chronic obstructive lung disease":ti,ab,kw (Word variations have been searched)
5	"COPD":ti,ab,kw or "chronic obstructive airway disease":ti,ab,kw or "chronic obstructive lung disease":ti,ab,kw or "chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched)
6	"budesonide":ti,ab,kw (Word variations have been searched)
7	"fluticasone":ti,ab,kw (Word variations have been searched)
8	fluticasone propionate:ti,ab,kw (Word variations have been searched)
9	"ciclesonide":ti,ab,kw (Word variations have been searched)
10	"mometasone":ti,ab,kw (Word variations have been searched)
11	"inhaled corticosteroid":ti,ab,kw (Word variations have been searched)
12	inhaled steroid:ti,ab,kw (Word variations have been searched)
13	inhaled glucocorticosteroid:ti,ab,kw (Word variations have been searched)
14	inhaled glucocorticoid:ti,ab,kw (Word variations have been searched)
15	"budesonide":ti,ab,kw or "fluticasone":ti,ab,kw or fluticasone propionate:ti,ab,kw or"ciclesonide":ti,ab,kw or mometasone:ti,ab,kw or "inhaled corticosteroid":ti,ab,kw or inhaled steroid:ti,ab,kw or inhaled glucocorticosteroid:ti,ab,kw or inhaled glucocorticosteroid'':ti,ab,kw (Word variations have been searched)
16	"smoking":ti,ab,kw (Word variations have been searched)
17	"cigarette smoke":ti,ab,kw (Word variations have been searched)
18	"smoker":ti,ab,kw (Word variations have been searched)
19	"non-smoker":ti,ab,kw (Word variations have been searched)
20	"smoking":ti,ab,kw or "cigarette smoke":ti,ab,kw or "smoker":ti,ab,kw or "non-smoker":ti,ab,kw (Word variations have been searched)
21	"randomized controlled trial":ti,ab,kw Publication Date to 2020, in Trials (Word variations have been searched)
22	"randomized controlled study":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)
23	"clinical trial":ti,ab,kw Publication Date from 2000 to 2014, in Trials (Word variations have been searched)
24	"controlled clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)
25	"randomized controlled trial":ti,ab,kw Publication Date to 2020, in Trials (Word variations have been searched) or "randomized controlled study":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched) or "clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word

Trial	Searches
	variations have been searched) or "controlled clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)
26	"COPD":ti,ab,kw or "chronic obstructive airway disease":ti,ab,kw or "chronic obstructive lung disease":ti,ab,kw or "chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched) and "budesonide":ti,ab,kw or "fluticasone":ti,ab,kw or fluticasone propionate:ti,ab,kw or"ciclesonide":ti,ab,kw or mometasone:ti,ab,kw or "inhaled corticosteroid":ti,ab,kw or inhaled steroid:ti,ab,kw or inhaled glucocorticosteroid:ti,ab,kw or inhaled glucocorticosteroid'':ti,ab,kw (Word variations have been searched)
27	"COPD":ti,ab,kw or "chronic obstructive airway disease":ti,ab,kw or "chronic obstructive lung disease":ti,ab,kw or "chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched) and "budesonide":ti,ab,kw or "fluticasone":ti,ab,kw or fluticasone propionate:ti,ab,kw or"ciclesonide":ti,ab,kw or mometasone:ti,ab,kw or "inhaled corticosteroid":ti,ab,kw or inhaled steroid:ti,ab,kw or inhaled glucocorticosteroid:ti,ab,kw or inhaled glucocorticosteroid'':ti,ab,kw (Word variations have been searched) and "smoking":ti,ab,kw or "cigarette smoke":ti,ab,kw or "smoker":ti,ab,kw or "non-smoker":ti,ab,kw (Word variations have been searched)
28	"COPD":ti,ab,kw or "chronic obstructive airway disease":ti,ab,kw or "chronic obstructive lung disease":ti,ab,kw or "chronic obstructive pulmonary disease":ti,ab,kw (Word variations have been searched) and "budesonide":ti,ab,kw or "fluticasone":ti,ab,kw or fluticasone propionate:ti,ab,kw or"ciclesonide":ti,ab,kw or mometasone:ti,ab,kw or "inhaled corticosteroid":ti,ab,kw or inhaled steroid:ti,ab,kw or inhaled glucocorticosteroid:ti,ab,kw or inhaled glucocorticosteroid'':ti,ab,kw (Word variations have been searched) and "smoking":ti,ab,kw or "cigarette smoke":ti,ab,kw or "smoker":ti,ab,kw or "non-smoker":ti,ab,kw (Word variations have been searched) and "randomized controlled trial":ti,ab,kw Publication Date to 2020, in Trials (Word variations have been searched) or "randomized controlled study":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched) or "clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched) or "controlled clinical trial":ti,ab,kw Publication Date from 2000 to 2020, in Trials (Word variations have been searched)

Appendix 2 COPD medcodes

152 Wheezy bronchitis
794 Emphysema
998 Chronic obstructive airways disease
1001 Chronic obstructive pulmonary disease
3243 Chronic bronchitis
4519 H/O: bronchitis
5710 Chronic obstructive airways disease NOS
5909 Chronic wheezy bronchitis
7092 Recurrent wheezy bronchitis
7884 Chron obstruct pulmonary dis wth acute exacerbation, unspec
9520 Chronic obstructive pulmonary disease monitoring
9876 Severe chronic obstructive pulmonary disease
10802 Moderate chronic obstructive pulmonary disease
10863 Mild chronic obstructive pulmonary disease
10980 Centrilobular emphysema
11019 Admit COPD emergency
11287 Chronic obstructive pulmonary disease annual review
14798 Emphysematous bronchitis
16342 H/O: chr.obstr. airway disease
18476 COPD follow-up
18501 COPD self-management plan given
18621 Chronic obstructive pulmonary disease follow-up
18792 Chronic obstructive pulmonary disease monitoring admin
19003 Emergency COPD admission since last appointment
19106 COPD accident and emergency attendance since last visit
19434 Suspected chronic obstructive pulmonary disease
19721 Chronic obstructive pulmonary disease leaflet given
21061 Chronic obstruct pulmonary dis with acute lower resp infectn
24814 Chronic respiratory failure
25083 FEV1/FVC < 70% of predicted
25603 Simple chronic bronchitis
26018 Chronic obstructive pulmonary disease monitoring by nurse
27819 Obstructive chronic bronchitis
28743 Number of COPD exacerbations in past year
28755 Chronic obstructive pulmonary disease monitoring 1st letter
34202 Chronic obstructive pulmonary disease monitoring 2nd letter
34215 Chronic obstructive pulmonary disease monitoring 3rd letter
37371 Chronic obstructive pulmonary disease monitoring due
38074 Chronic obstructive pulmonary disease monitor phone invite
40159 Purulent chronic bronchitis
42258 Chronic obstructive pulmonary disease monitoring verb invite

42313 Health education - chronic obstructive pulmonary disease
45770 Chronic obstructive pulmonary disease disturbs sleep
45771 Chronic obstructive pulmonary disease does not disturb sleep
45777 Chronic obstructive pulmonary disease clini management plan
45998 Chronic obstructive pulmonary disease monitoring by doctor
46036 Multiple COPD emergency hospital admissions
46578 Panlobular emphysema
47236 [V]Screening for chronic bronchitis
56860 Segmental bullous emphysema
60188 Giant bullous emphysema
61118 Simple chronic bronchitis NOS
65733 [X]Other specified chronic obstructive pulmonary disease
66043 Other chronic bronchitis
67040 Other specified chronic obstructive pulmonary disease
93568 Very severe chronic obstructive pulmonary disease
96931 At risk of chronic obstructive pulmonary diseas exacerbation
97800 COPD - enhanced services administration
98283 COPD structured smoking assessment declined - enh serv admin
98284 Refer COPD structured smoking assessment - enhanc serv admin
99536 Bullous emphysema with collapse
99948 COPD patient unsuitable for pulmonary rehab - enh serv admin
100237 Chronic obstructive pulmonary disease assessment test
100877 Clinical chronic obstructive pulmonary disease questionnaire
101042 Issue of chronic obstructive pulmonary disease rescue pack
102685 Chronic obstructive pulmonary disease 3 monthly review
103007 Chronic obstructive pulmonary disease 6 monthly review
103400 Referred for COPD structured smoking assessment
103558 Preferred place of care for next exacerbation of COPD
103678 Chronic obstructiv pulmonary disease medication optimisation
103758 Referral to COPD community nursing team
103760 COPD structured smoking assessment declined
103864 COPD patient unsuitable for pulmonary rehabilitation
104117 COPD self-management plan agreed
104169 COPD self-management plan review
104265 GP OOH service notified of COPD care plan
104481 Has chronic obstructive pulmonary disease care plan
104710 On COPD (chr obstruc pulmonary disease) supportv cre pathway
104985 On chronic obstructive pulmonary disease supprtv cre pathway
104998 Chronic obstructve pulmonry disease rescue pack not indicatd
105457 Chronic obstructive pulmonary disease care pathway
106637 Seen in chronic obstructive pulmonary disease clinic
106650 Eosinophilic bronchitis
106945 Chronic obstructive pulmonary disease rescue pack declined
107877 Chronic obstructive pulmon dis wr self managem plan declined

Appendix 3: COPD Prodcodes

8 Salbutamol 100micrograms/dose inhaler
17 Salbutamol 100micrograms/dose inhaler CFC free
31 Ventolin 100microgram/inhalation Inhalation powder (Glaxo Wellcome UK Ltd)
38 Beclometasone 100micrograms/dose inhaler
99 Becotide 100 inhaler (GlaxoSmithKline UK Ltd)
235 Bricanyl 250micrograms/dose inhaler (AstraZeneca UK Ltd)
454 Pulmicort 200microgram Inhaler (AstraZeneca UK Ltd)
465 Salmeterol 25micrograms/dose inhaler
510 Ventolin 5mg/ml respirator solution (GlaxoSmithKline UK Ltd)
534 Atrovent 20micrograms/dose inhaler (Boehringer Ingelheim Ltd)
549 Serevent 25micrograms/dose inhaler (GlaxoSmithKline UK Ltd)
556 Combivent inhaler (Boehringer Ingelheim Ltd)
638 Seretide 250 Accuhaler (GlaxoSmithKline UK Ltd)
665 Seretide 100 Accuhaler (GlaxoSmithKline UK Ltd)
674 Ventolin 2.5mg Nebules (GlaxoSmithKline UK Ltd)
719 Salmeterol 50micrograms/dose dry powder inhaler
746 Tiotropium 18 microgram Capsule
752 Carbocisteine 375mg capsules
862 Salbulin Inhalation powder (3M Health Care Ltd)
882 Salbutamol 200microgram inhalation powder capsules
883 Becodisks 200microgram Disc (Allen & Hanburys Ltd)
895 Beclazone 100 Easi-Breathe inhaler (Teva UK Ltd)
896 Becotide easi-breathe 100microgram/actuation Pressurised inhalation (Allen & Hanburys Ltd)
898 Ventolin evohaler 100 100microgram/inhalation Pressurised inhalation (Glaxo Wellcome UK Ltd)
907 Bricanyl turbohaler 500 500microgram Turbohaler (AstraZeneca UK Ltd)
908 Pulmicort 400 Turbohaler (AstraZeneca UK Ltd)
909 Budesonide 200micrograms/dose inhaler
910 Serevent diskhaler 50microgram Inhalation powder (Glaxo Wellcome UK Ltd)
911 Flixotide accuhaler 250 250microgram/inhalation Inhalation powder (Allen & Hanburys Ltd)
942 Aerolin 100micrograms/dose Autohaler (3M Health Care Ltd)
947 Budesonide 50micrograms/actuation refill canister
956 Pulmicort 200 Turbohaler (AstraZeneca UK Ltd)
957 Salamol easi-breathe 100microgram/actuation Pressurised inhalation (IVAX Pharmaceuticals UK Ltd)
958 Ventolin easi-breathe 100microgram/actuation Pressurised inhalation (Allen & Hanburys Ltd)
959 Budesonide 50micrograms/dose inhaler

960 Pulmicort 100 Turbohaler (AstraZeneca UK Ltd)
1087 Asmasal 95micrograms/dose Clickhaler (Focus Pharmaceuticals Ltd)
1093 Salamol 100microgram/actuation Inhalation powder (IVAX Pharmaceuticals UK Ltd)
1100 Beclazone 100 inhaler (Teva UK Ltd)
1236 Becloforte 250micrograms/dose inhaler (GlaxoSmithKline UK Ltd)
1242 Beclometasone 250micrograms/dose inhaler
1243 Beclazone 250 Easi-Breathe inhaler (Teva UK Ltd)
1258 Becotide 200 inhaler (GlaxoSmithKline UK Ltd)
1259 Beclometasone 200micrograms/dose inhaler
1269 Becotide 50microgram/ml Nebuliser liquid (Allen & Hanburys Ltd)
1346 Salbutamol 0.05mg/ml injection
1406 Becotide 50 inhaler (GlaxoSmithKline UK Ltd)
1409 Ipratropium bromide 20micrograms/dose inhaler
1410 Ipratropium bromide 0.25mg/ml
1411 Ipratropium bromide 250micrograms/ml
1412 Flixotide 250microgram/actuation Inhalation powder (Allen & Hanburys Ltd)
1414 Salamol 5mg/2.5ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
1415 Steri-neb ipratropium 250microgram/ml Nebuliser liquid (IVAX Pharmaceuticals UK Ltd)
1424 Flixotide 250microgram Disc (Allen & Hanburys Ltd)
1426 Flixotide 500microgram Disc (Allen & Hanburys Ltd)
1518 Flixotide 50microgram/actuation Inhalation powder (Allen & Hanburys Ltd)
1537 Becotide 200microgram Rotacaps (GlaxoSmithKline UK Ltd)
1551 Beclazone 250 inhaler (Teva UK Ltd)
1552 Becloforte easi-breathe 250microgram/actuation Pressurised inhalation (Allen & Hanburys Ltd)
1619 Terbutaline 500micrograms/dose dry powder inhaler
1620 Terbutaline 250micrograms/dose inhaler
1628 Terbutaline 250micrograms/actuation refill canister
1630 Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials
1642 Budesonide 400micrograms/dose dry powder inhaler
1676 Flixotide 125microgram/actuation Inhalation powder (Allen & Hanburys Ltd)
1680 Pulmicort LS 50micrograms/dose inhaler (AstraZeneca UK Ltd)
1697 Atrovent 20micrograms/dose Autohaler (Boehringer Ingelheim Ltd)
1698 Salbutamol 100micrograms/dose breath actuated inhaler
1711 Salbutamol 5mg/2.5ml nebuliser liquid unit dose vials
1725 Beclazone 50 Easi-Breathe inhaler (Teva UK Ltd)
1727 Becotide easi-breathe 50microgram/actuation Pressurised inhalation (Allen & Hanburys Ltd)
1734 Beclometasone 100micrograms/dose breath actuated inhaler
1741 Salbutamol 100micrograms/dose breath actuated inhaler CFC free
1801 Ventide inhaler (GlaxoSmithKline UK Ltd)
1861 AeroBec 100 Autohaler (Meda Pharmaceuticals Ltd)

1882 Ventodisks 200microgram/blister Disc (Allen & Hanburys Ltd)
1885 Beclazone 200 inhaler (Teva UK Ltd)
1950 Ventodisks 400microgram/blister Disc (Allen & Hanburys Ltd)
1951 Becodisks 400microgram Disc (Allen & Hanburys Ltd)
1952 Ventolin 400microgram Rotacaps (GlaxoSmithKline UK Ltd)
1956 Pulmicort 1mg Respules (AstraZeneca UK Ltd)
1957 Ventolin 5mg Nebules (GlaxoSmithKline UK Ltd)
1959 Pulmicort 0.5mg Respules (AstraZeneca UK Ltd)
1962 Atrovent udv 0.25mg/ml Nebuliser liquid (Boehringer Ingelheim Ltd)
1974 Oxis 12 Turbohaler (AstraZeneca UK Ltd)
1975 Oxis 6 Turbohaler (AstraZeneca UK Ltd)
2092 Budesonide 200micrograms/dose dry powder inhaler
2124 PULMICORT REFIL 200 MCG INH
2125 Pulmicort 200microgram Refill canister (AstraZeneca UK Ltd)
2148 Beclometasone 400microgram disc Beclometasone Dipropionate
2152 Ipratropium bromide with salbutamol 20mcg + 100mcg
2159 AeroBec 50 Autohaler (Meda Pharmaceuticals Ltd)
2160 Beclometasone 50micrograms/dose breath actuated inhaler
2224 Serevent 50micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
2229 Becodisks 100microgram Disc (Allen & Hanburys Ltd)
2282 Fluticasone propionate 500micrograms/dose dry powder inhaler
2335 Qvar 100 inhaler (Teva UK Ltd)
2440 Flixotide accuhaler 500 500microgram/inhalation Inhalation powder (Allen & Hanburys Ltd)
2600 Beclometasone 250micrograms/dose breath actuated inhaler
2655 Airomir 100micrograms/dose inhaler (Teva UK Ltd)
2722 Duovent inhaler (Boehringer Ingelheim Ltd)
2723 Fluticasone 25micrograms/dose inhaler
2758 Bricanyl Refill canister (AstraZeneca UK Ltd)
2850 Salbutamol 400microgram inhalation powder capsules
2851 Ventolin 200microgram Rotacaps (GlaxoSmithKline UK Ltd)
2862 Duovent Autohaler (Boehringer Ingelheim Ltd)
2892 Becloforte 400microgram disks (GlaxoSmithKline UK Ltd)
2893 Beclometasone 200micrograms disc
2951 Fluticasone 250microgram/actuation Pressurised inhalation
2978 Salbutamol 200micrograms/dose dry powder inhaler
2992 Beclazone 50 inhaler (Teva UK Ltd)
2994 Atrovent aerocaps 40microgram Inhalation powder (Boehringer Ingelheim Ltd)
3018 Beclometasone 50micrograms/dose inhaler
3065 Bextasol Inhalation powder (Allen & Hanburys Ltd)
3075 Becotide 400microgram Rotacaps (GlaxoSmithKline UK Ltd)
3119 Becloforte integra 250microgram/actuation Inhaler with compact spacer (Glaxo Laboratories Ltd)
3150 Beclometasone 100micrograms/actuation extrafine particle cfc free inhaler

3163 Salbutamol 200micrograms disc
3220 Qvar 50 Autohaler (Teva UK Ltd)
3289 Flixotide 25micrograms/dose inhaler (GlaxoSmithKline UK Ltd)
3297 Salmeterol 50micrograms disc
3305 Combivent nebuliser liquid 2.5ml UDVs (Boehringer Ingelheim Ltd)
3306 Atrovent Forte 40micrograms/dose inhaler (Boehringer Ingelheim Ltd)
3363 Becloforte 400microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
3443 Salbutamol 100microgram/inhalation Spacehaler (Celltech Pharma Europe Ltd)
3546 Qvar 50 inhaler (Teva UK Ltd)
3556 Beclometasone 50micrograms with salbutamol 100micrograms/inhalation inhaler
3570 Budesonide 200micrograms/actuation refill canister
3666 Seretide 500 Accuhaler (GlaxoSmithKline UK Ltd)
3743 Filair 50 inhaler (Meda Pharmaceuticals Ltd)
3786 Fenoterol 100micrograms/dose / Ipratropium 40micrograms/dose inhaler
3927 Filair 100 inhaler (Meda Pharmaceuticals Ltd)
3947 Becotide 100microgram Rotacaps (GlaxoSmithKline UK Ltd)
3988 FLIXOTIDE DISKHALER-COMMUNITY PACK 100 MCG
3989 Flixotide 100microgram Disc (Allen & Hanburys Ltd)
3993 Filair Forte 250micrograms/dose inhaler (Meda Pharmaceuticals Ltd)
4131 Fluticasone 100microgram Disc
4132 Fluticasone 125microgram/actuation Pressurised inhalation
4222 Bricanyl 10mg/ml respirator solution (AstraZeneca UK Ltd)
4268 Ipratropium bromide 40micrograms/dose inhaler
4365 Beclometasone 100micrograms disc
4413 Qvar 100 Autohaler (Teva UK Ltd)
4497 Ventolin accuhaler 200 200microgram/actuation Inhalation powder (Glaxo Wellcome UK Ltd)
4499 erobec 250microgram/actuation Pressurised inhalation (Meda Pharmaceuticals Ltd)
4545 Pulmicort LS 50microgram Refill canister (AstraZeneca UK Ltd)
4601 Asmabec 100 Clickhaler (Focus Pharmaceuticals Ltd)
4634 Salamol 2.5mg/2.5ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
4640 Bricanyl 5mg/2ml Nebuliser liquid (AstraZeneca UK Ltd)
4665 Salbulin 100micrograms/dose inhaler (3M Health Care Ltd)
4688 Fluticasone 50microgram/actuation Pressurised inhalation
4759 Beclometasone 100microgram inhalation powder capsules
4801 Budesonide 500micrograms/2ml nebuliser liquid unit dose vials
4803 Beclazone 250microgram/actuation Inhalation powder (Actavis UK Ltd)
4926 Flixotide accuhaler 100 100microgram/inhalation Inhalation powder (Allen & Hanburys Ltd)
4942 Budesonide 1mg/2ml nebuliser liquid unit dose vials
5143 Seretide 50 Evohaler (GlaxoSmithKline UK Ltd)
5161 Seretide 125 Evohaler (GlaxoSmithKline UK Ltd)
5170 Salamol 100micrograms/dose inhaler CFC free (Teva UK Ltd)

5172 Seretide 250 Evohaler (GlaxoSmithKline UK Ltd)
5223 Fluticasone 50micrograms/dose inhaler CFC free
5308 Terbutaline 5mg/2ml nebuliser liquid unit dose vials
5309 Flixotide 50micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
5516 Salamol 100micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
5521 Beclometasone 200micrograms/dose dry powder inhaler
5522 Beclometasone 100micrograms/dose dry powder inhaler
5551 Flixotide 0.5mg/2ml Nebules (GlaxoSmithKline UK Ltd)
5558 Salmeterol 50micrograms with fluticasone 500micrograms CFC free inhaler
5580 Flixotide accuhaler 50 50microgram/inhalation Inhalation powder (Allen & Hanburys Ltd)
5683 Flixotide 250micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
5718 Flixotide 125micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
5740 Airomir 100micrograms/dose Autohaler (Teva UK Ltd)
5753 Salbutamol 400micrograms disc
5804 Beclometasone 250micrograms/dose dry powder inhaler
5822 Fluticasone 250micrograms/dose inhaler CFC free
5837 Salamol steri-neb 5mg/2.5ml Nebuliser liquid (Numark Management Ltd)
5864 Salmeterol 25micrograms with fluticasone 250micrograms CFC free inhaler
5885 Fluticasone propionate 100micrograms/dose dry powder inhaler
5889 Salamol 100microgram/inhalation Inhalation powder (Kent Pharmaceuticals Ltd)
5898 Salamol steri-neb 2.5mg/2.5ml Nebuliser liquid (Numark Management Ltd)
5942 Salmeterol 50micrograms with fluticasone 250micrograms CFC free inhaler
5975 Fluticasone 125micrograms/dose inhaler CFC free
5992 Beclometasone 50micrograms/dose dry powder inhaler
6050 Spiriva 18 microgram Capsule (Boehringer Ingelheim Ltd)
6081 Ipratropium bromide 20micrograms/dose breath actuated inhaler
6276 Carbocisteine 250mg/5ml oral solution
6325 Symbicort 200/6 Turbohaler (AstraZeneca UK Ltd)
6462 Salbutamol 95micrograms/dose dry powder inhaler
6512 Atrovent 20micrograms/dose inhaler CFC free (Boehringer Ingelheim Ltd)
6522 Ipratropium bromide 20micrograms/dose inhaler CFC free
6526 Formoterol 12microgram inhalation powder capsules with device
6569 Salmeterol 25micrograms with fluticasone 125micrograms CFC free inhaler
6616 Salmeterol 25micrograms with fluticasone 50micrograms CFC free inhaler
6719 Ipratropium bromide 500micrograms/2ml nebuliser liquid unit dose vials
6746 Budesonide 400micrograms/dose / Formoterol 12micrograms/dose dry powder inhaler
6758 Ipratropium 250micrograms/1ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
6772 Ipratropium bromide 250micrograms/1ml nebuliser liquid unit dose vials
6780 Symbicort 400/12 Turbohaler (AstraZeneca UK Ltd)
6796 Budesonide 200micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler

6802 Mucodyne 375mg capsules (Sanofi)
6839 Alvesco 160 inhaler (Takeda UK Ltd)
6911 Atrovent 250micrograms/1ml nebuliser liquid UDVs (Boehringer Ingelheim Ltd)
6920 Mecysteine 100mg gastro-resistant tablets
6938 Salmeterol 50micrograms with fluticasone 100micrograms dry powder inhaler
7013 Symbicort 100/6 Turbohaler (AstraZeneca UK Ltd)
7017 Salbutamol 100micrograms/dose dry powder inhaler
7133 Formoterol 12micrograms/dose dry powder inhaler
7140 Atrovent 500micrograms/2ml nebuliser liquid UDVs (Boehringer Ingelheim Ltd)
7268 Serevent 25micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
7270 Salmeterol 25micrograms/dose inhaler CFC free
7356 Ciclesonide 80micrograms/dose inhaler CFC free
7602 Fluticasone 50microgram Disc
7638 Fluticasone 250microgram Disc
7653 Beclometasone 400microgram inhalation powder capsules
7711 Terbutaline 250micrograms/dose inhaler with spacer
7724 Betamethasone valerate 100micrograms/actuation inhaler
7788 Budesonide 100micrograms/dose dry powder inhaler
7891 Fluticasone 500microgram Disc
7935 Maxivent 100microgram/inhalation Inhalation powder (Ashbourne Pharmaceuticals Ltd)
7948 Fluticasone propionate 250micrograms/dose dry powder inhaler
7954 Bricanyl 250micrograms/dose spacer inhaler (AstraZeneca UK Ltd)
7964 Beclometasone 50micrograms/ml nebuliser suspension
7965 Salbutamol 5mg/ml nebuliser liquid
8111 Becloforte vm 250microgram/actuation VM pack (Allen & Hanburys Ltd)
8267 Sodium cromoglicate 1mg/dose / Salbutamol 100micrograms/dose inhaler
8333 Ipratropium bromide 40microgram inhalation powder capsules
8433 Budesonide 100micrograms/actuation inhaler
8635 Flixotide 50microgram Disc (Allen & Hanburys Ltd)
8676 Terbutaline 10mg/ml nebuliser liquid
8968 Acetylcysteine 200mg granules sachets
9018 Mucodyne 375mg Capsule (Aventis Pharma)
9164 Fluticasone propionate 50micrograms/dose dry powder inhaler
9233 Beclometasone 200microgram inhalation powder capsules
9270 Ipratropium bromide with fenoterol hydrobromide 500micrograms + 1.25mg/4ml
9477 Asmabec 100microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)
9571 Beclometasone 250micrograms/actuation vortex inhaler
9577 Asmabec 50 Clickhaler (Focus Pharmaceuticals Ltd)
9599 Beclazone 50microgram/actuation Inhalation powder (Actavis UK Ltd)
9642 Mucodyne 250mg/5ml Oral solution (Aventis Pharma)
9651 Asmasal 100microgram/inhalation Spacehaler (Celltech Pharma Europe Ltd)
9681 Atrovent aerohaler 40microgram Inhalation powder (Boehringer Ingelheim Ltd)
9711 Formoterol 6micrograms/dose dry powder inhaler

9906 Mucodyne 250mg/5ml syrup (Sanofi)
9921 Beclometasone 100micrograms/dose breath actuated inhaler CFC free
10090 Beclometasone 50micrograms/actuation extrafine particle cfc free inhaler
10102 Ciclesonide 160micrograms/dose inhaler CFC free
10218 Budesonide 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
10254 Mometasone 400micrograms/dose dry powder inhaler
10321 Budesonide 400microgram inhalation powder capsules
10360 Aerocrom inhaler (Castlemead Healthcare Ltd)
10808 Mucodyne Paediatric 125mg/5ml syrup (Sanofi)
10968 Foradil 12microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd)
11046 Ipratropium bromide with salbutamol 500micrograms + 2.5mg/2.5ml
11198 Beclometasons 50 micrograms/actuation vortex inhaler
11307 Salbutamol 100micrograms/dose / Beclometasone 50micrograms/dose inhaler
11410 Fluticasone propionate 500micrograms/dose / Salmeterol 50micrograms/dose
11478 Fluticasone 2mg/2ml nebuliser liquid unit dose vials
11497 Beclometasone 400micrograms/dose dry powder inhaler
11588 Fluticasone 125micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free
11618 Fluticasone 250micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free
11732 Beclometasone 50micrograms/dose breath actuated inhaler CFC free
11779 Ipratropium bromide 40microgram inhalation powder capsules with device
12529 Fabrol 200mg Granules (Novartis Consumer Health UK Ltd)
12530 Mucolex 250mg/5ml Oral solution (Parke-davis Research Laboratories)
12808 Fenoterol 100micrograms/dose / Ipratropium bromide 40micrograms/dose breath actuated inhaler
12822 Salbutamol 2.5mg with ipratropium bromide 500micrograms/2.5ml unit dose nebuilser solution
12909 Salbutamol 100micrograms/dose / Ipratropium 20micrograms/dose inhaler
12994 Fluticasone 50micrograms/dose / Salmeterol 25micrograms/dose inhaler CFC free
13037 Pulvinal Beclometasone Dipropionate 200micrograms/dose dry powder inhaler (Chiesi Ltd)
13038 Pulvinal Salbutamol 200micrograms/dose dry powder inhaler (Chiesi Ltd)
13040 Fluticasone propionate 250micrograms/dose / Salmeterol 50micrograms/dos
13181 Easyhaler Salbutamol sulfate 100micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
13273 Fluticasone propionate 100micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler
13290 Clenil Modulite 100micrograms/dose inhaler (Chiesi Ltd)
13757 Tropiovent steripoule 250microgram/ml Nebuliser liquid (Ashbourne Pharmaceuticals Ltd)

13815 Beclazone 100microgram/actuation Inhalation powder (Actavis UK Ltd)
13996 Salamol 100microgram/inhalation Inhalation powder (Sandoz Ltd)
14294 Qvar 50micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
14306 Formoterol 12micrograms/dose inhaler CFC free
14321 Beclometasone 200micrograms/dose inhaler CFC free
14524 Bdp 250microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)
14525 Salbutamol 100micrograms/inhalation vortex inhaler
14561 Salbutamol 400microgram / Beclometasone 200microgram inhalation powder capsules
14567 Asmabec 250 Clickhaler (Focus Pharmaceuticals Ltd)
14590 Asmabec 250microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)
14700 Budesonide 400micrograms/actuation inhaler
14736 Pulvinal Beclometasone Dipropionate 400micrograms/dose dry powder inhaler (Chiesi Ltd)
14757 Pulvinal Beclometasone Dipropionate 100micrograms/dose dry powder inhaler (Chiesi Ltd)
15301 Carbocisteine 125mg/5ml oral solution
15326 Beclometasone 100micrograms/dose inhaler CFC free
15706 Beclometasone 100 micrograms/actuation vortex inhaler
16018 Mometasone 200micrograms/dose dry powder inhaler
16054 Budesonide 200micrograms/actuation breath actuated powder inhaler
16148 Clenil Modulite 250micrograms/dose inhaler (Chiesi Ltd)
16151 Clenil Modulite 200micrograms/dose inhaler (Chiesi Ltd)
16158 Clenil Modulite 50micrograms/dose inhaler (Chiesi Ltd)
16207 Duovent UDVs nebuliser liquid 4ml (Boehringer Ingelheim Ltd)
16305 Flixotide 2mg/2ml Nebules (GlaxoSmithKline UK Ltd)
16433 Asmanex 200micrograms/dose Twisthaler (Merck Sharp & Dohme Ltd)
16577 Easyhaler Salbutamol sulfate 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
16584 eclometasone 50micrograms/dose inhaler CFC free
16625 Ventide Rotacaps (GlaxoSmithKline UK Ltd)
17465 Fluticasone 500micrograms/2ml nebuliser liquid unit dose vials
17590 Asmanex 400micrograms/dose Twisthaler (Merck Sharp & Dohme Ltd)
17654 Easyhaler Beclometasone 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
17670 Easyhaler Budesonide 100micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
18140 Respontin 500micrograms/2ml Nebules (GlaxoSmithKline UK Ltd)
18299 Fenoterol 1.25mg/4ml / Ipratropium 500micrograms/4ml nebuliser liquid unit dose vials
18314 Aerocrom Syncroner with spacer (Castlemead Healthcare Ltd)
18387 Brovon midget Inhalation powder (Torbet Laboratories Ltd)
18394 Bdp 50microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)
18421 Respontin nebules 250microgram/ml Nebuliser liquid (Glaxo Wellcome UK Ltd)

18456 Salbutamol 200microgram / Beclometasone 100microgram inhalation powder capsules
18484 Ventide Paediatric Rotacaps (GlaxoSmithKline UK Ltd)
18537 Budesonide 200microgram inhalation powder capsules
18848 Qvar 100micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)
19031 Bdp 100microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)
19121 Beclometasone 100micrograms with Salbutamol 200micrograms inhalation capsules
19376 Beclometasone 200micrograms with Salbutamol 400micrograms inhalation capsules
19389 Asmabec 50microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)
19401 Beclometasone 250micrograms/actuation inhaler and compact spacer
20825 Spacehaler BDP 250microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)
21005 Beclometasone 250micrograms/dose inhaler CFC free
21224 Alvesco 80 inhaler (Takeda UK Ltd)
21482 Beclometasone 100micrograms/dose inhaler (Mylan Ltd)
21859 Asmaven 100microgram Inhalation powder (Berk Pharmaceuticals Ltd)
22430 Spacehaler salbutamol 100microgram/inhalation Spacehaler (Celltech Pharma Europe Ltd)
22828 Carbocisteine 750mg/5ml forte oral solution
23269 Maxivent 2.5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Ashbourne Pharmaceuticals Ltd)
23567 Respontin 250micrograms/1ml Nebules (GlaxoSmithKline UK Ltd)
23709 Ipratropium 500micrograms/2ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)
23741 Novolizer budesonide 200microgram/actuation Pressurised inhalation (Meda Pharmaceuticals Ltd)
23961 Ipratropium bromide 250microgram/ml Inhalation vapour (Galen Ltd)
24380 Sodium cromoglicate 1mg/dose / Salbutamol 100micrograms/dose inhaler with spacer
24456 Carbocisteine 375mg tablets Carbocisteine
24898 Spacehaler BDP 100microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)
25204 Beclometasone 100micrograms/dose inhaler (A A H Pharmaceuticals Ltd)
25339 Maxivent 5mg/2.5ml nebuliser liquid unit dose Steripoule vials (Ashbourne Pharmaceuticals Ltd)
25784 Atimos Modulite 12micrograms/dose inhaler (Chiesi Ltd)
26063 Beclometasone 100micrograms/dose inhaler (Teva UK Ltd)
26616 Ipratropium bromide with fenoterol hydrobromide 0micrograms + 100micrograms/actuation
27188 Easyhaler Budesonide 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)

27505 Ipratropium bromide with fenoterol hydrobromide 40micrograms + 100micrograms/actuation
27679 Beclometasone 100microgram/actuation Pressurised inhalation (Approved Prescription Services Ltd)
28073 Beclometasone 250microgram/actuation Pressurised inhalation (Approved Prescription Services Ltd)
28508 Salbutamol 100microgram/inhalation Inhalation powder (IVAX Pharmaceuticals UK Ltd)
28640 Beclometasone 100microgram/actuation Inhalation powder (Actavis UK Ltd)
28761 Spacehaler BDP 50microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)
29325 Beclometasone 250micrograms/dose inhaler (Mylan Ltd)
30118 Salbutamol 100micrograms/dose inhaler CFC free (Teva UK Ltd)
30204 Salbutamol 200micrograms inahalation capsules
30210 Beclometasone 250micrograms/dose inhaler (Teva UK Ltd)
30212 Salbutamol cyclohaler
30229 Ipratropium bromide 250microgram/ml Nebuliser liquid (Galen Ltd)
30230 Salbutamol 100micrograms/actuation breath actuated inhaler
30238 Beclometasone 50microgram/actuation Pressurised inhalation (Approved Prescription Services Ltd)
30240 Aerolin autohaler 100microgram/actuation Pressurised inhalation (3M Health Care Ltd)
30649 Easyhaler Budesonide 400micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
31082 Salbuvent 5mg/ml Respirator solution (Pharmacia Ltd)
31774 Beclometasone 50micrograms/dose inhaler (Mylan Ltd)
31933 Salbutamol 100micrograms/dose inhaler (A A H Pharmaceuticals Ltd)
32050 Salbutamol 400 Cyclocaps (Teva UK Ltd)
32222 Isoprenaline hc 500micrograms + 50micrograms/metered Pressurised inhalation
32873 Beclometasone 50micrograms/dose nasal spray (Actavis UK Ltd)
32874 Beclometasone 50microgram/actuation Inhalation powder (Actavis UK Ltd)
33089 Salbutamol 100micrograms/dose inhaler (Kent Pharmaceuticals Ltd)
33258 Beclometasone 250micrograms/dose inhaler (A A H Pharmaceuticals Ltd)
33373 Salbutamol 200 Cyclocaps (Teva UK Ltd)
33588 Salbutamol 100micrograms/dose inhaler (Mylan Ltd)
33817 Salbutamol 100micrograms/dose inhaler CFC free (Actavis UK Ltd)
33849 Beclometasone 100microgram/actuation Inhalation powder (Neo Laboratories Ltd)
34018 Salbutamol 5mg/2.5ml Nebuliser liquid (Galen Ltd)
34029 Salbutamol 400micrograms inahalation capsules
34134 Aerolin 400 100microgram/actuation Inhalation powder (3M Health Care Ltd)
34162 Salbutamol 2.5mg/2.5ml Nebuliser liquid (Galen Ltd)
34310 Salbutamol 100micrograms/dose inhaler CFC free (A A H Pharmaceuticals Ltd)
34311 Salbutamol 100microgram/inhalation Inhalation powder (Berk Pharmaceuticals Ltd)

34315 Beclometasone 250microgram/actuation Inhalation powder (Actavis UK Ltd)
34428 Beclometasone 50microgram/actuation Inhalation powder (Neo Laboratories Ltd)
34619 Salbutamol 100microgram/inhalation Inhalation powder (Kent Pharmaceuticals Ltd)
34702 Salbutamol 100microgram/inhalation Inhalation powder (C P Pharmaceuticals Ltd)
34739 Beclometasone 50micrograms/dose inhaler (Teva UK Ltd)
34794 Beclometasone 200micrograms/dose inhaler (A A H Pharmaceuticals Ltd)
34859 Beclometasone 250microgram/actuation Inhalation powder (Neo Laboratories Ltd)
34919 Beclometasone 50micrograms/dose inhaler (A A H Pharmaceuticals Ltd)
34995 Spiriva 18microgram inhalation powder capsules with HandiHaler (Boehringer Ingelheim Ltd)
35000 Spiriva 18microgram inhalation powder capsules (Boehringer Ingelheim Ltd)
35011 Tiotropium bromide 18microgram inhalation powder capsules
35014 Tiotropium bromide 18microgram inhalation powder capsules with device
35015 Erdosteine 300mg capsules
35071 Becodisks 200microgram (GlaxoSmithKline UK Ltd)
35106 Becodisks 100microgram with Diskhaler (GlaxoSmithKline UK Ltd)
35107 Beclometasone 400microgram inhalation powder blisters with device
35113 Beclometasone 200microgram inhalation powder blisters
35118 Becodisks 400microgram with Diskhaler (GlaxoSmithKline UK Ltd)
35165 Serevent 50microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
35178 Erdotin 300mg capsules (Galen Ltd)
35225 Flixotide 100microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
35288 Beclometasone 400microgram inhalation powder blisters
35293 Beclometasone 200microgram inhalation powder blisters with device
35299 Becodisks 400microgram (GlaxoSmithKline UK Ltd)
35374 Flixotide 500microgram disks (GlaxoSmithKline UK Ltd)
35392 Flixotide 500microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
35408 Becodisks 100microgram (GlaxoSmithKline UK Ltd)
35430 Becodisks 200microgram with Diskhaler (GlaxoSmithKline UK Ltd)
35461 Flixotide 250microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
35503 Salmeterol 50microgram inhalation powder blisters
35510 Budesonide 200micrograms/dose dry powder inhalation cartridge with device
35542 Salmeterol 50microgram inhalation powder blisters with device
35557 Ipramol nebuliser solution 2.5ml Steri-Neb unit dose vials (Teva UK Ltd)
35580 Beclometasone 100microgram inhalation powder blisters with device
35602 Budesonide 200micrograms/dose dry powder inhalation cartridge
35611 Flixotide 250microgram disks (GlaxoSmithKline UK Ltd)
35631 Budelin Novolizer 200micrograms/dose inhalation powder (Meda Pharmaceuticals Ltd)
35638 Fluticasone propionate 100microgram inhalation powder blisters with device
35652 Beclometasone 100microgram inhalation powder blisters

35700 Fluticasone propionate 500microgram inhalation powder blisters with device
35724 Budelin Novolizer 200micrograms/dose inhalation powder refill (Meda Pharmaceuticals Ltd)
35725 Formoterol Easyhaler 12micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)
35772 Fluticasone propionate 100microgram inhalation powder blisters
35825 Serevent 50microgram disks (GlaxoSmithKline UK Ltd)
35905 Fluticasone propionate 250microgram inhalation powder blisters
35986 Flixotide 50microgram disks (GlaxoSmithKline UK Ltd)
36021 Fluticasone propionate 50microgram inhalation powder blisters with device
36090 Flixotide 100microgram disks (GlaxoSmithKline UK Ltd)
36290 Flixotide 50microgram disks with Diskhaler (GlaxoSmithKline UK Ltd)
36401 Fluticasone propionate 250microgram inhalation powder blisters with device
36462 Fluticasone propionate 500microgram inhalation powder blisters
36864 Tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device CFC free
36869 Spiriva Respimat 2.5micrograms/dose solution for inhalation cartridge with device (Boehringer Ingelheim Ltd)
37432 Fostair 100micrograms/dose / 6micrograms/dose inhaler (Chiesi Ltd)
37447 Fluticasone propionate 50microgram inhalation powder blisters
37470 Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose inhaler CFC free
37612 Terbutaline 5mg/2ml nebuliser liquid unit dose vials (Galen Ltd)
37666 Acetylcysteine 600mg tablets
37791 Ipratropium bromide 250microgram/ml
38079 Salbutamol 100micrograms/dose dry powder inhalation cartridge with device
38097 Salbutamol cyclocaps 200microgram Inhalation powder (DuPont Pharmaceuticals Ltd)
38136 Salbulin Novolizer 100micrograms/dose inhalation powder
38214 Salbutamol 100micrograms/dose dry powder inhalation cartridge
38226 Salbulin Novolizer 100micrograms/dose inhalation powder refill
38409 Sodium chloride nebuliser solution Sodium Chloride
38416 Salbutamol cyclocaps 400microgram Inhalation powder
39099 Pulmicort 100micrograms/dose inhaler CFC free (AstraZeneca UK Ltd)
39102 Budesonide 100micrograms/dose inhaler CFC free
39200 AeroBec Forte 250 Autohaler (Meda Pharmaceuticals Ltd)
39879 Budesonide 200micrograms/dose inhaler CFC free
40057 Pulmicort 200micrograms/dose inhaler CFC free (AstraZeneca UK Ltd)
40177 Ipratropium bromide 250microgram/ml Nebuliser liquid
40599 Salbutamol 5mg/2.5ml nebuliser liquid unit dose Steripoule vials
40637 Ipratropium 250micrograms/1ml nebuliser liquid unit dose Steripoule vials (Galen Ltd)
40655 Salbuvent 100microgram/actuation Inhalation powder (Pharmacia Ltd)
40709 Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose vials

40832 Ipratropium 500micrograms/2ml nebuliser liquid unit dose Steripoule vials
41269 Beclometasone 400 Cyclocaps (Teva UK Ltd)
41412 Beclometasone 400micrograms/actuation inhaler
42279 Salbutamol 2.5mg/2.5ml nebuliser liquid unit dose Steripoule vials
42830 Ventolin 100micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)
42858 Ventolin 200micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
42886 Bricanyl 500micrograms/dose Turbohaler (AstraZeneca UK Ltd)
42928 Flixotide 100micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
42985 Flixotide 50micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
42994 Flixotide 250micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
43046 Salipraneb 0.5mg/2.5mg nebuliser solution 2.5ml ampoules
43074 Flixotide 500micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)
43085 Bricanyl 5mg/2ml Respules (AstraZeneca UK Ltd)
43090 Atrovent 40microgram Aerocaps (Boehringer Ingelheim Ltd)
43105 Atrovent 40microgram Aerocaps with Aerohaler (Boehringer Ingelheim Ltd)
43738 Indacaterol 150microgram inhalation powder capsules with device
43893 Onbrez Breezhaler 150microgram inhalation powder capsules with device
44064 Onbrez Breezhaler 300microgram inhalation powder capsules with device
44713 Salbutamol 100microgram/inhalation Inhalation powder
45133 Acetylcysteine 600mg capsules
45610 Indacaterol 300microgram inhalation powder capsules with device
45863 Salbutamol 5mg/2.5ml Nebuliser liquid (Generics (UK) Ltd)
46157 Beclometasone 200 Cyclocaps (Teva UK Ltd)
46551 Salbutamol 100microgram/inhalation Inhalation powder
47943 Beclazone easi-breathe (roi) 100microgram/actuation Pressurised inhalation
48340 Clenil Modulite 100micrograms/dose inhaler
48410 Salbutamol 2.5mg/2.5ml / Ipratropium bromide 500micrograms/2.5ml nebuliser liquid ampoules
48547 Salamol 100micrograms/dose inhaler CFC free (Arrow Generics Ltd)
48666 Flutiform 250micrograms/dose / 10micrograms/dose inhaler
48709 Qvar 100micrograms/dose Easi-Breathe inhaler
49227 Aclidinium bromide 375micrograms/dose dry powder inhaler
49228 Eklira 322micrograms/dose Genuair (AstraZeneca UK Ltd)
49357 Acetylcysteine 600mg effervescent tablets
49367 Clenil Modulite 50micrograms/dose inhaler
49412 Clenil Modulite 200micrograms/dose inhaler
49868 Fluticasone 250micrograms/dose / Formoterol 10micrograms/dose inhaler CFC free
49904 Combivent nebuliser liquid 2.5ml UDVs (Lexon (UK) Ltd)
50036 Flutiform 125micrograms/dose / 5micrograms/dose inhaler
50037 Pulmicort 0.5mg Respules (Waymade Healthcare Plc)
50051 Serevent 25micrograms/dose Evohaler (Waymade Healthcare Plc)
50103 Spiriva 18microgram inhalation powder capsules with HandiHaler
50129 Qvar 100micrograms/dose Easi-Breathe inhaler (DE Pharmaceuticals)

50287 Qvar 100 inhaler (DE Pharmaceuticals)
50292 Spiriva 18microgram inhalation powder capsules
50557 Ventolin 200micrograms/dose Accuhaler (Lexon (UK) Ltd)
50577 Spiriva 18microgram inhalation powder capsules with HandiHaler (DE Pharmaceuticals)
50689 Flutiform 50micrograms/dose / 5micrograms/dose inhaler (Napp Pharmaceuticals Ltd)
50739 Symbicort 400/12 Turbohaler (Mawdsley-Brooks & Company Ltd)
50810 Atrovent 20micrograms/dose inhaler CFC free (DE Pharmaceuticals)
51209 Fluticasone 125micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free
51234 Qvar 100 inhaler (Waymade Healthcare Plc)
51270 Fluticasone 50micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free
51415 Qvar 50 inhaler (Mawdsley-Brooks & Company Ltd)
51480 Qvar 100 Autohaler (DE Pharmaceuticals)
51681 Qvar 100 inhaler (Sigma Pharmaceuticals Plc)
51967 Spiriva 18microgram inhalation powder capsules
52732 Pulmicort 0.5mg Respules (Necessity Supplies Ltd)
52806 Qvar 100 Autohaler (Lexon (UK) Ltd)
53174 Ipratropium bromide 500micrograms/2ml nebuliser liquid unit dose vials
53237 Symbicort 400/12 Turbohaler (DE Pharmaceuticals)
53303 Carbocisteine 375mg capsules (Actavis UK Ltd)
53480 Qvar 100 Autohaler (Stephar (U.K.) Ltd)
53747 OroNAC 600 capsules (Disposable Medical Equipment Ltd)
53761 Glycopyrronium bromide 55microgram inhalation powder capsules with device
53982 Seebri Breezhaler 44microgram inhalation powder capsules with device
54092 A-CYS 600mg capsules (Ennogen Healthcare Ltd)
54207 Qvar 50 inhaler (DE Pharmaceuticals)
54399 Qvar 100 Autohaler (Sigma Pharmaceuticals Plc)
54742 Salmeterol 25micrograms/dose inhaler CFC free
55132 Atrovent 500micrograms/2ml nebuliser liquid UDVs
56493 Qvar 50micrograms/dose Easi-Breathe inhaler (Sigma Pharmaceuticals Plc)
56987 EN-CYS 600mg tablets (Ennogen Healthcare Ltd)
57237 Acetylcysteine 100mg granules sachets
57365 OroNAC 600 tablets (Disposable Medical Equipment Ltd)
57557 Atrovent 20micrograms/dose inhaler CFC free (Lexon (UK) Ltd)
57694 Vertine 25micrograms/dose inhaler CFC free (Teva UK Ltd)
57820 N-Acetylcysteine 600mg tablets (Special Order)
58269 AirSalb 100micrograms/dose inhaler CFC free (Sandoz Ltd)
59327 Relvar Ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler
59409 Salbutamol 100micrograms/dose inhaler CFC free
59439 Fluticasone furoate 92micrograms/dose / Vilanterol 22micrograms/dose dry powder
59573 Relvar Ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler

59638 Spiriva 18microgram inhalation powder capsules with HandiHaler
59899 Fluticasone furoate 184micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler
60524 Acetylcysteine 100mg/5ml oral solution
60920 Atrovent 20micrograms/dose inhaler CFC free (Sigma Pharmaceuticals Plc)
61176 Anoro Ellipta 55micrograms/dose / 22micrograms/dose dry powder inhaler
61490 Umeclidinium bromide 65micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler
61582 Spiriva Respimat 2.5micrograms/dose solution for inhalation cartridge with device
61644 Fostair NEXThaler 100micrograms/dose / 6micrograms/dose dry powder inhaler
61664 Clenil Modulite 250micrograms/dose inhaler
61666 DuoResp Spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler
61782 DuoResp Spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler
61879 Incruse Ellipta 55micrograms/dose dry powder inhaler
61975 Budesonide 500micrograms/2ml nebuliser liquid unit dose vials (Almus Pharmaceuticals Ltd)
62030 Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
62109 Umeclidinium bromide 65micrograms/dose dry powder inhaler
62518 Beclometasone 100micrograms/dose inhaler CFC free
62535 Duaklir 340micrograms/dose / 12micrograms/dose Genuair
62662 Olodaterol 2.5micrograms/dose solution for inhalation cartridge with device CFC free
62667 Ultibro Breezhaler 85microgram/43microgram inhalation powder capsules with device
62739 Indacaterol 85micrograms/dose / Glycopyrronium bromide 54micrograms/dose
62838 Aclidinium bromide 396micrograms/dose / Formoterol 11.8micrograms/dose dry powder inhaler
63490 A-CYS 200mg granules sachets (Ennogen Healthcare Ltd)
63585 Beclometasone 50micrograms/dose inhaler (Almus Pharmaceuticals Ltd)
63992 Eklira 322micrograms/dose Genuair (Waymade)

Appendix 4: Spirometry Codes

852 Lung function tests
1252 Pulmonary function tests
1837 Lung function testing abnormal
2297 Lung function testing
6091 Percent predicted FEV1
6118 Spirometry
8512 FEV1/FVC percent
10320 Forced expired volume in 1 second
10336 Spirometry reversibility
10337 Spirometry screening
10420 Spirometry reversibility negative
10492 spirometry reversibility positive
10873 Forced vital capacity - FVC
13683 Referral for spirometry
14453 Forced expiratory volume - FEV
14454 Expected FEV1
14456 FEV1/FVC ratio
19830 FEV1 after bronchodilation
19832 FEV1/FVC ratio after bronchodilator
23234 Lung function mildly obstruct.
23236 Lung function signific. obstr.
23237 FEV1 before bronchodilation
23284 Expected FEV1/FVC ratio
23285 FEV1/FVC ratio abnormal
23286 FVC - forced vital capacity normal
23287 FVC - forced vital capacity abnormal
25083 FEV1/FVC < 70% of predicted
26186 Forced expiratory flow rate between 25+75% of vital capacity
26241 Spirometry indicated
27141 FEV1/FVC ratio before bronchodilator
29015 Spirometry
43040 FEV1 pre steroids
43041 FEV1 post steroids
45993 incentive spirometry
58632 FEV1/FVC ratio pre steroids
58633 FEV1/FVC ratio post steroids
88887 FEV1/VC percent
97571 Forced vital capacity before bronchodilation
99777 Forced expired volume in 1 second reversibility
99824 Percentage of predicted forced vital capacity

100391 Forced expired volume in 1 second percentage change
101079 Percentage predicted FEV1 after bronchodilation
102522 post bronchodilator spirometry
102575 Forced expired volume in one second/vital capacity ratio
105054 Lung function obstructed
107044 FEV1 after change of bronchodilator

Appendix 5: ICS Prodcodes

38 beclometasone 100micrograms/dose inhaler
99 becotide 100 inhaler (glaxosmithkline uk ltd)
454 pulmicort 200microgram inhaler (astrazeneca uk ltd)
638 seretide 250 accuhaler (glaxosmithkline uk ltd)
665 seretide 100 accuhaler (glaxosmithkline uk ltd)
883 becodisks 200microgram disc (allen & hanburys ltd)
895 beclazone 100 easi-breathe inhaler (teva uk ltd)
896 becotide easi-breathe 100microgram/actuation pressurised inhalation (allen & hanburys ltd)
908 pulmicort 400 turbohaler (astrazeneca uk ltd)
909 budesonide 200micrograms/dose inhaler
911 flixotide accuhaler 250 250microgram/inhalation inhalation powder (allen & hanburys ltd)
947 budesonide 50micrograms/actuation refill canister
956 pulmicort 200 turbohaler (astrazeneca uk ltd)
959 budesonide 50micrograms/dose inhaler
960 pulmicort 100 turbohaler (astrazeneca uk ltd)
1100 beclazone 100 inhaler (teva uk ltd)
1236 becloforte 250micrograms/dose inhaler (glaxosmithkline uk ltd)
1242 beclometasone 250micrograms/dose inhaler
1243 beclazone 250 easi-breathe inhaler (teva uk ltd)
1258 becotide 200 inhaler (glaxosmithkline uk ltd)
1259 beclometasone 200micrograms/dose inhaler
1269 becotide 50microgram/ml nebuliser liquid (allen & hanburys ltd)
1406 becotide 50 inhaler (glaxosmithkline uk ltd)
1412 flixotide 250microgram/actuation inhalation powder (allen & hanburys ltd)
1424 flixotide 250microgram disc (allen & hanburys ltd)
1426 flixotide 500microgram disc (allen & hanburys ltd)
1518 flixotide 50microgram/actuation inhalation powder (allen & hanburys ltd)
1537 becotide 200microgram rotacaps (glaxosmithkline uk ltd)
1551 beclazone 250 inhaler (teva uk ltd)
1552 becloforte easi-breathe 250microgram/actuation pressurised inhalation (allen & hanburys ltd)
1642 budesonide 400micrograms/dose dry powder inhaler
1676 flixotide 125microgram/actuation inhalation powder (allen & hanburys ltd)
1680 pulmicort ls 50micrograms/dose inhaler (astrazeneca uk ltd)
1725 beclazone 50 easi-breathe inhaler (teva uk ltd)
1727 becotide easi-breathe 50microgram/actuation pressurised inhalation (allen & hanburys ltd)
1734 beclometasone 100micrograms/dose breath actuated inhaler
1861 aerobec 100 autohaler (meda pharmaceuticals ltd)

1885 beclazone 200 inhaler (teva uk ltd)
1951 becodisks 400microgram disc (allen & hanburys ltd)
2092 budesonide 200micrograms/dose dry powder inhaler
2124 pulmicort refil 200 mcg inh
2125 pulmicort 200microgram refill canister (astrazeneca uk ltd)
2148 beclometasone 400microgram disc
2159 aerobec 50 autohaler (meda pharmaceuticals ltd)
2160 beclometasone 50micrograms/dose breath actuated inhaler
2229 becodisks 100microgram disc (allen & hanburys ltd)
2282 fluticasone 500micrograms/dose dry powder inhaler
2335 qvar 100 inhaler (teva uk ltd)
2440 flixotide accuhaler 500 500microgram/inhalation inhalation powder (allen & hanburys ltd)
2600 beclometasone 250micrograms/dose breath actuated inhaler
2723 fluticasone 25micrograms/dose inhaler
2892 becloforte 400microgram disks (glaxosmithkline uk ltd)
2893 beclometasone 200micrograms disc
2951 fluticasone 250microgram/actuation pressurised inhalation
2992 beclazone 50 inhaler (teva uk ltd)
3018 beclometasone 50micrograms/dose inhaler
3075 becotide 400microgram rotacaps (glaxosmithkline uk ltd)
3119 becloforte integra 250microgram/actuation inhaler with compact spacer (glaxo laboratories td)
3150 beclometasone 100micrograms/actuation extrafine particle cfc free inhaler
3188 pulmicort complete 50 mcg inh
3220 qvar 50 autohaler (teva uk ltd)
3289 flixotide 25micrograms/dose inhaler (glaxosmithkline uk ltd)
3363 becloforte 400microgram disks with diskhaler (glaxosmithkline uk ltd)
3442 pulmicort complete 200 mcg inh
3546 qvar 50 inhaler (teva uk ltd)
3556 beclometasone 50micrograms with salbutamol 100micrograms/inhalation inhaler
3570 budesonide 200micrograms/actuation refill canister
3666 seretide 500 accuhaler (glaxosmithkline uk ltd)
3743 filair 50 inhaler (meda pharmaceuticals ltd)
3753 flixotide diskhaler-community pack 250 mcg
3758 pulmadil inhalation powder (3m health care ltd)
3838 salbutamol 400mcg/beclometh.100mcg r/cap inh
3927 filair 100 inhaler (meda pharmaceuticals ltd)
3947 becotide 100microgram rotacaps (glaxosmithkline uk ltd)
3988 flixotide diskhaler-community pack 100 mcg
3989 flixotide 100microgram disc (allen & hanburys ltd)
3993 filair forte 250micrograms/dose inhaler (meda pharmaceuticals ltd)
4131 fluticasone 100microgram disc
4132 fluticasone 125microgram/actuation pressurised inhalation

4365 beclometasone 100micrograms disc
4413 qvar 100 autohaler (teva uk ltd)
4499 aerobec 250microgram/actuation pressurised inhalation (meda pharmaceuticals ltd)
4545 pulmicort ls 50microgram refill canister (astrazeneca uk ltd)
4601 asmabec 100 clickhaler (focus pharmaceuticals ltd)
4688 fluticasone 50microgram/actuation pressurised inhalation
4759 beclometasone 100microgram inhalation powder capsules
4803 beclazone 250microgram/actuation inhalation powder (actavis uk ltd)
4926 flixotide accuhaler 100 100microgram/inhalation inhalation powder (allen & hanburys ltd)
5143 seretide 50 evohaler (glaxosmithkline uk ltd)
5161 seretide 125 evohaler (glaxosmithkline uk ltd)
5172 seretide 250 evohaler (glaxosmithkline uk ltd)
5223 fluticasone 50micrograms/dose inhaler cfc free
5309 flixotide 50micrograms/dose evohaler (glaxosmithkline uk ltd)
5521 beclometasone 200micrograms/dose dry powder inhaler
5522 beclometasone 100micrograms/dose dry powder inhaler
5558 salmeterol 50micrograms with fluticasone 500micrograms cfc free inhaler
5580 flixotide accuhaler 50 50microgram/inhalation inhalation powder (allen & hanburys ltd)
5683 flixotide 250micrograms/dose evohaler (glaxosmithkline uk ltd)
5718 flixotide 125micrograms/dose evohaler (glaxosmithkline uk ltd)
5804 beclometasone 250micrograms/dose dry powder inhaler
5822 fluticasone 250micrograms/dose inhaler cfc free
5864 salmeterol 25micrograms with fluticasone 250micrograms cfc free inhaler
5885 fluticasone 100micrograms/dose dry powder inhaler
5942 salmeterol 50micrograms with fluticasone 250micrograms cfc free inhaler
5975 fluticasone 125micrograms/dose inhaler cfc free
5992 beclometasone 50micrograms/dose dry powder inhaler
6325 symbicort 200/6 turbohaler (astrazeneca uk ltd)
6569 salmeterol 25micrograms with fluticasone 125micrograms cfc free inhaler
6616 salmeterol 25micrograms with fluticasone 50micrograms cfc free inhaler
6746 budesonide 400micrograms/dose / formoterol 12micrograms/dose dry powder inhaler
6780 symbicort 400/12 turbohaler (astrazeneca uk ltd)
6796 budesonide 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler
6839 Alvesco 160 inhaler (Takeda UK Ltd) Ciclesonide160microgram/1dose Pressurised inhalation
7013 symbicort 100/6 turbohaler (astrazeneca uk ltd)
7356 Ciclesonide 80micrograms/dose inhaler CFC free
7602 fluticasone 50microgram disc
7638 fluticasone 250microgram disc

7653 beclometasone 400microgram inhalation powder capsules
7724 betamethasone valerate 100micrograms/actuation inhaler
7788 budesonide 100micrograms/dose dry powder inhaler
7891 fluticasone 500microgram disc
7948 fluticasone 250micrograms/dose dry powder inhaler
8111 becloforte vm 250microgram/actuation vm pack (allen & hanburys ltd)
8433 budesonide 100micrograms/actuation inhaler
8450 flixotide diskhaler-community pack 50 mcg
8635 flixotide 50microgram disc (allen & hanburys ltd)
9164 fluticasone 50micrograms/dose dry powder inhaler
9233 beclometasone 200microgram inhalation powder capsules
9477 asmabec 100microgram/actuation spacehaler (celltech pharma europe ltd)
9571 beclometasone 250micrograms/actuation vortex inhaler
9577 asmabec 50 clickhaler (focus pharmaceuticals ltd)
9599 beclazone 50microgram/actuation inhalation powder (actavis uk ltd)
9921 beclometasone 100micrograms/dose breath actuated inhaler cfc free
10090 beclometasone 50micrograms/actuation extrafine particle cfc free inhaler
10102 Ciclesonide 160micrograms/dose inhaler CFC free
10218 budesonide 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler
10321 budesonide 400microgram inhalation powder capsules
10858 pulmadil auto inhalation powder (3m health care ltd)
10968 foradil 12microgram inhalation powder capsules with device (novartis pharmaceuticals uk ltd)
11198 beclometasons 50 micrograms/actuation vortex inhaler
11307 salbutamol 100micrograms/dose / beclometasone 50micrograms/dose inhaler
11410 fluticasone 500micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler
11497 beclometasone 400micrograms/dose dry powder inhaler
11588 fluticasone 125micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free
11618 fluticasone 250micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free
11732 beclometasone 50micrograms/dose breath actuated inhaler cfc free
12994 fluticasone 50micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free
13037 pulvinal beclometasone dipropionate 200micrograms/dose dry powder inhaler (chiesi ltd)
13040 fluticasone 250micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler
13273 fluticasone 100micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler
13290 clenil modulite 100micrograms/dose inhaler (chiesi ltd)
13815 beclazone 100microgram/actuation inhalation powder (actavis uk ltd)
14294 qvar 50micrograms/dose easi-breathe inhaler (teva uk ltd)

14321 beclometasone 200micrograms/dose inhaler cfc free 14482 bricanyl 2.5 mg inj
14524 bdp 250microgram/actuation spacehaler (celltech pharma europe ltd)
14561 salbutamol 400microgram / beclometasone 200microgram inhalation powder capsules
14567 asmabec 250 clickhaler (focus pharmaceuticals ltd)
14590 asmabec 250microgram/actuation spacehaler (celltech pharma europe ltd)
14700 budesonide 400micrograms/actuation inhaler
14736 pulvinal beclometasone dipropionate 400micrograms/dose dry powder inhaler (chiesi ltd)
14757 pulvinal beclometasone dipropionate 100micrograms/dose dry powder inhaler (chiesi ltd)
15326 beclometasone 100micrograms/dose inhaler cfc free
15706 beclometasone 100 micrograms/actuation vortex inhaler
16054 budesonide 200micrograms/actuation breath actuated powder inhaler
16148 clenil modulite 250micrograms/dose inhaler (chiesi ltd)
16151 clenil modulite 200micrograms/dose inhaler (chiesi ltd)
16158 clenil modulite 50micrograms/dose inhaler (chiesi ltd)
16584 beclometasone 50micrograms/dose inhaler cfc free
17654 easyhaler beclometasone 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
17670 easyhaler budesonide 100micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
18394 bdp 50microgram/actuation spacehaler (celltech pharma europe ltd)
18456 salbutamol 200microgram / beclometasone 100microgram inhalation powder capsules
18537 budesonide 200microgram inhalation powder capsules
18848 qvar 100micrograms/dose easi-breathe inhaler (teva uk ltd)
19031 bdp 100microgram/actuation spacehaler (celltech pharma europe ltd)
19121 beclometasone 100micrograms with salbutamol 200micrograms inhalation capsules
19376 beclometasone 200micrograms with salbutamol 400micrograms inhalation capsules
19389 asmabec 50microgram/actuation spacehaler (celltech pharma europe ltd)
19401 beclometasone 250micrograms/actuation inhaler and compact spacer
20707 becotide 100
20763 becloforte
20812 pulmicort refill
20825 spacehaler bdp 250microgram/actuation spacehaler (celltech pharma europe ltd)
21005 beclometasone 250micrograms/dose inhaler cfc free
21224 Alvesco 80 inhaler (Takeda UK Ltd)Ciclesonide80microgram/1dose
21482 beclometasone 100micrograms/dose inhaler (generics (uk) ltd)
22225 beclomethasone /salbutamol
24219 becotide rotacaps

25204 beclometasone 100micrograms/dose inhaler (a a h pharmaceuticals ltd)
26063 beclometasone 100micrograms/dose inhaler (teva uk ltd)
27188 easyhaler budesonide 200micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
27525 becotide 50
27583 pulmicort
27679 beclometasone 100microgram/actuation pressurised inhalation (approved prescription services ltd)
27915 fluticasone prop disk refill
28073 beclometasone 250microgram/actuation pressurised inhalation (approved prescription services ltd)
28640 beclometasone 100microgram/actuation inhalation powder (actavis uk ltd)
29325 beclometasone 250micrograms/dose inhaler (generics (uk) ltd)
30210 beclometasone 250micrograms/dose inhaler (teva uk ltd)
30238 beclometasone 50microgram/actuation pressurised inhalation (approved prescription services ltd)
30649 easyhaler budesonide 400micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
31774 beclometasone 50micrograms/dose inhaler (generics (uk) ltd)
32874 beclometasone 50microgram/actuation inhalation powder (actavis uk ltd)
33258 beclometasone 250micrograms/dose inhaler (a a h pharmaceuticals ltd)
33849 beclometasone 100microgram/actuation inhalation powder (neo laboratories ltd)
34315 beclometasone 250microgram/actuation inhalation powder (actavis uk ltd)
34428 beclometasone 50microgram/actuation inhalation powder (neo laboratories ltd)
34739 beclometasone 50micrograms/dose inhaler (teva uk ltd)
34794 beclometasone 200micrograms/dose inhaler (a a h pharmaceuticals ltd)
34859 beclometasone 250microgram/actuation inhalation powder (neo laboratories ltd)
34919 beclometasone 50micrograms/dose inhaler (a a h pharmaceuticals ltd)
35071 becodisks 200microgram (glaxosmithkline uk ltd)
35106 becodisks 100microgram with diskhaler (glaxosmithkline uk ltd)
35107 beclometasone 400microgram inhalation powder blisters with device
35113 beclometasone 200microgram inhalation powder blisters
35118 becodisks 400microgram with diskhaler (glaxosmithkline uk ltd)
35225 flixotide 100microgram disks with diskhaler (glaxosmithkline uk ltd)
35288 beclometasone 400microgram inhalation powder blisters
35293 beclometasone 200microgram inhalation powder blisters with device
35299 becodisks 400microgram (glaxosmithkline uk ltd)
35374 flixotide 500microgram disks (glaxosmithkline uk ltd)
35392 flixotide 500microgram disks with diskhaler (glaxosmithkline uk ltd)
35408 becodisks 100microgram (glaxosmithkline uk ltd)
35430 becodisks 200microgram with diskhaler (glaxosmithkline uk ltd)
35461 flixotide 250microgram disks with diskhaler (glaxosmithkline uk ltd)

35510 budesonide 200micrograms/dose dry powder inhalation cartridge with device
35580 beclometasone 100microgram inhalation powder blisters with device
35602 budesonide 200micrograms/dose dry powder inhalation cartridge
35611 flixotide 250microgram disks (glaxosmithkline uk ltd)
35631 budelin novolizer 200micrograms/dose inhalation powder (meda pharmaceuticals ltd)
35638 fluticasone 100microgram inhalation powder blisters with device
35652 beclometasone 100microgram inhalation powder blisters
35700 fluticasone 500microgram inhalation powder blisters with device
35724 budelin novolizer 200micrograms/dose inhalation powder refill (meda pharmaceuticals ltd)
35725 formoterol easyhaler 12micrograms/dose dry powder inhaler (orion pharma (uk) ltd)
35744 bricanyl 2.5mg/5ml solution for injection ampoules (astrazeneca uk ltd)
35772 fluticasone 100microgram inhalation powder blisters
35905 fluticasone 250microgram inhalation powder blisters
35986 flixotide 50microgram disks (glaxosmithkline uk ltd)
36021 fluticasone 50microgram inhalation powder blisters with device
36090 flixotide 100microgram disks (glaxosmithkline uk ltd)
36290 flixotide 50microgram disks with diskhaler (glaxosmithkline uk ltd)
36401 fluticasone 250microgram inhalation powder blisters with device
36462 fluticasone 500microgram inhalation powder blisters
37432 fostair 100micrograms/dose/6micrograms/dose inhaler (chiesi ltd)
37447 fluticasone 50microgram inhalation powder blisters
37470 beclometasone 100micrograms/dose / formoterol 6micrograms/dose inhaler cfc free
39099 pulmicort 100micrograms/dose inhaler cfc free (astrazeneca uk ltd)
39102 budesonide 100micrograms/dose inhaler cfc free
39200 aerobec forte 250 autohaler (meda pharmaceuticals ltd)
39879 budesonide 200micrograms/dose inhaler cfc free
40057 pulmicort 200micrograms/dose inhaler cfc free (astrazeneca uk ltd)
41269 beclometasone 400 cyclocaps (teva uk ltd)
41412 beclometasone 400micrograms/actuation inhaler
42928 flixotide 100micrograms/dose accuhaler (glaxosmithkline uk ltd)
42985 flixotide 50micrograms/dose accuhaler (glaxosmithkline uk ltd)
42994 flixotide 250micrograms/dose accuhaler (glaxosmithkline uk ltd)
43074 flixotide 500micrograms/dose accuhaler (glaxosmithkline uk ltd)
43085 bricanyl 5mg/2ml respules (astrazeneca uk ltd)
48666 Flutiform 250micrograms/dose / 10micrograms/dose inhaler
50036 Flutiform 125micrograms/dose / 5micrograms/dose inhaler
50689 Flutiform 50micrograms/dose / 5micrograms/dose inhaler
51234 Qvar 100 inhaler (Waymade Healthcare Plc)
51270 Fluticasone 50micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free
51415 Qvar 50 inhaler (Mawdsley-Brooks & Company Ltd)

51480 Qvar 100 Autohaler (DE Pharmaceuticals)
51681 Qvar 100 inhaler (Sigma Pharmaceuticals Plc)
52732 Pulmicort 0.5mg Respules (Necessity Supplies Ltd)
52806 Qvar 100 Autohaler (Lexon (UK) Ltd)
53237 Symbicort 400/12 Turbohaler (DE Pharmaceuticals)
53480 Qvar 100 Autohaler (Stephar (U.K.) Ltd)
54207 Qvar 50 inhaler (DE Pharmaceuticals)
54399 Qvar 100 Autohaler (Sigma Pharmaceuticals Plc)
56493 Qvar 50micrograms/dose Easi-Breathe inhaler (Sigma Pharmaceuticals Plc)
59327 Relvar Ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler
59439 Fluticasone furoate 92micrograms/dose / Vilanterol 22micrograms/dose dry powder
59573 Relvar Ellipta 184micrograms/dose / 22micrograms/dose dry powder
59899 Fluticasone furoate 184micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler
61644 Fostair NEXThaler 100micrograms/dose / 6micrograms/dose dry powder inhaler
61664 Clenil Modulite 250micrograms/dose inhaler
61666 DuoResp Spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler
61782 DuoResp Spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler
61975 Budesonide 500micrograms/2ml nebuliser liquid unit dose vials (Almus Pharmaceuticals Ltd)
62030 Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler
62518 Beclometasone 100micrograms/dose inhaler CFC free
63585 Beclometasone 50micrograms/dose inhaler (Almus Pharmaceuticals Ltd

Appendix 6: COPD exacerbation definition

a. Oral corticosteroid prodcodes

22029	amiclav 250mg/125mg tablets (ashbourne pharmaceuticals ltd)
11634	amix 125 oral suspension (ashbourne pharmaceuticals ltd)
11613	amix 250 capsules (ashbourne pharmaceuticals ltd)
21844	amix 250 oral suspension (ashbourne pharmaceuticals ltd)
18786	amix 500 capsules (ashbourne pharmaceuticals ltd)
29697	amopen 125mg/5ml liquid (yorkshire pharmaceuticals ltd)
30498	amopen 250mg capsule (yorkshire pharmaceuticals ltd)
31423	amopen 250mg/5ml liquid (yorkshire pharmaceuticals ltd)
17711	amopen 500mg capsule (yorkshire pharmaceuticals ltd)
12378	amoram 125mg/5ml oral suspension (lpc medical (uk) ltd)
9243	amoram 250mg capsules (lpc medical (uk) ltd)
22438	amoram 250mg/5ml oral suspension (lpc medical (uk) ltd)
22415	amoram 500mg capsules (lpc medical (uk) ltd)
8906	amoxicillin 125mg / clavulanic acid 31mg/5ml oral suspension
13285	amoxicillin 125mg / clavulanic acid 31mg/5ml oral suspension
53942	amoxicillin 125mg / clavulanic acid 62.5mg/5ml oral suspension
41835	amoxicillin 125mg powder (ivax pharmaceuticals uk ltd)
3742	amoxicillin 125mg sugar free chewable tablets
13848	amoxicillin 125mg sugar free powder
485	amoxicillin 125mg/1.25ml oral suspension paediatric
42822	amoxicillin 125mg/5ml mixture (celltech pharma europe ltd)
28872	amoxicillin 125mg/5ml mixture (crosspharma ltd)
41818	amoxicillin 125mg/5ml oral solution (berk pharmaceuticals ltd)
42240	amoxicillin 125mg/5ml oral solution (co-pharma ltd)
29337	amoxicillin 125mg/5ml oral solution (neo laboratories ltd)
62	amoxicillin 125mg/5ml oral suspension
33690	amoxicillin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
34857	amoxicillin 125mg/5ml oral suspension (actavis uk ltd)
42545	amoxicillin 125mg/5ml oral suspension (almus pharmaceuticals ltd)
50002	amoxicillin 125mg/5ml oral suspension (bristol laboratories ltd)
32622	amoxicillin 125mg/5ml oral suspension (generics (uk) ltd)
23238	amoxicillin 125mg/5ml oral suspension (ivax pharmaceuticals uk ltd)
48038	amoxicillin 125mg/5ml oral suspension (kent pharmaceuticals ltd)
52685	amoxicillin 125mg/5ml oral suspension (phoenix healthcare distribution ltd)
28875	amoxicillin 125mg/5ml oral suspension (ranbaxy (uk) ltd)
43229	amoxicillin 125mg/5ml oral suspension (sandoz ltd)
55047	amoxicillin 125mg/5ml oral suspension (sandoz ltd)

28870	amoxicillin 125mg/5ml oral suspension (teva uk ltd)
56561	amoxicillin 125mg/5ml oral suspension (waymade healthcare plc)
503	amoxicillin 125mg/5ml oral suspension sugar free
33696	amoxicillin 125mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
34679	amoxicillin 125mg/5ml oral suspension sugar free (actavis uk ltd)
53078	amoxicillin 125mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
36054	amoxicillin 125mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)
52122	amoxicillin 125mg/5ml oral suspension sugar free (bristol laboratories ltd)
31014	amoxicillin 125mg/5ml oral suspension sugar free (generics (uk) ltd)
24150	amoxicillin 125mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
34384	amoxicillin 125mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)
52857	amoxicillin 125mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)
29858	amoxicillin 125mg/5ml oral suspension sugar free (sandoz ltd)
34638	amoxicillin 125mg/5ml oral suspension sugar free (teva uk ltd)
55626	amoxicillin 125mg/5ml oral suspension sugar free (waymade healthcare plc)
1391	amoxicillin 250mg / clavulanic acid 125mg tablets
7636	amoxicillin 250mg / clavulanic acid 62mg/5ml oral suspension
13262	amoxicillin 250mg / clavulanic acid 62mg/5ml oral suspension
42809	amoxicillin 250mg capsule (c p pharmaceuticals ltd)
31661	amoxicillin 250mg capsule (co-pharma ltd)
28882	amoxicillin 250mg capsule (crosspharma ltd)
34435	amoxicillin 250mg capsule (ddsa pharmaceuticals ltd)
33222	amoxicillin 250mg capsule (lagap)
32872	amoxicillin 250mg capsule (mepra-pharm)
34714	amoxicillin 250mg capsule (neo laboratories ltd)
45267	amoxicillin 250mg capsule (regent laboratories ltd)
9	amoxicillin 250mg capsules
25484	amoxicillin 250mg capsules (a a h pharmaceuticals ltd)
33343	amoxicillin 250mg capsules (actavis uk ltd)
54796	amoxicillin 250mg capsules (boston healthcare ltd)
54491	amoxicillin 250mg capsules (bristol laboratories ltd)
30745	amoxicillin 250mg capsules (generics (uk) ltd)
34042	amoxicillin 250mg capsules (ivax pharmaceuticals uk ltd)
30528	amoxicillin 250mg capsules (kent pharmaceuticals ltd)
54271	amoxicillin 250mg capsules (mawdsley-brooks & company ltd)
51536	amoxicillin 250mg capsules (milpharm ltd)
30743	amoxicillin 250mg capsules (ranbaxy (uk) ltd)
48006	amoxicillin 250mg capsules (sandoz ltd)
23967	amoxicillin 250mg capsules (teva uk ltd)
54185	amoxicillin 250mg capsules (wockhardt uk ltd)
870	amoxicillin 250mg sugar free chewable tablets

42815	amoxicillin 250mg/5ml mixture (celltech pharma europe ltd)
33570	amoxicillin 250mg/5ml mixture (crosspharma ltd)
40238	amoxicillin 250mg/5ml mixture (mepra-pharm)
45317	amoxicillin 250mg/5ml oral solution (neo laboratories ltd)
427	amoxicillin 250mg/5ml oral suspension
33165	amoxicillin 250mg/5ml oral suspension (a a h pharmaceuticals ltd)
34760	amoxicillin 250mg/5ml oral suspension (actavis uk ltd)
41090	amoxicillin 250mg/5ml oral suspension (almus pharmaceuticals ltd)
55018	amoxicillin 250mg/5ml oral suspension (bristol laboratories ltd)
33689	amoxicillin 250mg/5ml oral suspension (generics (uk) ltd)
32640	amoxicillin 250mg/5ml oral suspension (ivax pharmaceuticals uk ltd)
51382	amoxicillin 250mg/5ml oral suspension (phoenix healthcare distribution ltd)
55499	amoxicillin 250mg/5ml oral suspension (ranbaxy (uk) ltd)
56223	amoxicillin 250mg/5ml oral suspension (sandoz ltd)
37755	amoxicillin 250mg/5ml oral suspension (sandoz ltd)
53924	amoxicillin 250mg/5ml oral suspension (sigma pharmaceuticals plc)
27725	amoxicillin 250mg/5ml oral suspension (teva uk ltd)
585	amoxicillin 250mg/5ml oral suspension sugar free
34232	amoxicillin 250mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
40243	amoxicillin 250mg/5ml oral suspension sugar free (actavis uk ltd)
54222	amoxicillin 250mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
42732	amoxicillin 250mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)
49065	amoxicillin 250mg/5ml oral suspension sugar free (bristol laboratories ltd)
31535	amoxicillin 250mg/5ml oral suspension sugar free (generics (uk) ltd)
33699	amoxicillin 250mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
34855	amoxicillin 250mg/5ml oral suspension sugar free (kent pharmaceuticals ltd)
34775	amoxicillin 250mg/5ml oral suspension sugar free (teva uk ltd)
17746	amoxicillin 375mg soluble tablets
1140	amoxicillin 3g oral powder sachets sugar free
33383	amoxicillin 3g oral powder sachets sugar free (a a h pharmaceuticals ltd)
40168	amoxicillin 3g oral powder sachets sugar free (kent pharmaceuticals ltd)
28130	amoxicillin 3g oral powder sachets sugar free (teva uk ltd)
41734	amoxicillin 3g powder (actavis uk ltd)
15192	amoxicillin 400mg / clavulanic acid 57mg/5ml sugar free oral suspension
5662	amoxicillin 500mg / clarithromycin 500mg / lansoprazole 30mg triple pack
13216	amoxicillin 500mg / clavulanic acid 125mg tablets
38684	amoxicillin 500mg capsule (c p pharmaceuticals ltd)
35570	amoxicillin 500mg capsule (crosspharma ltd)
34885	amoxicillin 500mg capsule (ddsa pharmaceuticals ltd)
44854	amoxicillin 500mg capsule (lagap)
34912	amoxicillin 500mg capsule (neo laboratories ltd)
48	amoxicillin 500mg capsules

33692	amoxicillin 500mg capsules (a a h pharmaceuticals ltd)
53627	amoxicillin 500mg capsules (accord healthcare ltd)
26157	amoxicillin 500mg capsules (actavis uk ltd)
52820	amoxicillin 500mg capsules (alliance healthcare (distribution) ltd)
47640	amoxicillin 500mg capsules (almus pharmaceuticals ltd)
55527	amoxicillin 500mg capsules (boston healthcare ltd)
52771	amoxicillin 500mg capsules (bristol laboratories ltd)
23740	amoxicillin 500mg capsules (generics (uk) ltd)
29463	amoxicillin 500mg capsules (ivax pharmaceuticals uk ltd)
33706	amoxicillin 500mg capsules (kent pharmaceuticals ltd)
52058	amoxicillin 500mg capsules (medreich plc)
54725	amoxicillin 500mg capsules (milpharm ltd)
34852	amoxicillin 500mg capsules (ranbaxy (uk) ltd)
31801	amoxicillin 500mg capsules (sandoz ltd)
34001	amoxicillin 500mg capsules (teva uk ltd)
55394	amoxicillin 500mg capsules (wockhardt uk ltd)
1722	amoxicillin 500mg dispersible tablets
2281	amoxicillin 500mg sugar free chewable tablets
4582	amoxicillin 750mg soluble tablets
9343	amoxicillin 750mg sugar free powder
439	amoxicillin with clavulanic acid dispersible tablets
2171	amoxil 125mg/1.25ml paediatric oral suspension (glaxosmithkline uk ltd)
2153	amoxil 125mg/5ml syrup sucrose free (glaxosmithkline uk ltd)
133	amoxil 250mg capsules (glaxosmithkline uk ltd)
1812	amoxil 250mg/5ml syrup sucrose free (glaxosmithkline uk ltd)
2174	amoxil 3g oral powder sachets sucrose free (glaxosmithkline uk ltd)
847	amoxil 500mg capsules (glaxosmithkline uk ltd)
49590	amoxil 500mg capsules (lexon (uk) ltd)
51436	amoxil 500mg capsules (mawdsley-brooks & company ltd)
56700	amoxil 500mg capsules (necessity supplies ltd)
15148	amoxil 500mg dispersible tablet (smithkline beecham plc)
4010	amoxil 750mg sachets (glaxosmithkline uk ltd)
4154	amoxil fiztab 125mg tablet (bencard)
1637	amoxil fiztab 250mg tablet (bencard)
7737	amoxil fiztab 500mg tablet (bencard)
31571	amoxycillin
32505	amoxycillin
27897	amoxycillin
7592	amoxycillin 125 mg cap
22469	amoxycillin 125mg/31mg clavulanic acid
25034	amoxycillin 125mg/62mg clavulanic acid
7581	amoxycillin 125mg/62mg clavulanic acid syr
27886	amoxycillin 250/clavulanic acid 125 disp

19795	amoxycillin 250mg/clavulanic acid 125mg
1570	amoxycillin 500 mg tab
2902	amoxycillin fiztab 125 mg tab
1393	amoxycillin fiztab 250 mg tab
22293	amoxycillin trihydrate sachet
21982	amoxycillin trihydrate sachet
31286	amoxymed 125mg/5ml oral solution (medipharma ltd)
3669	amoxymed 250mg capsule (medipharma ltd)
33109	amrit 125mg/5ml liquid (bhr pharmaceuticals ltd)
27714	amrit 250mg capsule (bhr pharmaceuticals ltd)
33110	amrit 250mg/5ml liquid (bhr pharmaceuticals ltd)
33112	amrit 500mg capsule (bhr pharmaceuticals ltd)
27495	arpimycin 125mg/5ml liquid (rosemont pharmaceuticals ltd)
36544	arpimycin 125mg/5ml oral suspension (rosemont pharmaceuticals ltd)
24220	arpimycin 250mg/5ml liquid (rosemont pharmaceuticals ltd)
36514	arpimycin 250mg/5ml oral suspension (rosemont pharmaceuticals ltd)
37022	arpimycin 500mg/5ml liquid (rosemont pharmaceuticals ltd)
415	augmentin 125/31 sf oral suspension (glaxosmithkline uk ltd)
50595	augmentin 125/31 sf oral suspension (mawdsley-brooks & company ltd)
51164	augmentin 125/31 sf oral suspension (waymade healthcare plc)
569	augmentin 250/62 sf oral suspension (glaxosmithkline uk ltd)
52666	augmentin 250/62 sf oral suspension (sigma pharmaceuticals plc)
2507	augmentin 375mg dispersible tablets (glaxosmithkline uk ltd)
49063	augmentin 375mg tablets (doncaster pharmaceuticals ltd)
399	augmentin 375mg tablets (glaxosmithkline uk ltd)
48683	augmentin 375mg tablets (lexon (uk) ltd)
49374	augmentin 375mg tablets (mawdsley-brooks & company ltd)
49048	augmentin 375mg tablets (waymade healthcare plc)
50279	augmentin 625mg tablets (doncaster pharmaceuticals ltd)
509	augmentin 625mg tablets (glaxosmithkline uk ltd)
49656	augmentin 625mg tablets (lexon (uk) ltd)
52207	augmentin 625mg tablets (mawdsley-brooks & company ltd)
49321	augmentin 625mg tablets (sigma pharmaceuticals plc)
49683	augmentin 625mg tablets (waymade healthcare plc)
5341	augmentin-duo 400/57 oral suspension (glaxosmithkline uk ltd)
56591	augmentin-duo 400/57 oral suspension (lexon (uk) ltd)
51194	augmentin-duo 400/57 oral suspension (sigma pharmaceuticals plc)
31007	aureomycin powder (wyeth pharmaceuticals)
25127	avelox 400mg tablets (bayer plc)
26289	bacticlor mr 375mg tablets (ranbaxy (uk) ltd)
4895	benzoyl peroxide 5% / erythromycin 3% gel
21802	berkmycen 250mg tablet (berk pharmaceuticals ltd)
17093	bisolvomycin capsule (boehringer ingelheim ltd)

13910	cefaclor 125mg/5ml liquid (generics (uk) ltd)
14607	cefaclor 125mg/5ml liquid (lagap)
1038	cefaclor 125mg/5ml oral suspension
39703	cefaclor 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
34913	cefaclor 125mg/5ml oral suspension (genus pharmaceuticals ltd)
32235	cefaclor 125mg/5ml oral suspension (ranbaxy (uk) ltd)
7526	cefaclor 125mg/5ml oral suspension sugar free
56610	cefaclor 125mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)
9520	cefaclor 250mg capsule (lagap)
366	cefaclor 250mg capsules
30772	cefaclor 250mg capsules (ranbaxy (uk) ltd)
20420	cefaclor 250mg/5ml liquid (generics (uk) ltd)
20409	cefaclor 250mg/5ml liquid (lagap)
3737	cefaclor 250mg/5ml oral suspension
46973	cefaclor 250mg/5ml oral suspension (genus pharmaceuticals ltd)
48025	cefaclor 250mg/5ml oral suspension (ranbaxy (uk) ltd)
9293	cefaclor 250mg/5ml oral suspension sugar free
3180	cefaclor 375mg modified-release tablets
34838	cefaclor 375mg modified-release tablets (a a h pharmaceuticals ltd)
20881	cefaclor 375mg modified-release tablets (ranbaxy (uk) ltd)
4689	cefaclor 500mg capsule (lagap)
2976	cefaclor 500mg capsules
43425	cefaclor 500mg capsules (a a h pharmaceuticals ltd)
55211	cefaclor 500mg capsules (kent pharmaceuticals ltd)
30771	cefaclor 500mg capsules (ranbaxy (uk) ltd)
8051	cefaclor 500mg modified-release tablets
12248	cefalexin 125mg/1.25ml paediatric drops
1693	cefalexin 125mg/5ml oral suspension
29748	cefalexin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
32181	cefalexin 125mg/5ml oral suspension (actavis uk ltd)
53945	cefalexin 125mg/5ml oral suspension (alliance healthcare (distribution) ltd)
39417	cefalexin 125mg/5ml oral suspension (generics (uk) ltd)
32642	cefalexin 125mg/5ml oral suspension (kent pharmaceuticals ltd)
36578	cefalexin 125mg/5ml oral suspension (ranbaxy (uk) ltd)
33329	cefalexin 125mg/5ml oral suspension (teva uk ltd)
6651	cefalexin 125mg/5ml oral suspension sugar free
19144	cefalexin 125mg/5ml oral suspension sugar free (teva uk ltd)
1384	cefalexin 125mg/5ml suspension
18451	cefalexin 1g tablets
33802	cefalexin 250mg capsule (berk pharmaceuticals ltd)
155	cefalexin 250mg capsules
34253	cefalexin 250mg capsules (a a h pharmaceuticals ltd)
19152	cefalexin 250mg capsules (actavis uk ltd)

54864	cefalexin 250mg capsules (alliance healthcare (distribution) ltd)
52283	cefalexin 250mg capsules (arrow generics ltd)
19160	cefalexin 250mg capsules (generics (uk) ltd)
19133	cefalexin 250mg capsules (ivax pharmaceuticals uk ltd)
41736	cefalexin 250mg capsules (kent pharmaceuticals ltd)
52282	cefalexin 250mg capsules (milpharm ltd)
24090	cefalexin 250mg capsules (pliva pharma ltd)
36599	cefalexin 250mg capsules (ranbaxy (uk) ltd)
9690	cefalexin 250mg capsules (teva uk ltd)
40747	cefalexin 250mg chewable tablets
1146	cefalexin 250mg tablets
33334	cefalexin 250mg tablets (a a h pharmaceuticals ltd)
36330	cefalexin 250mg tablets (actavis uk ltd)
47163	cefalexin 250mg tablets (arrow generics ltd)
36701	cefalexin 250mg tablets (generics (uk) ltd)
31825	cefalexin 250mg tablets (ivax pharmaceuticals uk ltd)
9698	cefalexin 250mg tablets (teva uk ltd)
41825	cefalexin 250mg/5ml oral solution (c p pharmaceuticals ltd)
1860	cefalexin 250mg/5ml oral suspension
42008	cefalexin 250mg/5ml oral suspension (a a h pharmaceuticals ltd)
45221	cefalexin 250mg/5ml oral suspension (actavis uk ltd)
29464	cefalexin 250mg/5ml oral suspension (generics (uk) ltd)
41192	cefalexin 250mg/5ml oral suspension (ranbaxy (uk) ltd)
41968	cefalexin 250mg/5ml oral suspension (teva uk ltd)
6671	cefalexin 250mg/5ml oral suspension sugar free
34133	cefalexin 250mg/5ml oral suspension sugar free (teva uk ltd)
1713	cefalexin 250mg/5ml suspension
44755	cefalexin 500mg capsule (berk pharmaceuticals ltd)
400	cefalexin 500mg capsules
32643	cefalexin 500mg capsules (a a h pharmaceuticals ltd)
19138	cefalexin 500mg capsules (actavis uk ltd)
52851	cefalexin 500mg capsules (alliance healthcare (distribution) ltd)
19184	cefalexin 500mg capsules (generics (uk) ltd)
9664	cefalexin 500mg capsules (ivax pharmaceuticals uk ltd)
36569	cefalexin 500mg capsules (kent pharmaceuticals ltd)
54955	cefalexin 500mg capsules (milpharm ltd)
19161	cefalexin 500mg capsules (ranbaxy (uk) ltd)
29281	cefalexin 500mg capsules (teva uk ltd)
865	cefalexin 500mg tablets
29202	cefalexin 500mg tablets (a a h pharmaceuticals ltd)
22321	cefalexin 500mg tablets (generics (uk) ltd)
31827	cefalexin 500mg tablets (ivax pharmaceuticals uk ltd)
9689	cefalexin 500mg tablets (teva uk ltd)

2227	cefalexin 500mg/5ml oral suspension
17150	ceporex 125mg/1.25ml drops (glaxo laboratories ltd)
7560	ceporex 125mg/5ml liquid (galen ltd)
3609	ceporex 125mg/5ml oral solution (galen ltd)
41106	ceporex 125mg/5ml syrup (co-pharma ltd)
12235	ceporex 1g tablet (galen ltd)
192	ceporex 250mg capsule (galen ltd)
40884	ceporex 250mg capsules (co-pharma ltd)
8019	ceporex 250mg tablet (galen ltd)
41049	ceporex 250mg tablets (co-pharma ltd)
8625	ceporex 250mg/5ml liquid (galen ltd)
8008	ceporex 250mg/5ml oral solution (galen ltd)
40945	ceporex 250mg/5ml syrup (co-pharma ltd)
2661	ceporex 500mg capsule (galen ltd)
40915	ceporex 500mg capsules (co-pharma ltd)
8085	ceporex 500mg tablet (galen ltd)
40914	ceporex 500mg tablets (co-pharma ltd)
5859	ceporex 500mg/5ml oral solution (galen ltd)
41230	ceporex 500mg/5ml syrup (co-pharma ltd)
7881	chlortetracycline 250mg capsules
36689	chlortetracycline hcl syr
12016	chymocyclar capsule (rorer pharmaceuticals ltd)
27016	ciprofloxacin
498	ciprofloxacin 100mg tablets
42507	ciprofloxacin 100mg tablets (a a h pharmaceuticals ltd)
48031	ciprofloxacin 100mg tablets (almus pharmaceuticals ltd)
54555	ciprofloxacin 100mg tablets (doncaster pharmaceuticals ltd)
54674	ciprofloxacin 100mg tablets (phoenix healthcare distribution ltd)
39913	ciprofloxacin 100mg tablets (sandoz ltd)
52309	ciprofloxacin 100mg tablets (sigma pharmaceuticals plc)
52945	ciprofloxacin 200mg/100ml solution for infusion vials
56439	ciprofloxacin 200mg/100ml solution for infusion vials (a a h pharmaceuticals ltd)
34647	ciprofloxacin 250mg tablet (neo laboratories ltd)
281	ciprofloxacin 250mg tablets
29343	ciprofloxacin 250mg tablets (a a h pharmaceuticals ltd)
50601	ciprofloxacin 250mg tablets (accord healthcare ltd)
34308	ciprofloxacin 250mg tablets (actavis uk ltd)
51537	ciprofloxacin 250mg tablets (alliance healthcare (distribution) ltd)
54393	ciprofloxacin 250mg tablets (arrow generics ltd)
54701	ciprofloxacin 250mg tablets (bristol laboratories ltd)
56381	ciprofloxacin 250mg tablets (co-pharma ltd)
43814	ciprofloxacin 250mg tablets (dr reddy's laboratories (uk) ltd)
33989	ciprofloxacin 250mg tablets (generics (uk) ltd)

41561	ciprofloxacin 250mg tablets (ivax pharmaceuticals uk ltd)
54302	ciprofloxacin 250mg tablets (medreich plc)
34448	ciprofloxacin 250mg tablets (niche generics ltd)
34694	ciprofloxacin 250mg tablets (pliva pharma ltd)
34559	ciprofloxacin 250mg tablets (sandoz ltd)
34478	ciprofloxacin 250mg tablets (teva uk ltd)
34655	ciprofloxacin 250mg tablets (wockhardt uk ltd)
4091	ciprofloxacin 250mg/5ml oral suspension
10304	ciprofloxacin 2mg/ml infusion
45341	ciprofloxacin 500mg tablet (neo laboratories ltd)
34322	ciprofloxacin 500mg tablet (niche generics ltd)
583	ciprofloxacin 500mg tablets
29458	ciprofloxacin 500mg tablets (a a h pharmaceuticals ltd)
52501	ciprofloxacin 500mg tablets (accord healthcare ltd)
34605	ciprofloxacin 500mg tablets (actavis uk ltd)
49445	ciprofloxacin 500mg tablets (almus pharmaceuticals ltd)
56789	ciprofloxacin 500mg tablets (apc pharmaceuticals & chemicals (europe) ltd)
52616	ciprofloxacin 500mg tablets (arrow generics ltd)
53641	ciprofloxacin 500mg tablets (co-pharma ltd)
50055	ciprofloxacin 500mg tablets (doncaster pharmaceuticals ltd)
53088	ciprofloxacin 500mg tablets (dr reddy's laboratories (uk) ltd)
30707	ciprofloxacin 500mg tablets (generics (uk) ltd)
42174	ciprofloxacin 500mg tablets (ivax pharmaceuticals uk ltd)
55917	ciprofloxacin 500mg tablets (medreich plc)
43557	ciprofloxacin 500mg tablets (pliva pharma ltd)
53878	ciprofloxacin 500mg tablets (ranbaxy (uk) ltd)
43797	ciprofloxacin 500mg tablets (sandoz ltd)
45285	ciprofloxacin 500mg tablets (teva uk ltd)
34494	ciprofloxacin 500mg tablets (wockhardt uk ltd)
34973	ciprofloxacin 750mg tablet (niche generics ltd)
1837	ciprofloxacin 750mg tablets
29472	ciprofloxacin 750mg tablets (a a h pharmaceuticals ltd)
43517	ciprofloxacin 750mg tablets (actavis uk ltd)
52099	ciprofloxacin 750mg tablets (bristol laboratories ltd)
56856	ciprofloxacin 750mg tablets (ranbaxy (uk) ltd)
28544	ciprofloxaxin 400mg/200ml in glucose 5% infusion
9154	ciproxin 100mg tablets (bayer plc)
1202	ciproxin 250mg tablets (bayer plc)
52353	ciproxin 250mg tablets (doncaster pharmaceuticals ltd)
53519	ciproxin 250mg tablets (lexon (uk) ltd)
163	ciproxin 250mg/5ml oral suspension (bayer plc)
728	ciproxin 500mg tablets (bayer plc)
52807	ciproxin 500mg tablets (mawdsley-brooks & company ltd)

52177	ciproxin 500mg tablets (sigma pharmaceuticals plc)
49839	ciproxin 500mg tablets (waymade healthcare plc)
7752	ciproxin 750mg tablets (bayer plc)
45591	clarie xl 500mg tablets (teva uk ltd)
10326	clarithromycin 125mg granules straws
331	clarithromycin 125mg/5ml oral suspension
45795	clarithromycin 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
54903	clarithromycin 125mg/5ml oral suspension (alliance healthcare (distribution) ltd)
51831	clarithromycin 125mg/5ml oral suspension (phoenix healthcare distribution ltd)
41453	clarithromycin 125mg/5ml oral suspension (ranbaxy (uk) ltd)
53168	clarithromycin 125mg/5ml oral suspension (sandoz ltd)
26059	clarithromycin 187.5mg granules straws
765	clarithromycin 250mg granules sachets
17645	clarithromycin 250mg granules straws
537	clarithromycin 250mg tablets
34650	clarithromycin 250mg tablets (a a h pharmaceuticals ltd)
54472	clarithromycin 250mg tablets (accord healthcare ltd)
48163	clarithromycin 250mg tablets (actavis uk ltd)
52158	clarithromycin 250mg tablets (alliance healthcare (distribution) ltd)
54882	clarithromycin 250mg tablets (almus pharmaceuticals ltd)
52719	clarithromycin 250mg tablets (apotex uk ltd)
53086	clarithromycin 250mg tablets (doncaster pharmaceuticals ltd)
34394	clarithromycin 250mg tablets (generics (uk) ltd)
51154	clarithromycin 250mg tablets (kent pharmaceuticals ltd)
53153	clarithromycin 250mg tablets (phoenix healthcare distribution ltd)
53688	clarithromycin 250mg tablets (ranbaxy (uk) ltd)
47582	clarithromycin 250mg tablets (sandoz ltd)
50946	clarithromycin 250mg tablets (sigma pharmaceuticals plc)
54269	clarithromycin 250mg tablets (somex pharma)
34533	clarithromycin 250mg tablets (teva uk ltd)
54897	clarithromycin 250mg tablets (tillomed laboratories ltd)
53144	clarithromycin 250mg tablets (wockhardt uk ltd)
5357	clarithromycin 250mg/5ml oral suspension
54241	clarithromycin 250mg/5ml oral suspension (a a h pharmaceuticals ltd)
55148	clarithromycin 250mg/5ml oral suspension (alliance healthcare (distribution) ltd)
34811	clarithromycin 250mg/5ml oral suspension (ranbaxy (uk) ltd)
53179	clarithromycin 250mg/5ml oral suspension (sandoz ltd)
54208	clarithromycin 250mg/5ml oral suspension (sigma pharmaceuticals plc)
55428	clarithromycin 250mg/5ml oral suspension (waymade healthcare plc)
54529	clarithromycin 500mg modified-release tablet (hillcross pharmaceuticals ltd)
6803	clarithromycin 500mg modified-release tablets
681	clarithromycin 500mg tablets
38163	clarithromycin 500mg tablets (a a h pharmaceuticals ltd)

51426	clarithromycin 500mg tablets (accord healthcare ltd)
48023	clarithromycin 500mg tablets (actavis uk ltd)
49939	clarithromycin 500mg tablets (alliance healthcare (distribution) ltd)
53715	clarithromycin 500mg tablets (almus pharmaceuticals ltd)
53776	clarithromycin 500mg tablets (doncaster pharmaceuticals ltd)
34608	clarithromycin 500mg tablets (generics (uk) ltd)
53703	clarithromycin 500mg tablets (kent pharmaceuticals ltd)
46488	clarithromycin 500mg tablets (ranbaxy (uk) ltd)
40784	clarithromycin 500mg tablets (sandoz ltd)
53109	clarithromycin 500mg tablets (somex pharma)
34974	clarithromycin 500mg tablets (teva uk ltd)
53875	clarithromycin 500mg tablets (tillomed laboratories ltd)
11433	clarithromycin 500mg with lansoprazole 30mg and amoxicillin 500mg triple pack
6497	clarithromycin 500mg with metronidazole 400mg with lansoprazole 30mg triple pack
28349	clarosip 125mg granules for oral suspension straws (grunenthal ltd)
31689	clarosip 187.5mg granules for oral suspension straws (grunenthal ltd)
31690	clarosip 250mg granules for oral suspension straws (grunenthal ltd)
9925	clavulanic acid 125mg with amoxicillin 250mg tablets
13239	clavulanic acid 125mg with amoxicillin 500mg tablets
24006	clavulanic acid 31mg with amoxcillin 125mg/5ml oral suspension
21775	clavulanic acid 31mg with amoxicillin 125mg/5ml sugar free oral suspension
20432	clavulanic acid 57mg with amoxicillin 400mg/5ml sugar free suspension
42485	clavulanic acid 62mg with amoxicillin 250mg/5ml oral suspension
16612	clavulanic acid 62mg with amoxicillin 250mg/5ml sugar free suspension
24093	clavulanic acid with amoxicillin dispersible tablets
12504	clomocycline 170mg capsules
10200	co-amoxiclav 125mg/31mg/5ml oral suspension
54052	co-amoxiclav 125mg/31mg/5ml oral suspension (a a h pharmaceuticals ltd)
54732	co-amoxiclav 125mg/31mg/5ml oral suspension (generics (uk) ltd)
1638	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free
43548	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
54324	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (actavis uk ltd)
54452	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
54808	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)
28874	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
56884	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (phoenix healthcare distribution ltd)
34680	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (ranbaxy (uk) ltd)

34972	co-amoxiclav 125mg/31mg/5ml oral suspension sugar free (sandoz ltd)
829	co-amoxiclav 250mg/125mg dispersible tablets sugar free
545	co-amoxiclav 250mg/125mg tablets
30786	co-amoxiclav 250mg/125mg tablets (a a h pharmaceuticals ltd)
19209	co-amoxiclav 250mg/125mg tablets (actavis uk ltd)
51623	co-amoxiclav 250mg/125mg tablets (alliance healthcare (distribution) ltd)
48147	co-amoxiclav 250mg/125mg tablets (almus pharmaceuticals ltd)
34297	co-amoxiclav 250mg/125mg tablets (generics (uk) ltd)
28871	co-amoxiclav 250mg/125mg tablets (ivax pharmaceuticals uk ltd)
33693	co-amoxiclav 250mg/125mg tablets (kent pharmaceuticals ltd)
50446	co-amoxiclav 250mg/125mg tablets (phoenix healthcare distribution ltd)
30783	co-amoxiclav 250mg/125mg tablets (ranbaxy (uk) ltd)
19414	co-amoxiclav 250mg/125mg tablets (sandoz ltd)
34734	co-amoxiclav 250mg/125mg tablets (teva uk ltd)
55312	co-amoxiclav 250mg/125mg tablets (waymade healthcare plc)
46915	co-amoxiclav 250mg/125mg tablets (zentiva)
7364	co-amoxiclav 250mg/62mg/5ml oral suspension
54708	co-amoxiclav 250mg/62mg/5ml oral suspension (a a h pharmaceuticals ltd)
54780	co-amoxiclav 250mg/62mg/5ml oral suspension (generics (uk) ltd)
524	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free
42227	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
51678	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (almus pharmaceuticals ltd)
37304	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
40320	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (ranbaxy (uk) ltd)
46918	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (sandoz ltd)
34234	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (teva uk ltd)
56578	co-amoxiclav 250mg/62mg/5ml oral suspension sugar free (waymade healthcare plc)
6687	co-amoxiclav 400mg/57mg/5ml oral suspension sugar free
51637	co-amoxiclav 400mg/57mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
641	co-amoxiclav 500mg/125mg tablets
33701	co-amoxiclav 500mg/125mg tablets (a a h pharmaceuticals ltd)
50742	co-amoxiclav 500mg/125mg tablets (actavis uk ltd)
50341	co-amoxiclav 500mg/125mg tablets (alliance healthcare (distribution) ltd)
53609	co-amoxiclav 500mg/125mg tablets (apc pharmaceuticals & chemicals (europe) ltd)
53996	co-amoxiclav 500mg/125mg tablets (aurobindo pharma ltd)
30705	co-amoxiclav 500mg/125mg tablets (generics (uk) ltd)
29356	co-amoxiclav 500mg/125mg tablets (ivax pharmaceuticals uk ltd)
40148	co-amoxiclav 500mg/125mg tablets (kent pharmaceuticals ltd)

49610	co-amoxiclav 500mg/125mg tablets (medreich plc)
54591	co-amoxiclav 500mg/125mg tablets (phoenix healthcare distribution ltd)
34493	co-amoxiclav 500mg/125mg tablets (ranbaxy (uk) ltd)
32910	co-amoxiclav 500mg/125mg tablets (sandoz ltd)
29353	co-amoxiclav 500mg/125mg tablets (teva uk ltd)
44154	co-amoxiclav 500mg/125mg tablets (zentiva)
21860	cyclodox 100mg capsule (berk pharmaceuticals ltd)
21878	demix 100 capsules (ashbourne pharmaceuticals ltd)
21828	demix 50 capsules (ashbourne pharmaceuticals ltd)
2428	distaclor 125mg/5ml liquid (dista products ltd)
25384	distaclor 125mg/5ml oral suspension (flynn pharma ltd)
4576	distaclor 250mg capsule (dista products ltd)
9219	distaclor 250mg/5ml liquid (dista products ltd)
22042	distaclor 250mg/5ml oral suspension (flynn pharma ltd)
7889	distaclor 375mg modified-release tablet (dista products ltd)
319	distaclor 500mg capsule (dista products ltd)
18243	distaclor 500mg capsules (flynn pharma ltd)
3523	distaclor 500mg modified-release tablet (dista products ltd)
20992	distaclor mr 375mg tablets (flynn pharma ltd)
21038	doxatet 100mg tablet (manufacturer unknown)
2884	doxycycline (as hyclate) 100mg dispersible tablets
970	doxycycline (as hyclate) 100mg tablets
12987	doxycycline (as hyclate) 50mg capsules with microgranules
23819	doxycycline (as hyclate) 50mg capsules with microgranules
8724	doxycycline (as hyclate) 50mg/5ml oral solution
41560	doxycycline 100mg capsule (ivax pharmaceuticals uk ltd)
34594	doxycycline 100mg capsule (neo laboratories ltd)
34423	doxycycline 100mg capsule (pliva pharma ltd)
41605	doxycycline 100mg capsule (sandoz ltd)
1046	doxycycline 100mg capsules
24149	doxycycline 100mg capsules (a a h pharmaceuticals ltd)
34300	doxycycline 100mg capsules (actavis uk ltd)
49737	doxycycline 100mg capsules (alliance healthcare (distribution) ltd)
46807	doxycycline 100mg capsules (almus pharmaceuticals ltd)
32066	doxycycline 100mg capsules (generics (uk) ltd)
24126	doxycycline 100mg capsules (ivax pharmaceuticals uk ltd)
33671	doxycycline 100mg capsules (kent pharmaceuticals ltd)
53310	doxycycline 100mg capsules (sigma pharmaceuticals plc)
30739	doxycycline 100mg capsules (teva uk ltd)
55519	doxycycline 100mg capsules (waymade healthcare plc)
6396	doxycycline 100mg dispersible tablets sugar free
26747	doxycycline 100mg tablet (neo laboratories ltd)
40796	doxycycline 40mg modified-release capsules

264	doxycycline 50mg capsules
34175	doxycycline 50mg capsules (a a h pharmaceuticals ltd)
48095	doxycycline 50mg capsules (actavis uk ltd)
53973	doxycycline 50mg capsules (alliance healthcare (distribution) ltd)
34765	doxycycline 50mg capsules (generics (uk) ltd)
40391	doxycycline 50mg capsules (ivax pharmaceuticals uk ltd)
32419	doxycycline 50mg capsules (teva uk ltd)
23405	doxylar 100mg capsules (sandoz ltd)
23432	doxylar 50mg capsules (sandoz ltd)
17226	economycin 250mg capsule (ddsa pharmaceuticals ltd)
26111	economycin 250mg tablet (ddsa pharmaceuticals ltd)
40980	efracea 40mg modified-release capsules (galderma (uk) ltd)
4489	erycen 250mg tablet (berk pharmaceuticals ltd)
23017	erycen 500mg tablet (berk pharmaceuticals ltd)
318	erymax 250mg capsule (elan pharma)
10190	erymax 250mg gastro-resistant capsules (teva uk ltd)
14511	erymax sprinkle 125mg capsule (elan pharma)
9434	erymin 250mg/5ml oral suspension (elan pharma)
48017	erythoden 125mg/5ml liquid (stevenden healthcare)
41389	erythoden 250mg/5ml liquid (stevenden healthcare)
39616	erythrocin 250 tablets (amdipharm plc)
480	erythrocin 250mg tablet (abbott laboratories ltd)
1072	erythrocin 500 500mg tablet (abbott laboratories ltd)
39613	erythrocin 500 tablets (amdipharm plc)
53449	erythrocin 500 tablets (lexon (uk) ltd)
51984	erythrocin 500 tablets (mawdsley-brooks & company ltd)
53004	erythrocin 500 tablets (necessity supplies ltd)
50693	erythrocin 500 tablets (sigma pharmaceuticals plc)
50223	erythrocin 500 tablets (stephar (u.k.) ltd)
27768	erythrolar 250mg tablet (lagap)
50205	erythrolar 250mg tablets (ennogen pharma ltd)
4153	erythrolar 250mg/5ml liquid (lagap)
23954	erythrolar 500mg tablet (lagap)
49301	erythrolar 500mg tablets (ennogen pharma ltd)
3209	erythromid 250mg tablet (abbott laboratories ltd)
9148	erythromid ds 500mg tablet (abbott laboratories ltd)
1376	erythromycin 100 mg syr
7792	erythromycin 12 mg syr
14429	erythromycin 125mg sprinkle capsules
34231	erythromycin 125mg/5ml liquid (berk pharmaceuticals ltd)
33248	erythromycin 125mg/5ml liquid (ivax pharmaceuticals uk ltd)
397	erythromycin 125mg/5ml oral suspension
9656	erythromycin 2% gel

1969	erythromycin 250 mg mix
29154	erythromycin 250mg capsule (actavis uk ltd)
103	erythromycin 250mg gastro-resistant capsules
33686	erythromycin 250mg gastro-resistant capsules (a a h pharmaceuticals ltd)
50580	erythromycin 250mg gastro-resistant capsules (actavis uk ltd)
50694	erythromycin 250mg gastro-resistant capsules (alliance healthcare (distribution) ltd)
55133	erythromycin 250mg gastro-resistant capsules (kent pharmaceuticals ltd)
49952	erythromycin 250mg gastro-resistant capsules (phoenix healthcare distribution ltd)
34512	erythromycin 250mg gastro-resistant capsules (teva uk ltd)
55397	erythromycin 250mg gastro-resistant capsules (waymade healthcare plc)
34837	erythromycin 250mg gastro-resistant tablet (co-pharma ltd)
63	erythromycin 250mg gastro-resistant tablets
24127	erythromycin 250mg gastro-resistant tablets (a a h pharmaceuticals ltd)
33703	erythromycin 250mg gastro-resistant tablets (abbott laboratories ltd)
29344	erythromycin 250mg gastro-resistant tablets (actavis uk ltd)
52906	erythromycin 250mg gastro-resistant tablets (alliance healthcare (distribution) ltd)
42661	erythromycin 250mg gastro-resistant tablets (almus pharmaceuticals ltd)
52952	erythromycin 250mg gastro-resistant tablets (co-pharma ltd)
42296	erythromycin 250mg gastro-resistant tablets (dr reddy's laboratories (uk) ltd)
34334	erythromycin 250mg gastro-resistant tablets (generics (uk) ltd)
24129	erythromycin 250mg gastro-resistant tablets (ivax pharmaceuticals uk ltd)
53986	erythromycin 250mg gastro-resistant tablets (medreich plc)
55483	erythromycin 250mg gastro-resistant tablets (milpharm ltd)
52428	erythromycin 250mg gastro-resistant tablets (phoenix healthcare distribution ltd)
31530	erythromycin 250mg gastro-resistant tablets (ranbaxy (uk) ltd)
34479	erythromycin 250mg gastro-resistant tablets (sovereign medical ltd)
33685	erythromycin 250mg gastro-resistant tablets (teva uk ltd)
34873	erythromycin 250mg tablet (berk pharmaceuticals ltd)
34189	erythromycin 250mg tablet (c p pharmaceuticals ltd)
553	erythromycin 250mg.5ml oral suspension
47242	erythromycin 250mg/5ml liquid (c p pharmaceuticals ltd)
41584	erythromycin 250mg/5ml liquid (ivax pharmaceuticals uk ltd)
3408	erythromycin 500 mg cap
401	erythromycin 500mg ec gastro-resistant tablets
34869	erythromycin 500mg tablet (c p pharmaceuticals ltd)
41604	erythromycin 500mg tablet (hillcross pharmaceuticals ltd)
26365	erythromycin 500mg tablet (ivax pharmaceuticals uk ltd)
55300	erythromycin 500mg tablet (teva uk ltd)
47676	erythromycin 500mg/5ml liquid (c p pharmaceuticals ltd)
2326	erythromycin 500mg/5ml oral suspension
37796	erythromycin estolate 125mg/5ml suspension
9903	erythromycin estolate 250mg capsules

40073	erythromycin estolate 250mg/5ml suspension
37694	erythromycin estolate 500mg tablets
2429	erythromycin ethyl succinate 125mg/5ml oral suspension
13167	erythromycin ethyl succinate 125mg/5ml oral suspension (a a h pharmaceuticals ltd)
49978	erythromycin ethyl succinate 125mg/5ml oral suspension (focus pharmaceuticals ltd)
50948	erythromycin ethyl succinate 125mg/5ml oral suspension (phoenix healthcare distribution ltd)
47126	erythromycin ethyl succinate 125mg/5ml oral suspension (pinewood healthcare)
34779	erythromycin ethyl succinate 125mg/5ml oral suspension (sandoz ltd)
4672	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free
33697	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
42659	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (abbott laboratories ltd)
55589	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
48101	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (focus pharmaceuticals ltd)
33695	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (generics (uk) ltd)
34795	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
45870	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (pinewood healthcare)
33705	erythromycin ethyl succinate 125mg/5ml oral suspension sugar free (teva uk ltd)
2376	erythromycin ethyl succinate 250mg/5ml oral suspension
13120	erythromycin ethyl succinate 250mg/5ml oral suspension (a a h pharmaceuticals ltd)
32902	erythromycin ethyl succinate 250mg/5ml oral suspension (kent pharmaceuticals ltd)
46696	erythromycin ethyl succinate 250mg/5ml oral suspension (sandoz ltd)
2225	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free
32898	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (a a h pharmaceuticals ltd)
46154	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (abbott laboratories ltd)
52860	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (alliance healthcare (distribution) ltd)
33694	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (generics (uk) ltd)

30177	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
34853	erythromycin ethyl succinate 250mg/5ml oral suspension sugar free (teva uk ltd)
733	erythromycin ethyl succinate 500mg tablets
2226	erythromycin ethyl succinate 500mg/5ml oral suspension
30980	erythromycin ethyl succinate 500mg/5ml oral suspension (kent pharmaceuticals ltd)
14171	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free
31514	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (abbott laboratories ltd)
25595	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (ivax pharmaceuticals uk ltd)
27203	erythromycin ethyl succinate 500mg/5ml oral suspension sugar free (teva uk ltd)
25751	erythromycin ethylsuccinate (coated) 250mg/5ml oral suspension sugar free
30234	erythromycin ethylsuccinate 125mg sachets
12330	erythromycin ethylsuccinate 1g sachets
13635	erythromycin ethylsuccinate 250mg sachets
15713	erythromycin ethylsuccinate 500mg sachets
1037	erythromycin ethylsuccinate sf 125 mg/5ml sus
3907	erythromycin sf sach 250 mg
438	erythromycin stearate 250mg tablets
2350	erythromycin stearate 500mg tablets
3572	erythroped 250mg powder (abbott laboratories ltd)
16747	erythroped 250mg sachets (abbott laboratories ltd)
105	erythroped 250mg/5ml liquid (abbott laboratories ltd)
532	erythroped 250mg/5ml oral suspension (abbott laboratories ltd)
4596	erythroped a 1g sachets (abbott laboratories ltd)
327	erythroped a 500mg tablet (abbott laboratories ltd)
39632	erythroped a 500mg tablets (amdipharm plc)
54098	erythroped a 500mg tablets (lexon (uk) ltd)
56203	erythroped a 500mg tablets (sigma pharmaceuticals plc)
4372	erythroped forte 500mg sachets (abbott laboratories ltd)
993	erythroped forte 500mg/5ml liquid (abbott laboratories ltd)
4610	erythroped forte 500mg/5ml oral suspension (abbott laboratories ltd)
39642	erythroped forte sf 500mg/5ml oral suspension (amdipharm plc)
3042	erythroped pi 125mg sachets (abbott laboratories ltd)
997	erythroped pi 125mg/5ml liquid (abbott laboratories ltd)
825	erythroped pi 125mg/5ml oral suspension (abbott laboratories ltd)
39623	erythroped pi sf 125mg/5ml oral suspension (amdipharm plc)
39669	erythroped sf 250mg/5ml oral suspension (amdipharm plc)
18930	flemoxin 375mg soluble tablet (paines & byrne ltd)
24396	flemoxin 750mg soluble tablet (paines & byrne ltd)
14386	galenamox 125mg/5ml oral suspension (galen ltd)

14371	galenamox 250mg capsules (galen ltd)
14407	galenamox 250mg/5ml oral suspension (galen ltd)
14396	galenamox 500mg capsules (galen ltd)
18682	ilosone 125mg/5ml liquid (dista products ltd)
17207	ilosone 250mg capsule (dista products ltd)
19330	ilosone 250mg/5ml liquid (dista products ltd)
18643	ilosone 500mg tablet (dista products ltd)
23244	ilotycin 250mg tablet (eli lilly and company ltd)
12541	imperacin 250mg tablet (astrazeneca uk ltd)
7485	keflex 125mg/5ml liquid (eli lilly and company ltd)
27072	keflex 125mg/5ml oral suspension (flynn pharma ltd)
7430	keflex 250mg capsule (eli lilly and company ltd)
11989	keflex 250mg capsules (flynn pharma ltd)
9157	keflex 250mg tablet (eli lilly and company ltd)
830	keflex 250mg tablets (flynn pharma ltd)
10455	keflex 250mg/5ml liquid (eli lilly and company ltd)
28722	keflex 250mg/5ml oral suspension (flynn pharma ltd)
12276	keflex 500mg capsule (eli lilly and company ltd)
24618	keflex 500mg capsules (flynn pharma ltd)
9603	keflex 500mg tablet (eli lilly and company ltd)
31110	keflex 500mg tablets (flynn pharma ltd)
26233	keftid 125mg/5ml oral suspension (co-pharma ltd)
26207	keftid 250mg capsules (co-pharma ltd)
41853	keftid 250mg/5ml oral suspension (co-pharma ltd)
26236	keftid 500mg capsules (co-pharma ltd)
33304	kerymax 250mg gastro-resistant capsules (kent pharmaceuticals ltd)
26989	kiflone 125mg/5ml oral solution (berk pharmaceuticals ltd)
21835	kiflone 250mg capsule (berk pharmaceuticals ltd)
21979	kiflone 250mg/5ml oral solution (berk pharmaceuticals ltd)
27017	kiflone 500mg capsule (berk pharmaceuticals ltd)
26992	kiflone 500mg tablet (berk pharmaceuticals ltd)
3736	klaricid 125mg/5ml oral suspension (abbott laboratories ltd)
2719	klaricid 250mg tablets (abbott laboratories ltd)
52411	klaricid 250mg tablets (necessity supplies ltd)
9583	klaricid 250mg/5ml oral suspension (abbott laboratories ltd)
6623	klaricid 500 tablets (abbott laboratories ltd)
14816	klaricid adult 250mg granules sachets (abbott laboratories ltd)
38997	klaricid paediatric 125mg/5ml oral suspension (abbott laboratories ltd)
39010	klaricid paediatric 250mg/5ml oral suspension (abbott laboratories ltd)
6121	klaricid xl 500mg tablets (abbott laboratories ltd)
15290	lansoprazole with amoxicillin and clarithromycin 30mg + 500mg + 500mg triple pack
7439	ledermycin 150mg capsule (wyeth pharmaceuticals)
16613	ledermycin 150mg capsules (mercury pharma group ltd)

22076	ledermycin 300mg tablet (wyeth pharmaceuticals)
6295	levofloxacin 250mg tablets
55708	levofloxacin 250mg tablets (actavis uk ltd)
56012	levofloxacin 250mg tablets (dr reddy's laboratories (uk) ltd)
5238	levofloxacin 500mg tablets
53673	levofloxacin 500mg/100ml infusion bags
19001	megaclor 170mg capsule (pharmax ltd)
6306	moxifloxacin 400mg tablets
17222	mysteclin oral solution (bristol-myers squibb pharmaceuticals ltd)
15071	nordox 100mg capsule (sankyo pharma uk ltd)
8393	novobiocin/tetracycline 125 mg cap
25752	nystatin with tetracycline hc capsule
9361	oxymycin 250mg tablets (dr reddy's laboratories (uk) ltd)
2458	oxytetracycline 100 mg tab
9034	oxytetracycline 125mg/5ml syrup
8285	oxytetracycline 250 mg syr
132	oxytetracycline 250mg capsules
34888	oxytetracycline 250mg tablet (c p pharmaceuticals ltd)
77	oxytetracycline 250mg tablets
34044	oxytetracycline 250mg tablets (a a h pharmaceuticals ltd)
34040	oxytetracycline 250mg tablets (actavis uk ltd)
34336	oxytetracycline 250mg tablets (ivax pharmaceuticals uk ltd)
40483	oxytetracycline 250mg tablets (sandoz ltd)
34141	oxytetracycline 250mg tablets (teva uk ltd)
28291	oxytetracycline 3%/hydrocortisone 1%
10542	oxytetracycline hcl/hydrocortisone .5 % ear
17703	oxytetramix 250 tablets (ashbourne pharmaceuticals ltd)
30520	primacine 125mg/5ml liquid (pinewood healthcare)
39118	primacine 250mg/5ml liquid (pinewood healthcare)
27504	primacine 500mg/5ml liquid (pinewood healthcare)
27681	ranclav 125mg/31mg/5ml sf oral suspension (ranbaxy (uk) ltd)
25370	ranclav 375mg tablets (ranbaxy (uk) ltd)
22017	respillin 125mg/5ml oral solution (opd pharm)
22015	respillin 125mg/5ml oral solution (opd pharm)
24203	respillin 250mg capsule (opd pharm)
24200	respillin 500mg capsule (opd pharm)
31428	retcin 250mg tablet (ddsa pharmaceuticals ltd)
21808	rommix 125mg/5ml oral suspension sugar free (ashbourne pharmaceuticals ltd)
11611	rommix 250 ec tablets (ashbourne pharmaceuticals ltd)
25278	rommix 500mg tablet (ashbourne pharmaceuticals ltd)
24097	rondomycin 150mg capsule (pfizer ltd)
18109	sebomin mr 100mg capsules (actavis uk ltd)
37440	sebren mr 100mg capsules (teva uk ltd)

19693	sustamycin 250mg capsule (boehringer mannheim uk ltd)
17693	tavanic 250mg tablets (sanofi)
6206	tavanic 500mg tablets (sanofi)
27254	tenkorex 500mg capsule (opd pharm)
7455	terramycin 250mg capsule (pfizer ltd)
17467	terramycin 250mg tablets (pfizer ltd)
9014	tetrabid-organon 250mg capsule (organon laboratories ltd)
8219	tetrachel 250mg capsule (berk pharmaceuticals ltd)
3816	tetrachel 250mg tablet (berk pharmaceuticals ltd)
25017	tetracycline
56044	tetracycline 125mg/5ml oral solution
8284	tetracycline 125mg/5ml syrup
21804	tetracycline 125mg/5ml syrup
41547	tetracycline 250mg capsule (berk pharmaceuticals ltd)
121	tetracycline 250mg capsules
34011	tetracycline 250mg capsules
56181	tetracycline 250mg tablet (celltech pharma europe ltd)
45271	tetracycline 250mg tablet (numark management ltd)
386	tetracycline 250mg tablets
43538	tetracycline 250mg tablets (a a h pharmaceuticals ltd)
41636	tetracycline 250mg tablets (actavis uk ltd)
54214	tetracycline 250mg tablets (alliance healthcare (distribution) ltd)
53117	tetracycline 250mg tablets (almus pharmaceuticals ltd)
48100	tetracycline 250mg tablets (teva uk ltd)
2922	tetracycline 250mg with nystatin 250000units tablets
2636	tetracycline 500 mg cap
3528	tetracycline 500 mg tab
21654	tetracycline ear/eye
21629	tetracycline eye
31425	tetracycline hcl/pancreatic concentrate cap
28736	tetracycline hydrochloride/amphotericin syr
15355	tetracycline with chlortetracycline & demeclocycline tablets
25071	tetracycline with nystatin capsules
4951	tetralysal 300 capsules (galderma (uk) ltd)
20054	tetralysal 408mg capsule (pharmacia ltd)
25280	tiloryth 250mg gastro-resistant capsules (tillomed laboratories ltd)
268	vibramycin 100mg capsules (pfizer ltd)
3152	vibramycin 100mg dispersible tablet (pfizer ltd)
10454	vibramycin 50mg/5ml oral solution (pfizer ltd)
9267	vibramycin acne pack 50mg capsules (pfizer ltd)
56198	vibramycin-d 100mg dispersible tablets (mawdsley-brooks & company ltd)
14904	vibramycin-d 100mg dispersible tablets (pfizer ltd)
52967	vibramycin-d 100mg dispersible tablets (stephar (u.k.) ltd)

53135 vibramycin-d 100mg dispersible tablets (waymade healthcare plc)
26392 vibrox 100mg capsules (kent pharmaceuticals ltd)
21829 zoxycil 250mg capsule (trinity pharmaceuticals ltd)
26262 zoxycil 500mg capsule (trinity pharmaceuticals ltd)

b. COPD exacerbation antibiotic prodcodes

95 prednisolone 5mg tablets
1063 prednesol 5mg tablet (sovereign medical ltd)
2044 prednisone 2.5 mg tab
2368 prednisolone 2.5mg tablet
2390 prednisolone e/c 1 mg tab
2799 prednisolone 10 mg tab
2949 prednisone 5mg tablets
3059 prednisolone 50 mg tab
3345 sintisone tablet (pharmacia ltd)
3557 prednisone 1mg tablets
7584 prednisolone 4 mg tab
7710 prednisolone 15 mg tab
7934 prednisone 30 mg tab
9727 prednisolone 50mg tablets
13522 prednisolone 2 mg tab
13615 prednisone 10 mg tab
16724 prednisone 50 mg tab
20095 precortisyl forte 25mg tablet (aventis pharma)
20670 prednisolone e/c
21833 decortisyl 5mg tablet (roussel laboratories ltd)
23512 precortisyl 5mg tablet (hoechst marion roussel)
24716 prednisolone e/c
25272 precortisyl 1mg tablet (hoechst marion roussel)
27889 prednisolone
27959 prednisolone
27962 deltastab 1mg tablet (waymade healthcare plc)
28376 prednisolone 2.5mg gastro-resistant tablet (biorex laboratories ltd)
28859 deltastab 5mg tablet (waymade healthcare plc)
30390 deltastab 2 mg tab
30971 decortisyl 25 mg tab
31327 prednisolone steaglate 6.65mg tablet
33691 prednisolone 5mg gastro-resistant tablet (biorex laboratories ltd)
33988 prednisolone 5mg tablet (co-pharma ltd)
33990 prednisolone 5mg tablet (ivax pharmaceuticals uk ltd)

34109	prednisolone 5 mg gastro-resistant tablet
34631	prednisolone 1mg tablet (co-pharma ltd)
34914	prednisolone 1mg tablet (celltech pharma europe ltd)
38407	prednisolone 20mg tablet
43544	prednisone 5mg tablet (knoll ltd)
44380	prednisone 1mg modified-release tablets
44723	prednisone 5mg modified-release tablets
44802	lodotra 5mg modified-release tablets (napp pharmaceuticals ltd)
44803	lodotra 2mg modified-release tablets (napp pharmaceuticals ltd)
45302	prednisolone 5mg tablet (biorex laboratories ltd)
46711	prednisone 2mg modified-release tablets
47142	prednisolone 5mg soluble tablet (amdipharm plc)
54432	lodotra 1mg modified-release tablets (napp pharmaceuticals ltd)

c. COPD exacerbation symptom medcodes

Cough codes

92	Cough
292	Chesty cough
1025	Bronchial cough
1160	[D]Cough
1234	Productive cough NOS
1273	C/O - cough
3068	Night cough present
3645	Coughing up phlegm
4070	Morning cough
4836	Nocturnal cough / wheeze
4931	Dry cough
7706	Productive cough -clear sputum
7707	Cough symptom NOS
7708	Productive cough-yellow sputum
7773	Productive cough -green sputum
8239	[D]Cough with haemorrhage
18907	Cough with fever
22318	Difficulty in coughing up sputum
29318	Evening cough
60903	Cough aggravates symptom
100515	Cough swab

Breathlessness codes

735	[D]Breathlessness
741	[D]Shortness of breath
1429	Breathlessness
2563	[D]Respiratory distress
2575	Short of breath on exertion
2737	Respiratory distress syndrome
2931	Difficulty breathing
3092	[D]Dyspnoea
4822	Shortness of breath
5175	Breathlessness symptom
5349	Shortness of breath symptom
5896	Dyspnoea - symptom
6326	Breathless - moderate exertion
6434	Paroxysmal nocturnal dyspnoea
7000	O/E - dyspnoea
7534	O/E - respiratory distress
7683	Breathless - lying flat
7932	Breathless - mild exertion
9297	[D]Respiratory insufficiency
18116	Nocturnal dyspnoea
21801	Breathlessness NOS
22094	Short of breath dressing/undressing
24889	Breathless - strenuous exertion
31143	Breathless - at rest
40813	Unable to complete a sentence in one breath
53771	Dyspnoea on exertion

Sputum codes

292	Chesty cough
1025	Bronchial cough
1234	Productive cough NOS
1251	[D]Abnormal sputum
3645	Coughing up phlegm
3727	Sputum sent for C/S
7706	Productive cough -clear sputum
7708	Productive cough-yellow sputum
7773	Productive cough -green sputum

8287	Sputum sample obtained
8760	[D]Positive culture findings in sputum
9807	Sputum - symptom
11072	Acute purulent bronchitis
14271	Sputum culture
14272	Sputum microscopy
14273	Sputum appearance
14804	Sputum appears infected
15430	[D]Sputum abnormal - colour
16026	Sputum examination: abnormal
18964	Sputum clearance
20086	[D]Sputum abnormal - amount
22318	Difficulty in coughing up sputum
23252	Sputum microscopy NOS
23582	[D]Abnormal sputum NOS
24181	Sputum: mucopurulent
30754	Yellow sputum
30904	Sputum sent for examination
36515	[D]Abnormal sputum - tenacious
36880	Green sputum
43270	Sputum evidence of infection
44214	[D]Sputum abnormal - odour
49144	Sputum: pus cells present
49694	Sputum: organism on gram stain
54177	Sputum: excessive - mucoid
100484	Volume of sputum
100524	Moderate sputum
100629	White sputum
100647	Copious sputum
100931	Brown sputum
101782	Profuse sputum
103209	Grey sputum

d. COPD exacerbation medcodes

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

e. LRTI diagnostic medcode

68	Chest infection
312	Acute bronchitis
556	Influenza
1019	Acute bronchiolitis
1382	Acute viral bronchitis unspecified
2157	Flu like illness
2476	Chest cold
2581	Chest infection NOS
3358	Lower resp tract infection
5947	Influenza like illness
5978	Acute wheezy bronchitis
6124	Acute lower respiratory tract infection
6181	Obliterating fibrous bronchiolitis
8980	Influenza-like symptoms
9043	Acute pneumococcal bronchitis
11072	Acute purulent bronchitis
14791	Influenza with gastrointestinal tract involvement
15774	Influenza with laryngitis
16388	Influenza NOS
17185	Acute bronchiolitis with bronchospasm
17359	Chest infection - unspecified bronchitis
17917	Acute bronchiolitis NOS
18451	Acute bronchiolitis due to respiratory syncytial virus
20198	Acute bronchitis NOS
21061	Chronic obstruct pulmonary dis with acute lower resp infectn
21145	Acute croupous bronchitis
21492	Acute haemophilus influenzae bronchitis
23488	Influenza with respiratory manifestations NOS
24316	Chest infection with infectious disease EC
24800	Acute bacterial bronchitis unspecified
26125	Bronchiolitis obliterans
29273	Acute bronchitis due to parainfluenza virus
29617	Influenza with pharyngitis
29669	Acute bronchitis and bronchiolitis
31363	Influenza with other manifestations NOS
37447	Acute lower respiratory tract infection
41137	Acute bronchitis or bronchiolitis NOS
41589	Acute obliterating bronchiolitis
43362	Acute streptococcal bronchitis
43625	Influenza with other respiratory manifestation

46157	Influenza with encephalopathy
47472	Influenza with other manifestations
48593	Acute bronchitis due to respiratory syncytial virus
49794	Acute neisseria catarrhalis bronchitis
54533	Acute capillary bronchiolitis
63697	Avian influenza virus nucleic acid detection
64890	Acute bronchitis due to rhinovirus
65916	Acute bronchitis due to echovirus
66228	Acute bronchiolitis due to other specified organisms
66397	[X]Other acute lower respiratory infections
69192	Acute exudative bronchiolitis
71370	Acute pseudomembranous bronchitis
73100	[X]Acute bronchitis due to other specified organisms
91123	Parainfluenza type 3 nucleic acid detection
93153	Acute bronchitis due to coxsackievirus
94130	Parainfluenza type 1 nucleic acid detection
94858	Parainfluenza type 2 nucleic acid detection
94930	Avian influenza
96017	Influenza B virus detected
96018	Influenza H3 virus detected
96019	Influenza H1 virus detected
96286	Human parainfluenza virus detected
97062	Influenza A virus, other or untyped strain detected
97279	[X]Influenza+other manifestations, virus not identified
97605	[X]Influenza+oth respiratory manifestatns,virus not identifd
97936	[X]Influenza+other manifestations,influenza virus identified
98102	Influenza A (H1N1) swine flu
98103	Possible influenza A virus H1N1 subtype
98115	Suspected swine influenza
98125	Suspected influenza A virus subtype H1N1 infection
98129	Influenza due to Influenza A virus subtype H1N1
98143	Influenza A virus H1N1 subtype detected
98156	Influenza H5 virus detected
98257	[X]Flu+oth respiratory manifestations,'flu virus identified
99214	[X]Acute bronchiolitis due to other specified organisms
101775	Acute membranous bronchitis
102918	Influenza H2 virus detected

Appendix 7: Asthma medcodes

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

16070 asthma nos
16667 asthma control step 2
16785 asthma control step 1
18223 step down change in asthma management plan
18224 asthma control step 3
18323 intrinsic asthma with asthma attack
19167 asthma monitoring by nurse
19519 asthma treatment compliance unsatisfactory
19520 asthma treatment compliance satisfactory
20860 asthma control step 5
20886 asthma control step 4
21232 allergic asthma nec
22752 occupational asthma
24479 emergency asthma admission since last appointment
24506 further asthma - drug prevent.
24884 asthma causes daytime symptoms 1 to 2 times per week
25181 asthma restricts exercise
25791 asthma clinical management plan
26501 asthma never causes daytime symptoms
26503 asthma causes daytime symptoms most days
26504 asthma never restricts exercise
26506 asthma severely restricts exercise
26861 asthma sometimes restricts exercise
27926 extrinsic asthma with status asthmaticus
29325 intrinsic asthma without status asthmaticus
30458 asthma monitoring by doctor
30815 asthma causing night waking
31167 asthma night-time symptoms
31225 asthma causes daytime symptoms 1 to 2 times per month
38143 asthma never disturbs sleep
38144 asthma limits walking up hills or stairs
38145 asthma limits walking on the flat
38146 asthma disturbs sleep weekly
39478 wood asthma
39570 asthma causes night symptoms 1 to 2 times per month
40823 brittle asthma
41017 aspirin induced asthma
41020 absent from work or school due to asthma
42824 asthma daytime symptoms
45073 intrinsic asthma nos
45782 extrinsic asthma nos
46529 attends asthma monitoring
47337 asthma accident and emergency attendance since last visit
47684 detergent asthma

58196 intrinsic asthma with status asthmaticus
73522 work aggravated asthma
93353 sequoiosis (red-cedar asthma)
93736 royal college of physicians asthma assessment
98185 asthma control test
99793 patient has a written asthma personal action plan
100107 health education - asthma self management
100397 asthma control questionnaire
100509 under care of asthma specialist nurse
100740 health education - structured asthma discussion
102170 asthma review using roy colleg of physicians three questions
102209 mini asthma quality of life questionnaire
102301 asthma trigger - seasonal
102341 asthma trigger - pollen
102395 asthma causes symptoms most nights
102400 asthma causes night time symptoms 1 to 2 times per week
102449 asthma trigger - respiratory infection
102713 asthma limits activities 1 to 2 times per month
102871 asthma trigger - exercise
102888 asthma limits activities 1 to 2 times per week
102952 asthma trigger - warm air
103318 health education - structured patient focused asthma discuss
103321 asthma trigger - animals
103612 asthma never causes night symptoms
103631 royal college physician asthma assessment 3 question score
103813 asthma trigger - cold air
103944 asthma trigger - airborne dust
103945 asthma trigger - damp
103952 asthma trigger - emotion
103955 asthma trigger - tobacco smoke
103998 asthma limits activities most days
105420 asthma self-management plan review
105674 asthma self-management plan agreed
106805 chronic asthma with fixed airflow obstruction
107167 number days absent from school due to asthma in past 6 month

Non-specific asthma codes

719 h/o: asthma
1208 childhood asthma
5138 patient in asthma study
5515 seen in asthma clinic
7229 asthma prophylactic medication used
11022 asthma trigger

11387 refuses asthma monitoring
11673 excepted from asthma quality indicators: patient unsuitable
11695 excepted from asthma quality indicators: informed dissent
13066 asthma - currently dormant
13173 asthma not disturbing sleep
13174 asthma not limiting activities
16655 asthma monitoring admin.
18141 asthma monitoring due
18692 exception reporting: asthma quality indicators
18763 referral to asthma clinic
19539 asthma monitoring check done
20422 asthma clinic administration
25705 asthma monitor 3rd letter
25706 asthma monitor 2nd letter
25707 asthma monitor 1st letter
25796 mixed asthma
26496 health education - asthma
29645 asthma control step 0
30308 dna - did not attend asthma clinic
30382 asthma monitoring admin.nos
31135 asthma monitor phone invite
35927 asthma leaflet given
37943 asthma monitor verbal invite
41554 asthma monitor offer default
43770 asthma society member
92109 asthma outreach clinic

Appendix 8: Co-morbidity medcodes

2860	Viral (serum) hepatitis B
32164	Acute hep B with delta-agent (coinfectn) without hep coma
30926	Other specified viral hepatitis without coma
2834	Viral hepatitis C without mention of hepatic coma
32657	Acute delta-(super)infection of hepatitis B carrier
26367	Chronic viral hepatitis
24813	Chronic viral hepatitis B with delta-agent
30586	Chronic viral hepatitis C
20137	Unspecified viral hepatitis
2413	Hepatitis C
782	Neoplasms
2755	Cancers
34075	Malig neop of respiratory tract and intrathoracic organs
45307	Carcinoma of respiratory tract and intrathoracic organs
26652	Malig neop nasal cavities, middle ear and accessory sinuses
23389	Malignant neoplasm of nasal cavities
62182	Malignant neoplasm of vestibule of nose
42856	Malignant neoplasm of nasal cavities NOS
32174	Malignant neoplasm of maxillary sinus
319	Malignant neoplasm of larynx
318	Malignant neoplasm of glottis
26165	Malignant neoplasm of supraglottis
43111	Malignant neoplasm of laryngeal cartilage
63460	Malignant neoplasm of arytenoid cartilage
47862	Malignant neoplasm of thyroid cartilage
55374	Malignant neoplasm of epiglottis NOS
26813	Malignant neoplasm of larynx, other specified site
9237	Malignant neoplasm of larynx NOS
13243	Malignant neoplasm of trachea, bronchus and lung
15221	Malignant neoplasm of trachea
37810	Malignant neoplasm of trachea NOS
12870	Malignant neoplasm of main bronchus
17391	Malignant neoplasm of carina of bronchus
33444	Malignant neoplasm of hilus of lung
21698	Malignant neoplasm of main bronchus NOS
10358	Malignant neoplasm of upper lobe, bronchus or lung
20170	Pancoast's syndrome
31700	Malignant neoplasm of upper lobe bronchus
25886	Malignant neoplasm of upper lobe of lung
44169	Malignant neoplasm of upper lobe, bronchus or lung NOS

31268	Malignant neoplasm of middle lobe, bronchus or lung
41523	Malignant neoplasm of middle lobe bronchus
39923	Malignant neoplasm of middle lobe of lung
31188	Malignant neoplasm of lower lobe, bronchus or lung
18678	Malignant neoplasm of lower lobe bronchus
12582	Malignant neoplasm of lower lobe of lung
42566	Malignant neoplasm of lower lobe, bronchus or lung NOS
7484	Mesothelioma
38961	Malignant neoplasm of other sites of bronchus or lung
3903	Malignant neoplasm of bronchus or lung NOS
2587	Lung cancer
31573	Malignant neoplasm of pleura
9600	Mesothelioma of pleura
34742	Malignant neoplasm of pleura NOS
27483	Malignant neoplasm of thymus
63430	Malignant neoplasm of endocardium
27715	Malignant neoplasm of anterior mediastinum
9618	Secondary and unspecified malignant neoplasm of lymph nodes
7830	Lymph node metastases
49214	Secondary and unspec malig neop lymph nodes head/face/neck
33395	Secondary and unspec malig neop superficial cervical LN
39433	Secondary and unspec malig neop submandibular lymph nodes
67129	Secondary unspec malig neop lymph nodes head/face/neck NOS
67797	Secondary and unspec malig neop superfic tracheobronchial LN
52190	Secondary and unspec malig neop pulmonary lymph nodes
44931	Secondary and unspec malig neop intra-abdominal LN NOS
37540	Secondary and unspec malig neop axillary lymph nodes
50904	Secondary and unspec malig neop infraclavicular lymph nodes
35053	Secondary malig neop of respiratory and digestive systems
6471	Metastases of respiratory and/or digestive systems
4137	Secondary malignant neoplasm of lung
28727	Secondary malignant neoplasm of colon
62909	Secondary malignant neoplasm of rectum
8154	Malignant ascites
15103	Secondary malignant neoplasm of liver
4403	Liver metastases
5842	Secondary malignant neoplasm of other specified sites
27651	Secondary carcinoma of other specified sites
1952	Secondary malignant neoplasm of kidney
22146	Secondary malignant neoplasm of bladder
19945	Secondary malignant neoplasm of skin
35999	Secondary malignant neoplasm of skin of neck
41144	Secondary malignant neoplasm of skin of trunk

5198	Secondary malignant neoplasm of brain
5199	Cerebral metastasis
54120	Secondary malignant neoplasm of other part of nervous system
7654	Secondary malignant neoplasm of bone and bone marrow
18676	Pathological fracture due to metastatic bone disease
44615	Secondary malignant neoplasm of ovary
36401	Secondary malignant neoplasm of adrenal gland
18616	Secondary malignant neoplasm of other specified sites
16760	Secondary malignant neoplasm of breast
60335	Secondary malignant neoplasm of vulva
21590	Secondary malignant neoplasm of prostate
49145	Secondary malignant neoplasm of penis
22524	Secondary malignant neoplasm of other specified site NOS
16500	Secondary malignant neoplasm of other specified site NOS
47810	Malignant neoplasm of unspecified site
13569	Disseminated malignancy NOS
6170	Carcinomatosis
12323	Malignant neoplasm of lymphatic and haemopoietic tissue
1481	Reticulosarcoma
99240	Reticulosarcoma NOS
27416	Lymphosarcoma
21402	Burkitt's lymphoma
2462	Hodgkin's disease
38939	Hodgkin's disease, lymphocytic-histiocytic predominance
29178	Hodgkin's disease, nodular sclerosis
63054	Hodgkin's disease, nodular sclerosis NOS
53397	Hodgkin's disease NOS
61662	Hodgkin's disease NOS, unspecified site
59778	Hodgkin's disease NOS of lymph nodes of head, face and neck
59755	Hodgkin's disease NOS of intrathoracic lymph nodes
42461	Hodgkin's disease NOS
33333	Other malignant neoplasm of lymphoid and histiocytic tissue
5179	Nodular lymphoma (Brill - Symmers disease)
12006	Mycosis fungoides
38005	Mycosis fungoides NOS
35014	Sezary's disease
44267	Malignant histiocytosis
27330	Leukaemic reticuloendotheliosis
5137	Leukaemic reticuloendotheliosis
87335	Hairy cell leukaemia
34926	Letterer-Siwe disease
15036	Malignant mast cell tumours
3604	Non - Hodgkin's lymphoma

28639	Follicular non-Hodgkin's small cleaved cell lymphoma
49262	Follicular non-Hodgkin's large cell lymphoma
50695	Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma
53551	Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma
17460	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma
31576	Other types of follicular non-Hodgkin's lymphoma
21549	Follicular non-Hodgkin's lymphoma
17182	Follicular lymphoma NOS
31794	Unspecified B-cell non-Hodgkin's lymphoma
39798	Diffuse non-Hodgkin's lymphoma, unspecified
17887	Malignant lymphoma otherwise specified
57737	Lymphoepithelioid lymphoma
12464	Peripheral T-cell lymphoma
44318	Oth and unspecif peripheral & cutaneous T-cell lymphomas
12335	Malignant lymphoma NOS
71262	Malignant lymphoma NOS of intrapelvic lymph nodes
15504	Malignant lymphoma NOS of lymph nodes of multiple sites
15027	Malignant lymphoma NOS
37182	Multiple myeloma and immunoproliferative neoplasms
4944	Multiple myeloma
43552	Kahler's disease
15211	Myelomatosis
19028	Solitary myeloma
21329	Plasmacytoma NOS
46042	Lambda light chain myeloma
39187	Plasma cell leukaemia
19372	Lymphoid leukaemia
4222	Lymphatic leukaemia
4251	Acute lymphoid leukaemia
8625	Chronic lymphoid leukaemia
27790	Chronic lymphatic leukaemia
31586	Prolymphocytic leukaemia
38331	Other lymphoid leukaemia NOS
38914	Lymphoid leukaemia NOS
7176	Myeloid leukaemia
4413	Acute myeloid leukaemia
10726	Chronic myeloid leukaemia
31701	Chronic granulocytic leukaemia
52327	Chloroma
66089	Other myeloid leukaemia NOS
35875	Monocytic leukaemia
27458	Chronic monocytic leukaemia
37272	Other specified leukaemia

42539	Acute erythraemia and erythroleukaemia
27340	Di Guglielmo's disease
37468	Chronic erythraemia
63653	Heilmeyer - Schoner disease
28276	Acute myelofibrosis
30632	Other specified leukaemia NOS
25191	Leukaemia of unspecified cell type
4072	Acute leukaemia NOS
16416	Chronic leukaemia NOS
34692	Other leukaemia of unspecified cell type
4250	Leukaemia NOS
20440	Myelomonocytic leukaemia
22050	Chronic myelomonocytic leukaemia
6115	Myeloproliferative disorder
17056	Myeloproliferative disease
39336	Myelosclerosis with myeloid metaplasia
49301	Malignant neoplasm lymphatic or haematopoietic tissue NOS
22809	Neoplasms of uncertain behaviour
43348	Neoplasm of uncertain behaviour of larynx
17379	Neoplasm of uncertain behaviour of vocal cord
25475	Neoplasm of uncertain behaviour of bronchus
3915	Neoplasm of uncertain behaviour of lung
64443	Neoplasm of uncertain behaviour of pleura
39374	Neoplasm of uncertain behaviour of mediastinum
54233	Neoplasm of uncertain behaviour of maxillary sinus
2481	Polycythaemia vera
5542	Polycythaemia rubra vera
36790	Primary polycythaemia
45414	Neoplasm of uncertain behaviour of histiocytic and mast cell
29789	Histiocytic tumour NOS
4661	Mastocytoma NOS
59663	Neoplasm of uncertain behaviour of plasma cells
38321	Plasmacytoma NOS
31560	Idiopathic thrombocythaemia
14927	Myelodysplasia
22890	Refractory anaemia without sideroblasts, so stated
10817	Refractory anaemia with sideroblasts
23875	Refractory anaemia with excess of blasts
11950	Essential (haemorrhagic) thrombocythaemia
12265	Primary thrombocythaemia
17386	Idiopathic thrombocythaemia
45285	Myelodysplastic syndrome, unspecified
4561	Myelodysplasia

19130	Refractory anaemia, unspecified
35532	[M]Morphology of neoplasms
21207	[M]Tumour morphology
10258	[M]Neoplasms NOS
15543	[M]Neoplasm, uncertain whether benign or malignant
21868	[M]Neoplasm, malignant
3197	[M]Neoplasm, metastatic
6985	[M]Secondary neoplasm
22267	[M]Neoplasm, malig, uncertain whether primary or metastatic
5932	[M]Tumour cells, uncertain whether benign or malignant
8627	[M]Tumour cells, malignant
22156	[M]Malignant tumour, small cell type
24511	[M]Malignant tumour, giant cell type
33508	[M]Unspecified tumour cell NOS
20653	[M]Epithelial neoplasms NOS
20564	[M]Carcinoma in situ NOS
21914	[M]Intraepithelial carcinoma NOS
8695	[M]Carcinoma NOS
3152	[M]Carcinoma, metastatic, NOS
9366	[M]Secondary carcinoma
16692	[M]Carcinomatosis
57336	[M]Epithelioma, malignant
25961	[M]Large cell carcinoma NOS
21609	[M]Carcinoma, undifferentiated type, NOS
12609	[M]Carcinoma, anaplastic type, NOS
26413	[M]Pleomorphic carcinoma
48048	[M]Giant cell and spindle cell carcinoma
6966	[M]Spindle cell carcinoma
9291	[M]Small cell carcinoma NOS
9156	[M]Oat cell carcinoma
30988	[M]Small cell carcinoma, intermediate cell
21217	[M]Small cell-large cell carcinoma
40494	[M]Papillary and squamous cell neoplasms
11782	[M]Papillary neoplasms
7967	[M]Squamous cell neoplasms
38651	[M]Papillary carcinoma in situ
10541	[M]Papillary carcinoma NOS
46432	[M]Verrucous papilloma
34395	[M]Verrucous carcinoma NOS
155	[M]Squamous cell papilloma
48321	[M]Dyskeratotic papilloma
20807	[M]Papillary squamous cell carcinoma
48182	[M]Epidermoid carcinoma in situ

19041	[M]Intraepidermal carcinoma NOS
19678	[M]Intraepithelial squamous cell carcinoma
1624	[M]Squamous cell carcinoma NOS
56600	[M]Epidermoid carcinoma NOS
24293	[M]Squamous cell carcinoma, metastatic NOS
29787	[M]Squamous cell carcinoma, keratinising type NOS
57513	[M]Epidermoid carcinoma, keratinising type
41816	[M]Squamous cell carcinoma, small cell, non-keratinising
33497	[M]Squamous cell carcinoma, microinvasive
41481	[M]Queyrat's erythroplasia
45510	[M]Lymphoepithelial carcinoma
44534	[M]Intraepit neop,grade III,of cervix, vulva and vagina
49399	[M]Papillary or squamous cell neoplasm NOS
13574	[M]Metatypical carcinoma
20869	[M]Trichoepithelioma
22060	[M]Trichofolliculoma
24711	[M]Tricholemmoma
6280	[M]Pilomatrixoma
28812	[M]Malherbe's calcified epithelioma
1950	[M]Transitional cell papillomas and carcinomas
41726	[M]Transitional cell papilloma NOS
50294	[M]Urothelial papilloma
1904	[M]Urinary bladder papilloma
21652	[M]Transitional cell carcinoma in situ
6436	[M]Transitional cell carcinoma NOS
12388	[M]Urothelial carcinoma
42001	[M]Schneiderian papilloma
38454	[M]Basaloid carcinoma
9712	[M]Papillary transitional cell carcinoma
33897	[M]Transitional cell papilloma or carcinoma NOS
19091	[M]Adenomas and adenocarcinomas
2272	[M]Adenocarcinomas
27827	[M]Adenocarcinoma in situ
29170	[M]Adenocarcinoma in situ in villous adenoma
37137	[M]Adenocarcinoma in situ in tubulovillous adenoma
8930	[M]Adenocarcinoma NOS
44778	[M]Adenocarcinoma in tubulovillous adenoma
5455	[M]Adenocarcinoma, metastatic, NOS
48223	[M]Scirrhous adenocarcinoma
27440	[M]Linitis plastica
28272	[M]Adenocarcinoma, intestinal type
59240	[M]Carcinoma, diffuse type
8032	[M]Pancreatic adenomas and carcinomas

9224	[M]Insulinoma NOS
58022	[M]Glucagonoma NOS
21659	[M]Pancreatic adenoma or carcinoma NOS
26858	[M]Gastrinoma and carcinomas
43594	[M]Gastrinoma or carcinoma NOS
8711	[M]Cholangiocarcinoma
29792	[M]Liver cell adenoma
40240	[M]Hepatocellular carcinoma NOS
20234	[M]Hepatoma NOS
25641	[M]Liver cell carcinoma
53987	[M]Hepatobiliary adenoma or carcinoma NOS
36124	[M]Eccrine dermal cylindroma
50753	[M]Turban tumour
33775	[M]Adenoid cystic carcinoma
5265	[M]Cylindroma NOS
18255	[M]Adenomatous and adenocarcinomatous polyps
52326	[M]Adenocarcinoma in adenomatous polyp
36286	[M]Adenomatous or adenocarcinomatous polyp NOS
6746	[M]Tubular adenomas and adenocarcinomas
60045	[M]Tubular adenocarcinoma
39148	[M]Tubular adenoma or adenocarcinoma NOS
41702	[M]Adenomatous and adenocarcinomatous polyps of colon
33904	[M]Adenomatous polyposis coli
12494	[M]Familial polyposis coli
73275	[M]Adenocarcinoma in adenomatous polposis coli
39875	[M]Adenomatous or adenocarcinomatous polyps of the colon NOS
3923	[M]Carcinoid tumours
38444	[M]Carcinoid tumour NOS
34110	[M]Carcinoid tumour, malignant
23081	[M]Carcinoid bronchial adenoma
26253	[M]Neuroendocrine carcinoma
32641	[M]Merkel cell carcinoma
45573	[M]Carcinoid tumours NOS
41260	[M]Bronchial adenoma NOS
34015	[M]Bronchiolo-alveolar adenocarcinoma
36530	[M]Alveolar cell carcinoma
16723	[M]Bronchiolar carcinoma
72290	[M]Alveolar adenoma
42273	[M]Papillary adenomas and adenocarcinomas
35348	[M]Papillary adenocarcinoma NOS
6920	[M]Villous adenomas and adenocarcinomas
29449	[M]Villous papilloma

67342	[M]Adenocarcinoma in villous adenoma
35891	[M]Villoglandular adenoma
26120	[M]Pituitary adenomas and carcinomas
39727	[M]Chromophobe adenoma
40622	[M]Mucoid cell carcinoma
57422	[M]Pituitary adenoma or carcinoma NOS
28806	[M]Oncocytoma
29008	[M]Hurthle cell adenocarcinoma
36882	[M]Clear cell adenomas and adenocarcinomas
37354	[M]Clear cell adenocarcinoma NOS
27697	[M]Hypernephroid tumour
8101	[M]Renal adenoma and carcinoma
10668	[M]Renal cell carcinoma
15419	[M]Hypernephroma
35467	[M]Renal adenoma or carcinoma NOS
34096	[M]Granular cell carcinoma
4217	[M]Parathyroid adenomas and adenocarcinomas
42169	[M]Parathyroid adenoma or adenocarcinoma NOS
40371	[M]Lipoadenoma
19263	[M]Thyroid adenoma and adenocarcinoma
21741	[M]Follicular adenocarcinoma NOS
21847	[M]Follicular carcinoma
31061	[M]Colloid adenoma
40266	[M]Multiple endocrine adenomas
40883	[M]Adrenal cortical tumours
62256	[M]Adrenal cortical tumours NOS
8606	[M]Endometrioid adenomas and carcinomas
37728	[M]Endometrioid cystadenoma NOS
9447	[M]Endometrioid carcinoma
28388	[M]Endometrioid adenoma or carcinoma NOS
16902	[M]Basal cell adenocarcinoma
49900	[M]Klatskin's tumour
5707	[M]Prolactinoma
35975	[M]Adenoma or adenocarcinoma NOS
29563	[M]Adnexal and skin appendage neoplasms
11182	[M]Hidradenoma NOS
44066	[M]Eccrine acrospiroma
60071	[M]Clear cell hidradenoma
6753	[M]Eccrine poroma
17501	[M]Eccrine spiradenoma
30293	[M]Spiradenoma NOS
28563	[M]Hidrocystoma
12254	[M]Papillary hydradenoma

17676	[M]Syringoma NOS
28291	[M]Sebaceous adenoma and adenocarcinoma
34269	[M]Sebaceous adenocarcinoma
10315	[M]Adnexal and skin appendage neoplasm NOS
34627	[M]Mucoepidermoid neoplasms
59100	[M]Mucoepidermoid tumour
28625	[M]Mucoepidermoid carcinoma
21651	[M]Cystic, mucinous and serous neoplasms
34984	[M]Cystadenoma and carcinoma
18633	[M]Cystadenoma NOS
34000	[M]Cystadenocarcinoma NOS
69978	[M]Borderline mucinous cystadenoma of the ovary
2979	[M]Ovarian cystic, mucinous and serous neoplasms
17151	[M]Ovarian cystadenoma or carcinoma
18638	[M]Ovarian mucinous tumour
39007	[M]Ovarian papillary tumour
28939	[M]Serous cystadenoma NOS
52263	[M]Serous cystadenoma, borderline malignancy
38442	[M]Serous cystadenocarcinoma, NOS
60406	[M]Papillary serous cystadenoma NOS
44930	[M]Papillary serous cystadenocarcinoma
20210	[M]Mucinous cystadenoma NOS
38808	[M]Pseudomucinous cystadenoma NOS
28396	[M]Mucinous cystadenoma, borderline malignancy
66876	[M]Pseudomucinous adenocarcinoma
21131	[M]Serous cystadenoma, borderline malignancy
40632	[M]Mucinous adenoma and adenocarcinoma
12497	[M]Mucinous adenocarcinoma
30416	[M]Colloid adenocarcinoma
17098	[M]Pseudomyxoma peritonei
44074	[M]Mucin-producing adenocarcinoma
53694	[M]Krukenberg tumour
18029	[M]Ductal, lobular and medullary neoplasms
27728	[M]Intraductal carcinoma, noninfiltrating NOS
8351	[M]Infiltrating duct carcinoma
21833	[M]Duct carcinoma NOS
30189	[M]Intraductal papillary adenocarcinoma with invasion
39760	[M]Infiltrating duct and lobular carcinoma
40359	[M]Juvenile breast carcinoma
18417	[M]Intraductal papilloma
31740	[M]Ductal papilloma
39394	[M]Intracystic papillary adenoma
67932	[M]Intraductal papillomatosis NOS

39145	[M]Subareolar duct papillomatosis
36488	[M]Adenoma of the nipple
16677	[M]Medullary carcinoma NOS
21861	[M]Lobular carcinoma in situ
12427	[M]Lobular carcinoma NOS
7319	[M]Infiltrating ductular carcinoma
42542	[M]Paget's disease and infiltrating breast duct carcinoma
12480	[M]Paget's disease and intraductal carcinoma of breast
24523	[M]Paget's disease, extramammary, exc Paget's disease bone
3969	[M]Intracystic carcinoma NOS
60683	[M]Ductal, lobular or medullary neoplasm NOS
12580	[M]Adenosquamous carcinoma
31793	[M]Thymoma
31343	[M]Thymoma, benign
39294	[M]Specialised gonadal neoplasms
54654	[M]Sex cord-stromal tumour
21435	[M]Ovarian stromal tumour
21319	[M]Testicular stromal tumour
40742	[M]Thecoma, luteinized
6751	[M]Granulosa cell tumour NOS
48957	[M]Granulosa cell-theca cell tumour
18065	[M]Sertoli-Leydig cell tumour
38979	[M]Sertoli cell tumour
40954	[M]Testicular adenoma
31170	[M]Leydig cell tumour
39734	[M]Hilar cell tumour
59995	[M]Lipid cell tumour of ovary
11754	[M]Sclerosing stromal tumour
24924	[M]Paragangliomas and glomus tumours
10913	[M]Paraganglioma NOS
45953	[M]Glomus jugulare tumour
36209	[M]Carotid body tumour
48326	[M]Chemodectoma
50605	[M]Glomangiosarcoma
45969	[M]Glomus tumour
4916	[M]Glomangioma
52070	[M]Gangliocytic paraganglioma
34712	[M]Glomangiomyoma
7693	[M]Naevi and melanomas
579	[M]Malignant melanoma NOS
24551	[M]Melanocarcinoma
7483	[M]Melanoma NOS
51353	[M]Malignant melanoma, regressing

58835	[M]Desmoplastic melanoma, malignant
20982	[M]Nodular melanoma
17232	[M]Amelanotic melanoma
62088	[M]Malignant melanoma in Hutchinson's melanotic freckle
11922	[M]Lentigo maligna melanoma
22692	[M]Acral lentiginous melanoma, malignant
24208	[M]Superficial spreading melanoma
4871	[M]Juvenila melanoma
44061	[M]Spindle cell melanoma NOS
39059	[M]Melanoma in situ
3376	[M]Dysplastic naevus
33734	[M]Naevi or melanoma NOS
17366	[M]Soft tissue tumours and sarcomas NOS
8085	[M]Sarcoma NOS
31026	[M]Spindle cell sarcoma
46581	[M]Pleomorphic cell sarcoma
38869	[M]Fibromatous neoplasms
31323	[M]Fibrosarcoma NOS
50574	[M]Myxofibroma NOS
23919	[M]Periosteal fibroma
50423	[M]Elastofibroma
55886	[M]Aggressive fibromatosis
2776	[M]Desmoid NOS
44277	[M]Invasive fibroma
18566	[M]Abdominal desmoid
27674	[M]Atypical fibrous histiocytoma
37680	[M]Fibrous histiocytoma, malignant
41839	[M]Fibroxanthoma NOS
34276	[M]Atypical fibroxanthoma
35034	[M]Fibroxanthosarcoma
22655	[M]Sclerosing haemangioma
27905	[M]Subepidermal nodular fibrosis
31772	[M]Dermatofibrosarcoma NOS
8985	[M]Myxoma NOS
21732	[M]Myxosarcoma
26171	[M]Angiomyxoma
12268	[M]Lipomatous neoplasms
45882	[M]Lipoma NOS
28599	[M]Liposarcoma NOS
56676	[M]Myxoid liposarcoma
59651	[M]Mixed type liposarcoma
18521	[M]Angiolipomatous neoplasms
37857	[M]Angiomyolipoma

27596	[M]Angiolipoma NOS
42528	[M]Hibernoma
7856	[M]Dedifferentiated liposarcoma
57628	[M]Lipomatous neoplasms NOS
10588	[M]Leiomyosarcoma NOS
64596	[M]Myxoid leiomyosarcoma
42526	[M]Angiomyomatous neoplasms
47811	[M]Angiomyoma
17530	[M]Angioleiomyoma
62662	[M]Angiomyomatous neoplasm NOS
31818	[M]Myoma and myosarcoma
55268	[M]Myosarcoma
31421	[M]Rhabdomyosarcoma NOS
48275	[M]Embryonal rhabdomyosarcoma
37081	[M]Smooth muscle tumour NOS
47874	[M]Complex mixed and stromal neoplasms
34030	[M]Endometrial stromal sarcoma
21419	[M]Chondroid syringoma
44217	[M]Mixed tumour NOS
21173	[M]Mullerian mixed tumour
49811	[M]Mesodermal mixed tumour
17314	[M]Wilms' tumour
45668	[M]Myoepithelioma
44060	[M]Mesenchymomas
17212	[M]Rhabdoid sarcoma
18771	[M]Clear cell sarcoma of kidney
25810	[M]Brenner tumours
48254	[M]Intracanalicular fibroadenoma NOS
9066	[M]Adenofibroma NOS
17446	[M]Cystadenofibroma NOS
37507	[M]Serous adenofibroma
40514	[M]Mucinous adenofibroma
62431	[M]Cellular intracanalicular fibroadenoma
36701	[M]Giant fibroadenoma NOS
50905	[M]Juvenile fibroadenoma
7966	[M]Fibroepithelial neoplasm NOS
35883	[M]Synovial neoplasms
34332	[M]Synovioma, benign
17409	[M]Synovioma NOS
16474	[M]Mesothelial neoplasms
27509	[M]Mesothelioma, malignant
21882	[M]Adenomatoid tumour NOS
21770	[M]Mesothelioma, unspecified

17468	[M]Germ cell neoplasms
32191	[M]Dysgerminoma
7476	[M]Seminomas
35223	[M]Spermatocytic seminoma
9859	[M]Seminoma NOS
27971	[M]Germinoma
28941	[M]Embryonal carcinoma NOS
17435	[M]Teratomas
50432	[M]Teratoma, benign
19180	[M]Teratoma NOS
33636	[M]Teratoma, malignant, NOS
52493	[M]Teratoblastoma, malignant
21682	[M]Malignant teratoma, intermediate type
42300	[M]Teratoma NOS
65861	[M]Dermoid cyst with malignant transformation
11404	[M]Hydatidiform mole NOS
10875	[M]Hydatid mole
47339	[M]Invasive mole NOS
29945	[M]Malignant teratoma, trophoblastic
4873	[M]Partial hydatidiform mole
28635	[M]Classical hydatidiform mole
36646	[M]Haemangiomatous tumours
62348	[M]Haemangiosarcoma
22650	[M]Angiosarcoma
11719	[M]Arteriovenous haemangioma
40853	[M]Angioendothelioma
50658	[M]Infantile haemangioma
27439	[M]Kaposi's sarcoma
5430	[M]Angiofibroma NOS
34385	[M]Juvenile angiofibroma
41349	[M]Angioblastoma
53774	[M]Epithelioid haemangioma
22712	[M]Epithelioid haemangioendothelioma NOS
38417	[M]Cavernous lymphangioma
1325	[M]Cystic hygroma
44191	[M]Hygroma
63571	[M]Parosteal osteosarcoma
44556	[M]Osteoma NOS
8660	[M]Osteosarcoma NOS
49862	[M]Osteoblastic sarcoma
5052	[M]Osteogenic sarcoma NOS
24539	[M]Chondroblastic osteosarcoma
22561	[M]Telangiectatic osteosarcoma

33993	[M]Osteoid osteoma NOS
62492	[M]Osteoblastoma
21224	[M]Giant osteoid osteoma
4118	[M]Myxoid chondrosarcoma
29337	[M] Small cell osteosarcoma
36503	[M]Chondromatous neoplasms
40469	[M]Ecchondroma
5773	[M]Osteocartilaginous exostosis
16204	[M]Osteochondromatosis NOS
33589	[M]Chondromatosis NOS
7941	[M]Chondrosarcoma NOS
49568	[M]Chondromyxoid fibroma
33973	[M]Chondromatous neoplasm NOS
22330	[M]Giant cell tumours
38477	[M]Giant cell tumour of bone NOS
29385	[M]Osteoclastoma
45364	[M]Giant cell tumour of soft parts NOS
37830	[M]Giant cell tumour NOS
9102	[M]Miscellaneous bone tumours
4473	[M]Ewing's sarcoma
6080	[M]Ossifying fibroma
41274	[M]Odontogenic tumours
44210	[M]Odontoma NOS
22057	[M]Ameloblastic fibro-odontoma
40467	[M]Ameloblastoma NOS
45189	[M]Squamous odontogenic tumour
68730	[M]Ameloblastic fibrosarcoma
28178	[M]Craniopharyngioma
48477	[M]Pinealoma
33951	[M]Pineocytoma
21758	[M]Chordoma
28950	[M]Miscellaneous tumour NOS
12309	[M]Gliomas
31574	[M]Glioma, malignant
8523	[M]Glioma NOS
38551	[M]Gliomatosis cerebri
50834	[M]Subependymoma
26157	[M]Choroid plexus papilloma NOS
20084	[M]Ependymoma NOS
70151	[M]Papillary ependymoma
43114	[M]Myxopapillary ependymoma
8547	[M]Astrocytoma NOS
27748	[M]Astrocytic glioma

8328	[M]Astrocytoma, anaplastic type
45531	[M]Gemistocytic astrocytoma
27846	[M]Fibrillary astrocytoma
30273	[M]Pilocytic astrocytoma
23083	[M]Glioblastoma NOS
9575	[M]Glioblastoma multiforme
66064	[M]Giant cell glioblastoma
27744	[M]Oligodendroglioma NOS
46404	[M]Oligodendroblastoma
34763	[M]Medulloblastoma NOS
37473	[M]Cerebellar sarcoma NOS
32357	[M]Ganglioneuromatous neoplasms
34713	[M]Ganglioneuroma
2123	[M]Neuroblastoma NOS
31629	[M]Ganglioglioma
28836	[M]Retinoblastomas
48952	[M]Retinoblastoma NOS
58902	[M]Olfactory neurogenic tumour
38870	[M]Psammomatous meningioma
21598	[M]Haemangioblastic meningioma
50822	[M]Haemangiopericytic meningioma
47848	[M]Meningioma NOS
18690	[M]Nerve sheath tumour
765	[M]Neurofibromatosis NOS
36785	[M]Multiple neurofibromatosis
62941	[M]Neurofibrosarcoma
59749	[M]Melanotic neurofibroma
12016	[M]Plexiform neurofibroma
22843	[M]Neurilemmoma NOS
21247	[M]Acoustic neuroma
60590	[M]Neurinomatosis
18266	[M]Granular cell tumour NOS
71869	[M]Alveolar soft part sarcoma
17178	[M]Lymphomas, NOS or diffuse
36114	[M]Malignant lymphoma NOS
1483	[M]Lymphoma NOS
23711	[M]Malignant lymphoma, diffuse NOS
16460	[M]Malignant lymphoma, non Hodgkin's type
3371	[M]Non Hodgkins lymphoma
46931	[M]Malignant lymphoma, stem cell type
41754	[M]Malignant lymphoma, lymphoplasmacytoid type
21463	[M]Lymphocytic lymphoma NOS
39906	[M]Malignant lymphoma, centrocytic

34352	[M]Lymphoblastic lymphoma NOS
52591	[M]Lymphoblastoma NOS
31726	[M]Malignant lymphoma, small cleaved cell, diffuse
71652	[M]Malignant lymphoma, mixed small and large cell, diffuse
51895	[M]Lymphoma, diffuse or NOS
49825	[M]Reticulum cell sarcoma NOS
20710	[M]Hodgkin's disease
61997	[M]Hodgkin's disease NOS
65584	[M]Hodgkin,s disease, lymphocytic predominance, diffuse
64343	[M]Hodgkin,s disease, nodular sclerosis, mixed cellularity
20437	[M]Lymphomas, nodular or follicular
63699	[M]Malignant lymphoma, nodular NOS
40513	[M]Lymphoma, nodular or follicular NOS
46967	[M]Mycosis fungoides
57544	[M]True histiocytic lymphoma
40766	[M] Peripheral T-cell lymphoma NOS
10395	[M] Monoclonal gammopathy
54190	[M] Angioimmunoblastic lymphadenopathy
31492	[M] Monocytoid B-cell lymphoma
49530	[M] T-gamma lymphoproliferative disease
16774	[M] Cutaneous lymphoma
18383	[M] Large cell lymphoma
9172	[M]Waldenstrom's macroglobulinaemia
43459	[M]Plasma cell tumours
31671	[M]Plasma cell myeloma
18744	[M]Multiple myeloma
3672	[M]Myeloma NOS
39490	[M]Plasmacytic myeloma
37128	[M]Mast cell tumours
4637	[M]Leukaemias
40420	[M]Leukaemias unspecified
6316	[M]Acute leukaemia NOS
22071	[M]Blast cell leukaemia
31750	[M]Chronic leukaemia NOS
12146	[M]Lymphoid leukaemia NOS
20635	[M]Lymphatic leukaemia
37410	[M]Acute lymphoid leukaemia
41500	[M]Chronic lymphoid leukaemia
37723	[M]Granulocytic leukaemia NOS
48049	[M]Chronic myelomonocytic leukaemia
5915	[M]Hairy cell leukaemia
42297	[M]Leukaemia NOS
30139	[M]Misc myeloproliferative and lymphoproliferative disorders

16922	[M]Polycythaemia vera
58888	[M]Polycythaemia rubra vera
17091	[M]Chronic myeloproliferative disease
30043	[M]Idiopathic thrombocythaemia
9673	[M]Chronic lymphoproliferative disease
7799	[M]Myelodysplastic syndrome
31749	[M]Monocytoid B-cell lymphoma
45700	Neoplasms otherwise specified
60053	[X]Additional neoplasm classification terms
35325	[X]Malignant neoplasm of respiratory and intrathoracic orga
40595	[X]Malignant neoplasm of bronchus or lung, unspecified
21715	[X]Mesothelioma of lung
40740	[X]Malignant neoplasms of lymphoid, haematopoietic and rela
8649	[X]Non-Hodgkin's lymphoma, unspecified type
7940	[X]Non-Hodgkin's lymphoma NOS
711	Diabetes mellitus
38986	Diabetes mellitus with no mention of complication
24490	Diabetes mellitus, juvenile type, no mention of complication
1038	Insulin dependent diabetes mellitus
14803	Diabetes mellitus, adult onset, no mention of complication
14889	Maturity onset diabetes
506	Non-insulin dependent diabetes mellitus
50972	Diabetes mellitus NOS with no mention of complication
1682	Diabetes mellitus with ketoacidosis
42505	Diabetes mellitus NOS with ketoacidosis
21482	Diabetes mellitus with hyperosmolar coma
15690	Diabetes mellitus with ketoacidotic coma
68843	Diabetes mellitus, adult onset, with ketoacidotic coma
65062	Diabetes mellitus NOS with ketoacidotic coma
1647	Insulin dependent diabetes mellitus
18505	IDDM-Insulin dependent diabetes mellitus
17858	Type 1 diabetes mellitus
24423	Type I diabetes mellitus
6791	Insulin dependent diabetes mellitus - poor control
46850	Type I diabetes mellitus - poor control
45914	Type 1 diabetes mellitus - poor control
31310	Insulin dependent diabetes maturity onset
44440	Insulin dependent diabetes mellitus with hypoglycaemic coma
4513	Non-insulin dependent diabetes mellitus
5884	NIDDM - Non-insulin dependent diabetes mellitus
17859	Type 2 diabetes mellitus
18219	Type II diabetes mellitus
8403	Non-insulin dependent diabetes mellitus - poor control

24458	Type II diabetes mellitus - poor control
45913	Type 2 diabetes mellitus - poor control
39406	Reaven's syndrome
29979	Non-insulin-dependent diabetes mellitus without complication
43785	Non-insulin dependent diabetes mellitus with hypoglyca coma
61071	Type 2 diabetes mellitus with hypoglycaemic coma
18278	Insulin treated Type 2 diabetes mellitus
37648	Insulin treated non-insulin dependent diabetes mellitus
18264	Insulin treated Type II diabetes mellitus
36633	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
11551	Diabetes mellitus induced by steroids
26108	Steroid induced diabetes mellitus without complication
46624	Maturity onset diabetes in youth
36695	Diabetes mellitus autosomal dominant type 2
59991	Maturity onset diabetes in youth type 2
1549	Type 1 diabetes mellitus
12455	Type I diabetes mellitus
51261	Insulin dependent diabetes mellitus
47650	Type 1 diabetes mellitus with multiple complications
43921	Unstable type 1 diabetes mellitus
35288	Type 1 diabetes mellitus - poor control
39070	Type 1 diabetes mellitus with hypoglycaemic coma
10692	Type 1 diabetes mellitus with ketoacidosis
40837	Type 1 diabetes mellitus with ketoacidotic coma
758	Type 2 diabetes mellitus
22884	Type II diabetes mellitus
25627	Type 2 diabetes mellitus - poor control
54773	Reaven's syndrome
39481	Metabolic syndrome X
47954	Type 2 diabetes mellitus without complication
46917	Type 2 diabetes mellitus with hypoglycaemic coma
1407	Insulin treated Type 2 diabetes mellitus
64668	Insulin treated Type II diabetes mellitus
34450	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
32627	Type 2 diabetes mellitus with ketoacidosis
25591	Type 2 diabetes mellitus with exudative maculopathy
51697	Secondary pancreatic diabetes mellitus
33343	Diabetes mellitus with other specified manifestation
4090	Plasma protein metabolism disorders
17775	Polyclonal hypergammaglobulinaemia
15883	Monoclonal paraproteinaemia
7586	Monoclonal gammopathy
3451	Other paraproteinaemias

57569	Cryoglobulinaemic purpura
12306	Benign paraproteinaemia
12386	Paraproteinaemia NOS
16527	Macroglobulinaemia
10411	Waldenstrom's macroglobulinaemia
71994	Macroglobulinaemia NOS
5073	Hypoproteinaemia
6220	Cystic fibrosis
13264	Fibrocystic disease
18914	Cystic fibrosis with pulmonary manifestations
18905	Cystic fibrosis with intestinal manifestations
52212	[X]Diabetes mellitus
37539	Aplastic and other anaemias
15422	Aplastic anaemia
44913	Hypoplastic anaemia - familial
37320	Congenital hypoplastic anaemia
34754	Fanconi's familial refractory anaemia
61462	Congenital red cell hypoplasia
15658	Acquired aplastic anaemia
16108	Aplastic anaemia due to chronic disease
32715	Hypoplastic anaemia due to drug or chemical substance
5823	Pancytopenia - acquired
938	Pancytopenia NOS
30994	[X]Pure red cell aplasia
41142	Idiopathic aplastic anaemia
3265	Other and unspecified anaemias
15936	Sideroblastic anaemia
2743	Acute posthaemorrhagic anaemia
30637	Anaemia in neoplastic disease
16052	Refractory Anaemia
12176	Chronic anaemia
16929	Anaemia secondary to renal failure
25394	Anaemia secondary to chronic renal failure
34934	Other specified anaemias
58695	Other specified other anaemia
28768	Other specified anaemia NOS
739	Anaemia unspecified
4670	Secondary anaemia NOS
1702	Normocytic anaemia due to unspecified cause
797	Macrocytic anaemia of unspecified cause
25876	Other specified anaemias
35160	Other anaemias NOS
4818	Agranulocytosis

2071	Neutropenia
18054	Idiopathic neutropenia
35719	Neutropenia - drug induced
40310	Neutropenia due to irradiation
17705	Neutropenia due to infection
30008	Drug-induced neutropenia
65903	Acquired agranulocytosis NEC
32141	Cyclical neutropenia
3372	Leucopenia
42394	Job's syndrome
18781	Chronic granulomatous disease
5495	Eosinophilia
52907	Secondary eosinophilia NOS
55214	Eosinophilia NOS
56991	Other white blood cell disease
3189	Lymphocytosis
9248	Monocytosis
23377	Plasmacytosis
11240	Lymphopenia
4760	Leucocytosis
42870	Other diseases of blood or blood forming organs
5086	Secondary polycythaemia
15311	Stress polycythaemia
17486	Spurious polycythaemia
37129	High altitude polycythaemia
17605	Polycythaemia due to cyanotic heart disease
44611	Polycythaemia due to cyanotic respiratory disease
44894	Renal polycythaemia
15301	Secondary polycythaemia NOS
4252	Chronic lymphadenitis
31912	Kikuchi disease
32947	Nonspecific mesenteric lymphadenitis
16586	Mesenteric lymphadenitis
1450	Mesenteric adenitis
14953	Acute mesenteric lymphadenitis
29526	Chronic mesenteric lymphadenitis
15230	Nonspecific mesenteric lymphadenitis NOS
1480	Unspecified lymphadenitis, excluding mesenteric lymphadenit
10702	Hypersplenism
23652	Other diseases of spleen
35702	Splenic abscess
29319	Splenic cyst
9368	Splenic infarction

49038	Wandering spleen
39034	Hyposplenism
31432	Disease of spleen NOS
23423	Familial polycythaemia
31410	Methaemoglobinaemia
25717	Calcified lymph nodes
42915	Other specified diseases of blood and blood forming organs
34150	Hypergammaglobulinaemia
5572	Myelofibrosis
2337	Pseudocholinesterase deficiency
33911	Cholinesterase deficiency
30628	Bone marrow depression
25195	Idiopathic erythrocytosis
53210	Other specified disease of blood or blood forming organ NOS
4526	Macrocytosis - no anaemia
4259	Blood dyscrasia NOS
46081	White blood cell or other blood diseases NOS
33707	Senile and presenile organic psychotic conditions
1916	Senile dementia
1350	Senile/presenile dementia
7323	Uncomplicated senile dementia
15165	Presenile dementia
49513	Presenile dementia with delirium
30032	Presenile dementia with paranoia
27677	Presenile dementia with depression
38438	Presenile dementia NOS
44674	Senile dementia with depressive or paranoid features
18386	Senile dementia with paranoia
21887	Senile dementia with depression
37015	Senile dementia with delirium
19477	Arteriosclerotic dementia
8634	Multi infarct dementia
43089	Uncomplicated arteriosclerotic dementia
55467	Arteriosclerotic dementia with paranoia
43292	Arteriosclerotic dementia with depression
42279	Arteriosclerotic dementia NOS
15249	Other senile and presenile organic psychoses
2882	Senile or presenile psychoses NOS
16237	Alcoholic psychoses
16225	Alcohol withdrawal delirium
22277	DTs - delirium tremens
1476	Delirium tremens
20762	Alcohol amnestic syndrome

4500	Korsakov's alcoholic psychosis
11106	Korsakov's alcoholic psychosis with peripheral neuritis
18636	Wernicke-Korsakov syndrome
41920	Alcohol amnestic syndrome NOS
54505	Other alcoholic dementia
27342	Alcoholic dementia NOS
25110	Alcohol withdrawal hallucinosis
20407	Drunkenness - pathological
30404	Alcoholic paranoia
33670	Other alcoholic psychosis
2082	Alcohol withdrawal syndrome
67651	Alcoholic psychosis NOS
16256	Drug psychoses
3844	Drug withdrawal syndrome
45997	Drug-induced paranoia or hallucinatory states
12628	Drug-induced paranoid state
20026	Drug-induced hallucinosis
26481	Drug-induced paranoia or hallucinatory state NOS
15876	Pathological drug intoxication
6359	Nicotine withdrawal
51135	Other drug psychoses
29783	Drug-induced delirium
46244	Drug-induced depressive state
22103	Drug-induced personality disorder
28767	Other drug psychoses NOS
26002	Drug psychosis NOS
15958	Non-organic psychoses
854	Schizophrenic disorders
32222	Simple schizophrenia
15733	Unspecified schizophrenia
3984	Chronic schizophrenic
44498	Acute exacerbation of chronic schizophrenia
53625	Simple schizophrenia NOS
30619	Hebephrenic schizophrenia
25546	Catatonic schizophrenia
1494	Paranoid schizophrenia
33383	Unspecified paranoid schizophrenia
31362	Chronic paranoid schizophrenia
53032	Acute exacerbation of chronic paranoid schizophrenia
36172	Paranoid schizophrenia in remission
9281	Paranoid schizophrenia NOS
576	Acute schizophrenic episode
38063	Residual schizophrenia

2117	Schizo-affective schizophrenia
58862	Unspecified schizo-affective schizophrenia
43800	Chronic schizo-affective schizophrenia
56438	Schizo-affective schizophrenia in remission
10575	Schizo-affective schizophrenia NOS
33338	Atypical schizophrenia
49761	Other schizophrenia NOS
8407	Schizophrenia NOS
14656	Affective psychoses
8567	Bipolar psychoses
2560	Depressive psychoses
26161	Manic psychoses
37070	Manic disorder, single episode
18909	Hypomanic psychoses
20110	Single manic episode, unspecified
14728	Single manic episode, mild
24640	Single manic episode, moderate
26227	Recurrent manic episodes
19967	Recurrent manic episodes, unspecified
46425	Recurrent manic episodes, mild
32295	Recurrent manic episodes, severe, with psychosis
37178	Recurrent manic episodes, in full remission
10610	Single major depressive episode
5879	Agitated depression
6546	Endogenous depression first episode
6950	Endogenous depression first episode
595	Endogenous depression
34390	Single major depressive episode, unspecified
16506	Single major depressive episode, mild
15155	Single major depressive episode, moderate
15219	Single major depressive episode, severe, without psychosis
32159	Single major depressive episode, severe, with psychosis
43324	Single major depressive episode, partial or unspec remission
57409	Single major depressive episode, in full remission
7011	Single major depressive episode NOS
15099	Recurrent major depressive episode
6932	Endogenous depression - recurrent
35671	Recurrent major depressive episodes, unspecified
29342	Recurrent major depressive episodes, mild
14709	Recurrent major depressive episodes, moderate
25697	Recurrent major depressive episodes, severe, no psychosis
24171	Recurrent major depressive episodes, severe, with psychosis
56273	Recurrent major depressive episodes,partial/unspec remission

55384	Recurrent major depressive episodes, in full remission
6482	Recurrent depression
25563	Recurrent major depressive episode NOS
3702	Bipolar affective disorder, currently manic
17385	Manic-depressive - now manic
35738	Bipolar affective disorder, currently manic, unspecified
36126	Bipolar affective disorder, currently manic, mild
46434	Bipolar affective disorder, currently manic, moderate
55829	Bipolar affect disord, currently manic,severe with psychosis
57605	Bipolar affective disorder, currently manic, NOS
4677	Bipolar affective disorder, currently depressed
12831	Manic-depressive - now depressed
15923	Bipolar affective disorder, currently depressed, unspecified
35734	Bipolar affective disorder, currently depressed, mild
27890	Bipolar affective disorder, currently depressed, moderate
63701	Bipolar affect disord, now depressed, severe with psychosis
37296	Bipolar affective disorder, currently depressed, NOS
31316	Mixed bipolar affective disorder
31535	Mixed bipolar affective disorder, unspecified
24689	Mixed bipolar affective disorder, mild
54195	Mixed bipolar affective disorder, severe, with psychosis
55064	Mixed bipolar affective disorder, in full remission
63583	Mixed bipolar affective disorder, NOS
14784	Unspecified bipolar affective disorder
27986	Unspecified bipolar affective disorder, NOS
10825	Seasonal affective disorder
60178	Other and unspecified manic-depressive psychoses
11596	Unspecified manic-depressive psychoses
27491	Atypical depressive disorder
33426	Other and unspecified manic-depressive psychoses NOS
41992	Other and unspecified affective psychoses
54607	Unspecified affective psychoses NOS
3489	Rebound mood swings
9183	Masked depression
33425	Other affective psychosis NOS
4261	Paranoid states
14743	Simple paranoid state
3890	Chronic paranoid psychosis
14971	Paraphrenia
31589	Other paranoid states
31455	Other paranoid states NOS
12771	Paranoid psychosis NOS
31984	Other nonorganic psychoses

20228	Reactive psychoses
8478	Reactive depressive psychosis
17770	Psychotic reactive depression
29937	Acute hysterical psychosis
7332	Reactive confusion
15053	Acute paranoid reaction
24345	Psychogenic paranoid psychosis
1055	Agitated depression
23538	Brief reactive psychosis
26119	Other reactive psychoses NOS
14965	Nonorganic psychosis NOS
3636	Psychotic episode NOS
22098	Infantile autism
1276	Autism
7302	Childhood autism
36662	Infantile autism NOS
31599	Heller's syndrome
24244	Atypical childhood psychoses
37395	Childhood schizophrenia NOS
16537	Other specified non-organic psychoses
22188	Non-organic psychosis NOS
2084	Alcohol dependence syndrome
2081	Alcoholism
1399	Alcohol problem drinking
5740	Acute alcoholic intoxication in alcoholism
57714	Alcohol dependence with acute alcoholic intoxication
40530	Acute alcoholic intoxication, unspecified, in alcoholism
56947	Continuous acute alcoholic intoxication in alcoholism
21624	Episodic acute alcoholic intoxication in alcoholism
59574	Acute alcoholic intoxication in remission, in alcoholism
36296	Acute alcoholic intoxication in alcoholism NOS
31443	Chronic alcoholism
43193	Unspecified chronic alcoholism
24064	Continuous chronic alcoholism
26106	Episodic chronic alcoholism
24485	Chronic alcoholism in remission
33635	Chronic alcoholism NOS
6169	Alcohol dependence syndrome NOS
5105	Drug dependence
3519	Drug addiction
16243	Opioid type drug dependence
689	Heroin dependence
16374	Methadone dependence

22059	Morphine dependence
32804	Opium dependence
38034	Unspecified opioid dependence
43075	Continuous opioid dependence
20962	Episodic opioid dependence
27960	Opioid dependence in remission
24441	Opioid drug dependence NOS
25344	Hypnotic or anxiolytic dependence
35733	Anxiolytic dependence
23436	Barbiturate dependence
460	Benzodiazepine dependence
18210	Diazepam dependence
31862	Librium dependence
36223	Sedative dependence
37130	Valium dependence
53025	Hypnotic or anxiolytic dependence, unspecified
26208	Hypnotic or anxiolytic dependence, continuous
48702	Hypnotic or anxiolytic dependence in remission
29797	Hypnotic or anxiolytic dependence NOS
11840	Cocaine type drug dependence
25808	Cocaine dependence, unspecified
25748	Cocaine dependence, continuous
33942	Cocaine drug dependence NOS
8284	Cannabis type drug dependence
37316	Marihuana dependence
24616	Cannabis dependence, unspecified
42923	Cannabis dependence, continuous
52794	Cannabis dependence, episodic
33462	Cannabis drug dependence NOS
22186	Amphetamine or other psychostimulant dependence
38360	Amphetamine or psychostimulant dependence, continuous
49585	Amphetamine or psychostimulant dependence, episodic
25646	Amphetamine or psychostimulant dependence NOS
21683	LSD dependence
5203	Glue sniffing dependence
38072	Glue sniffing dependence, unspecified
33774	Glue sniffing dependence, episodic
59184	Glue sniffing dependence NOS
51197	Other specified drug dependence
64269	Other specified drug dependence in remission
26061	Combined opioid with other drug dependence
64265	Combined opioid with other drug dependence, continuous
64277	Combined opioid with other drug dependence, episodic

52451	Combined opioid with other drug dependence in remission
14809	Combined drug dependence, excluding opioids
21087	Ecstasy type drug dependence
29446	Drug dependence NOS
7747	Nondependent abuse of drugs
7746	Nondependent alcohol abuse
12271	Drunkenness NOS
27518	Hangover (alcohol)
17777	Inebriety NOS
3782	Intoxication - alcohol
669	Nondependent alcohol abuse, unspecified
23610	Nondependent alcohol abuse, continuous
12974	Nondependent alcohol abuse, episodic
31569	Nondependent alcohol abuse in remission
28150	Nondependent alcohol abuse NOS
32687	Tobacco dependence
68658	Tobacco dependence NOS
3635	Nondependent cannabis abuse
42140	Nondependent cannabis abuse, unspecified
39983	Nondependent cannabis abuse, continuous
25448	Nondependent cannabis abuse, episodic
53071	Nondependent cannabis abuse in remission
25526	Nondependent cannabis abuse NOS
5610	Nondependent hallucinogen abuse
16071	LSD reaction
29075	Barbiturate abuse
43296	Hypnotic or anxiolytic abuse
18285	Tranquilliser abuse
26831	Nondependent opioid abuse
40536	Nondependent opioid abuse, unspecified
64382	Nondependent opioid abuse, episodic
10860	Nondependent cocaine abuse
22481	Nondependent amphetamine or other psychostimulant abuse
32751	Psychostimulant abuse
25229	Nondependent amphetamine or psychostimulant abuse, episodic
43176	Nondependent amphetamine/psychostimulant abuse in remission
47836	Nondependent amphetamine or psychostimulant abuse NOS
46962	Nondependent antidepressant type drug abuse
53008	Nondependent mixed drug abuse
52842	Nondependent mixed drug abuse in remission
25175	Misuse of prescription only drugs

16161	Nondependent other drug abuse
8608	Analgesic abuse
10903	Laxative abuse
22730	Steroid abuse
64316	Nondependent other drug abuse NOS
1588	Misuse of drugs NOS
19921	Other adjustment reaction with withdrawal
7664	[X]Dementia in Alzheimer's disease
49263	[X]Dementia in Alzheimer's disease with early onset
25704	[X]Presenile dementia,Alzheimer's type
38678	[X]Dementia in Alzheimer's disease with late onset
11379	[X]Senile dementia,Alzheimer's type
30706	[X]Dementia in Alzheimer's dis, atypical or mixed type
29386	[X]Dementia in Alzheimer's disease, unspecified
8195	[X]Alzheimer's dementia unspec
6578	[X]Vascular dementia
9565	[X]Arteriosclerotic dementia
11175	[X]Multi-infarct dementia
8934	[X]Subcortical vascular dementia
31016	[X]Mixed cortical and subcortical vascular dementia
19393	[X]Vascular dementia, unspecified
12621	[X]Dementia in other diseases classified elsewhere
28402	[X]Dementia in Pick's disease
37014	[X]Dementia in Huntington's disease
9509	[X]Dementia in Parkinson's disease
26270	[X]Lewy body dementia
64267	[X]Dementia in other specified diseases classif elsewhere
4693	[X] Unspecified dementia
48501	[X] Presenile dementia NOS
47619	[X] Presenile psychosis NOS
34944	[X] Primary degenerative dementia NOS
4357	[X] Senile dementia NOS
27935	[X] Senile psychosis NOS
27759	[X] Senile dementia, depressed or paranoid type
53446	[X]Delirium superimposed on dementia
30034	[X]Mental and behavioural disorders due to psychoactive subs
5611	[X]Mental and behavioural disorders due to use of alcohol
44299	[X]Mental & behav dis due to use alcohol: acute intoxication
9508	[X]Acute alcoholic drunkenness
21879	[X]Mental and behav dis due to use of alcohol: harmful use
39327	[X]Mental and behav dis due to use alcohol: dependence syndr
28780	[X]Alcohol addiction
5758	[X]Chronic alcoholism

20514	[X]Mental and behav dis due to use alcohol: withdrawal state
64101	[X]Men & behav dis due alcohl: withdrawl state with delirium
17259	[X]Delirium tremens, alcohol induced
12353	[X]Mental & behav dis due to use alcohol: psychotic disorder
6467	[X]Alcoholic hallucinosis
30162	[X]Alcoholic paranoia
17607	[X]Alcoholic psychosis NOS
39799	[X]Mental and behav dis due to use alcohol: amnesic syndrome
11670	[X]Korsakov's psychosis, alcohol induced
62000	[X]Men & behav dis due alcoh: resid & late-onset psychot dis
26323	[X]Alcoholic dementia NOS
37691	[X]Chronic alcoholic brain syndrome
32927	[X]Alcohol withdrawal-induced seizure
47335	[X]Mental and behavioural disorders due to use of opioids
42456	[X]Mental & behav dis due to use opioids: acute intoxication
34249	[X]Mental and behav dis due to use opioids: dependence syndr
10538	[X]Drug addiction - opioids
4564	[X]Heroin addiction
25527	[X]Cold turkey, opiate withdrawal
50964	[X]Mental & behav dis due to use opioids: psychotic disorder
10655	[X]Mental and behavioural disorders due to use cannabinoids
56504	[X]Mental and behav dis due to cannabinoids: dependence synd
21662	[X]Drug addiction - cannabis
38429	[X]Mental & behav dis due to cannabinoids: psychotic disordr
41317	[X]Mental and behavioural dis due use sedatives/hypnotics
44330	[X]Mental and behav dis due to seds/hypntcs: dependence synd
25757	[X]Drug addiction- sedative / hypnotics
61342	[X]Mental and behav dis due seds/hypntcs: withdrawal state
69138	[X]Mental & behav dis due to seds/hypntcs: psychotic disordr
32052	[X]Mental and behavioural disorders due to use of cocaine
50302	[X]Mental and behav dis due to use cocaine: dependence syndr
11746	[X]Drug addiction - cocaine
49565	[X]Mental & behav dis due to use cocaine: psychotic disorder
43101	[X]Mental & behav disorder due other stimulants inc caffein
44742	[X]Mnt/beh dis due oth stim inc caffein: acute intoxication
10045	[X]Drug addiction-other stimul
49879	[X]Mental/behav dis oth stims inc caffeine: psychotic dis
50265	[X]Mental and behavioural disorders due to use hallucinogens
47784	[X]Drug addiction - hallucinogen
54983	[X]Mental & behav dis due to hallucinogens: psychotic disord
31736	[X]Mental & behav disorders due to use of volatile solvents
33585	[X]Drug addiction - solvent
10656	[X]Men & behav disorder multiple drug use/psychoactive subst

60676	[X]Mental/behav dis multi drg use/psychoac subs: acute intox
45208	[X]Mental and behav dis mlti/oth psych sbs: dependence syndr
9615	[X]Drug addiction NOS
56948	[X]Men/beh dis mlt drg use/oth subs: resid/late psychot dis
17281	[X]Schizophrenia, schizotypal and delusional disorders
34236	[X]Schizophrenia
16764	[X]Paranoid schizophrenia
50060	[X]Paraphrenic schizophrenia
35877	[X]Schizophrenic catatonia
20785	[X]Post-schizophrenic depression
24107	[X]Chronic undifferentiated schizophrenia
35848	[X]Simple schizophrenia
94001	[X]Schizophreniform disord NOS
18053	[X]Schizophrenifrm psychos NOS
34966	[X]Schizophrenia, unspecified
39316	[X]Schizotypal disorder
54387	[X]Borderline schizophrenia
26859	[X]Schizotypal personality disorder
28562	[X]Persistent delusional disorders
34389	[X]Delusional disorder
2113	[X]Paranoid psychosis
11172	[X]Paranoid state
47947	[X]Paraphrenia - late
4843	[X]Paranoia
62405	[X]Delusional misidentification syndrome
66077	[X]Other persistent delusional disorders
40981	[X]Delusional dysmorphophobia
25019	[X]Acute and transient psychotic disorders
36720	[X]Acute polymorphic psychot disord without symp of schizoph
21455	[X]Cycloid psychosis
21595	[X]Acute polymorphic psychot disord with symp of schizophren
11778	[X]Acute schizophrenia-like psychotic disorder
59096	[X]Brief schizophreniform disorder
44307	[X]Other acute predominantly delusional psychotic disorders
27770	[X]Psychogenic paranoid psychosis
34168	[X]Acute and transient psychotic disorder, unspecified
31707	[X]Brief reactive psychosis NOS
29651	[X]Reactive psychosis
51302	[X]Induced delusional disorder
47230	[X]Induced paranoid disorder
11973	[X]Induced psychotic disorder
9422	[X]Schizoaffective disorders
33847	[X]Schizoaffective disorder, manic type

16905	[X]Schizoaffective psychosis, manic type
11055	[X]Schizoaffective disorder, depressive type
35274	[X]Schizoaffective psychosis, depressive type
41022	[X]Schizophreniform psychosis, depressive type
33693	[X]Schizoaffective disorder, mixed type
37580	[X]Mixed schizophrenic and affective psychosis
37681	[X]Schizoaffective disorder, unspecified
33410	[X]Schizoaffective psychosis NOS
30985	[X]Other nonorganic psychotic disorders
31738	[X]Chronic hallucinatory psychosis
11244	[X]Unspecified nonorganic psychosis
694	[X]Psychosis NOS
5726	[X]Mood - affective disorders
12173	[X]Manic episode
9521	[X]Bipolar disorder, single manic episode
2741	[X]Hypomania
13024	[X]Mania without psychotic symptoms
21065	[X]Mania with psychotic symptoms
37102	[X]Mania with mood-congruent psychotic symptoms
48632	[X]Mania with mood-incongruent psychotic symptoms
32088	[X]Other manic episodes
44513	[X]Manic episode, unspecified
4678	[X]Mania NOS
6874	[X]Bipolar affective disorder
1531	[X]Manic-depressive illness
6710	[X]Manic-depressive psychosis
66153	[X]Manic-depressive reaction
16808	[X]Bipolar affective disorder, current episode hypomanic
28277	[X]Bipolar affect disorder cur epi manic with psychotic symp
16562	[X]Bipolar affect disorder cur epi mild or moderate depressn
23713	[X]Bipol aff disord, curr epis sev depress, no psychot symp
4732	[X]Bipolar affect dis cur epi severe depres with psyc symp
44693	[X]Bipolar affective disorder, current episode mixed
27584	[X]Bipolar affective disorder, currently in remission
53840	[X]Other bipolar affective disorders
51032	[X]Recurrent manic episodes
33751	[X]Bipolar affective disorder, unspecified
3292	[X]Recurrent depressive disorder
8851	[X]Recurrent episodes of depressive reaction
19696	[X]Recurrent episodes of psychogenic depression
8902	[X]Recurrent episodes of reactive depression
8826	[X]SAD - Seasonal affective disorder
29784	[X]Recurrent depressive disorder, current episode mild

29520	[X]Recurrent depressive disorder, current episode moderate
33469	[X]Recurr depress disorder cur epi severe without psyc sympt
11329	[X]Endogenous depression without psychotic symptoms
11252	[X]Major depression, recurrent without psychotic symptoms
29451	[X]Manic-depress psychosis,depressd,no psychotic symptoms
47009	[X]Recurrent depress disorder cur epi severe with psyc symp
23731	[X]Endogenous depression with psychotic symptoms
28677	[X]Manic-depress psychosis,depressed type+psychotic symptoms
32941	[X]Recurr severe episodes/major depression+psychotic symptom
31757	[X]Recurr severe episodes/psychogenic depressive psychosis
16861	[X]Recurrent severe episodes of psychotic depression
37764	[X]Recurrent severe episodes/reactive depressive psychosis
1917	Alzheimer's disease
16797	Alzheimer's disease with early onset
32057	Alzheimer's disease with late onset
11136	Pick's disease
29512	Senile degeneration of brain
4321	Parkinson's disease
51105	Postencephalitic parkinsonism
24001	Secondary parkinsonism due to other external agents
26181	Secondary parkinsonism, unspecified
14912	Parkinson's disease NOS
35006	Other extrapyramidal disease and abnormal movement disorders
21863	Other basal ganglia degenerative diseases
8956	Parkinsonism with orthostatic hypotension
40553	Progressive supranuclear ophthalmoplegia
35839	Shy-Drager syndrome
6787	Other/unspecified extrapyramidal/abnormal movement disorders
33868	Unspecified extrapyramidal disease
36319	Extrapyramidal disease and abnormal movement disorder NOS
21216	Spinocerebellar disease
8692	Cerebellar disease
4165	Friedreich's ataxia
3514	Hereditary spastic paraplegia
5128	Primary cerebellar degeneration
2336	Cerebellar ataxia NOS
33839	Cerebellar ataxia due to alcoholism
20206	Cerebellar ataxia in disease NOS
27331	Spinocerebellar disease NOS
21889	Anterior horn cell disease

9179	Spinal muscular atrophy
4796	Motor neurone disease
27377	Progressive bulbar palsy
18084	Pseudobulbar palsy
20845	Primary lateral sclerosis
20120	Motor neurone disease NOS
17194	Other diseases of spinal cord
5195	Syringomyelia
47358	Syringobulbia
56342	Vascular myelopathies
17216	Myelopathy due to acute infarction of spinal cord
45714	Subacute necrotic myelopathy
33535	Anterior spinal artery thrombosis
7736	Subacute combined degeneration of spinal cord
67422	Myelopathy due to neoplastic disease
8920	Myelopathy due to spondylosis
62758	Radiation induced myelopathy
4844	Myelopathy NOS
8816	Cord compression NOS
16564	Spinal cord compression NOS
34445	Other central nervous system disorders
40501	Central pontine myelinosis
5095	Binswanger's disease
54300	Other specified central nervous system demyelination NOS
12054	Central nervous system demyelination NOS
1749	Hemiplegia
807	Hemiparesis
20122	Spastic hemiplegia
35106	Spastic foot
8933	Left hemiplegia
8862	Left sided weakness
3293	Right hemiplegia
2713	Right sided weakness
8492	Hemiplegia NOS
2069	Congenital cerebral palsy
15530	Congenital spastic cerebral palsy
5560	Infantile cerebral palsy
25324	Congenital diplegia
37160	Congenital paraplegia
5512	Cerebral palsy with spastic diplegia
45551	Congenital diplegia NOS
27966	Congenital hemiplegia
21249	Congenital quadriplegia

33925	Congenital monoplegia
2019	Infantile hemiplegia NOS
53178	Other congenital cerebral palsy
25570	Spastic cerebral palsy
52659	Ataxic diplegic cerebral palsy
12666	Other infantile cerebral palsy NOS
28306	Congenital cerebral palsy NOS
39630	Other paralytic syndromes
9271	Quadriplegia
16117	Tetraplegia
35540	Spastic tetraplegia
3063	Paraplegia
9375	Spastic paraplegia
22907	Diplegia of upper limbs
16033	Monoplegia of lower limb
23632	Monoplegia of upper limb
45795	Monoplegia unspecified
15277	Cauda equina syndrome
30941	Atonic bladder
5309	Neurogenic bladder
37444	Neuropathic bladder
2848	Other specified paralytic syndromes
9385	Progressive supranuclear palsy
18688	Todd's paralysis
7037	Steele-Richardson-Olszewski syndrome
39082	Other paralytic syndromes NOS
7167	Specified palsy NEC
2640	Paralysis NOS
573	Epilepsy
11186	Generalised nonconvulsive epilepsy
2907	Petit mal (minor) epilepsy
1715	Epileptic absences
24309	Epileptic seizures - atonic
31830	Epileptic seizures - akinetic
17399	Juvenile absence epilepsy
26144	Generalised convulsive epilepsy
988	Grand mal (major) epilepsy
22804	Tonic-clonic epilepsy
37782	Neonatal myoclonic epilepsy
18471	Epileptic seizures - clonic
4801	Epileptic seizures - myoclonic
5152	Epileptic seizures - tonic
8187	Tonic-clonic epilepsy

5668	Grand mal seizure
45927	Other specified generalised convulsive epilepsy
40806	Generalised convulsive epilepsy NOS
9886	Petit mal status
5117	Grand mal status
4093	Status epilepticus
32288	Partial epilepsy with impairment of consciousness
3175	Temporal lobe epilepsy
23634	Psychomotor epilepsy
55665	Limbic system epilepsy
34079	Epileptic automatism
11394	Complex partial epileptic seizure
31920	Partial epilepsy with impairment of consciousness NOS
26015	Partial epilepsy without impairment of consciousness
9569	Jacksonian, focal or motor epilepsy
5525	Focal epilepsy
48134	Sensory induced epilepsy
37592	Somatosensory epilepsy
26733	Partial epilepsy without impairment of consciousness OS
27526	Partial epilepsy without impairment of consciousness NOS
4478	Infantile spasms
7945	Hypsarrhythmia
23415	Salaam attacks
21885	Post-ictal state
19363	Juvenile myoclonic epilepsy
30604	Alcohol-induced epilepsy
56359	Menstrual epilepsy
30635	Photosensitive epilepsy
6271	Status epilepticus, unspecified
38307	Other forms of epilepsy
9887	Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset
25330	Complex partial status epilepticus
19170	Benign Rolandic epilepsy
9979	Other forms of epilepsy NOS
9747	Epilepsy NOS
3607	Fit (in known epileptic) NOS
18987	Cataplexy
11779	Narcolepsy
34338	Other conditions of brain
15469	Cerebral cysts
5585	Arachnoid cyst
39908	Porencephalic cyst
55176	Cerebral cyst NOS

5118	Anoxic brain damage
5644	Anoxic - ischaemic encephalopathy
38532	Persistent vegetative state
5433	Benign intracranial hypertension
3802	Unspecified encephalopathy
67435	Compression of brain
54324	Brain stem compression
61725	Posterior fossa compression syndrome
9560	Cerebral oedema
32762	Cerebral calcification
60547	Cerebral fungus
23625	Other conditions of brain NOS
27300	Brain conditions NOS
59568	Other nervous system disorders
19510	Intracranial hypotension following ventricular shunting
24459	Meninges disorder NEC
40237	Cyst of the spinal meninges
26159	Chemical meningitis
35306	Disorder of central nervous system, unspecified
20641	Cerebrospinal fluid rhinorrhoea
22034	Pseudomeningocoele
5457	Cord compression
12547	Spinal cord compression
12793	Hemiparesis
65275	Hemiparesis NOS
5110	Vascular headache, not elsewhere classified
36531	Other specified disorders of central nervous system
41646	Other central nervous system disorders NOS
7603	Sleep apnoea
8148	Obstructive sleep apnoea
38686	Sleep-related respiratory failure
69831	[X]Other epilepsy
53773	[X]Other hydrocephalus
33673	Conduction disorders
19191	Conduction disorders of heart
4549	Heart block
3810	Complete atrioventricular block
24377	Third degree atrioventricular block
3603	Partial atrioventricular block
12149	First degree atrioventricular block
10922	Mobitz type II atrioventricular block
27928	Mobitz type I (Wenckebach) atrioventricular block
36629	Second degree atrioventricular block

27375	Atrioventricular block NOS
7482	Left bundle branch hemiblock
17840	Left bundle branch block
53826	Left bundle branch hemiblock NOS
26318	Left main stem bundle branch block
9906	Right bundle branch block
18117	Other bundle branch block
3032	Bundle branch block unspecified
10712	Trifascicular block
17206	Bifascicular block
39003	Other bundle branch block NOS
39843	Other heart block
18437	Sinoatrial block
46178	Other heart block NOS
25147	Anomalous atrioventricular excitation
32059	Ventricular pre-excitation
8230	Wolff-Parkinson-White syndrome
27874	Other conduction disorders
34326	Lown-Ganong-Levine syndrome
5714	Atrioventricular dissociation
19337	Long Q-T syndrome
3769	Stokes-Adams syndrome
36227	Conduction disorders NOS
4044	Cardiac dysrhythmias
6503	Cardiac arrhythmias
23647	Paroxysmal atrioventricular tachycardia
51845	Paroxysmal junctional tachycardia
29491	Paroxysmal nodal tachycardia
3418	Paroxysmal ventricular tachycardia
7794	Ventricular tachycardia
25266	Paroxysmal tachycardia unspecified
1381	Paroxysmal tachycardia NOS
2212	Atrial fibrillation and flutter
1664	Atrial fibrillation
1757	Atrial flutter
1268	Paroxysmal atrial fibrillation
23437	Atrial fibrillation and flutter NOS
4374	Ventricular fibrillation and flutter
4827	Ventricular fibrillation
25583	Cardiac arrest-ventricular fibrillation
41916	Ventricular fibrillation and flutter NOS
2099	Cardiac arrest
25407	Cardio-respiratory arrest

33402	Asystole
33899	Cardiac arrest with successful resuscitation
49882	Cardiac arrest, unspecified
9023	Atrial premature depolarization
29654	Junctional premature depolarization
31809	Ventricular premature depolarization
7827	Other cardiac dysrhythmias
27463	Pulsus alternans
18268	Severe sinus bradycardia
5576	Sick sinus syndrome
7410	Sinoatrial node dysfunction NOS
23494	Wandering atrial pacemaker
8651	Nodal rhythm disorder
9515	Bigeminal pulse
31690	Re-entry ventricular arrhythmia
31133	Other cardiac dysrhythmia NOS
1535	Cardiac dysrhythmia NOS
2062	Heart failure
1223	Cardiac failure
398	Congestive heart failure
2906	Congestive cardiac failure
10079	Right heart failure
10154	Right ventricular failure
9524	Biventricular failure
23707	Acute congestive heart failure
32671	Chronic congestive heart failure
27884	Decompensated cardiac failure
11424	Compensated cardiac failure
884	Left ventricular failure
23481	Asthma - cardiac
5942	Impaired left ventricular function
5255	Acute left ventricular failure
27964	Acute heart failure
4024	Heart failure NOS
12590	Weak heart
17278	Cardiac failure NOS
509	Cardiomegaly
13578	Dilatation - cardiac
15889	Atrial dilatation
3729	Ventricular dilatation
42014	Cardiac dilatation NOS
33348	Atrial hypertrophy
2724	Ventricular hypertrophy

562	Left ventricular hypertrophy
61124	Cardiac hypertrophy NOS
14904	Cardiomegaly NOS
8966	Left ventricular systolic dysfunction
12550	Left ventricular diastolic dysfunction
2418	Cerebrovascular disease
1786	Subarachnoid haemorrhage
29939	Ruptured berry aneurysm
19412	Subarachnoid haemorrhage from middle cerebral artery
42331	Subarachnoid haemorrhage from anterior communicating artery
9696	Subarachnoid haemorrhage from posterior communicating artery
41910	Subarachnoid haemorrhage from basilar artery
17326	Subarachnoid haemorrh from intracranial artery, unspecif
23580	Subarachnoid haemorrhage NOS
5051	Intracerebral haemorrhage
6960	CVA - cerebrovascular accid due to intracerebral haemorrhage
18604	Stroke due to intracerebral haemorrhage
31595	Cortical haemorrhage
40338	Internal capsule haemorrhage
46316	Basal nucleus haemorrhage
13564	Cerebellar haemorrhage
7912	Pontine haemorrhage
62342	Bulbar haemorrhage
30202	Intracerebral haemorrhage, intraventricular
57315	Intracerebral haemorrhage, multiple localized
31060	Intracerebral haemorrhage in hemisphere, unspecified
28314	Left sided intracerebral haemorrhage, unspecified
19201	Right sided intracerebral haemorrhage, unspecified
3535	Intracerebral haemorrhage NOS
31805	Other and unspecified intracranial haemorrhage
36178	Extradural haemorrhage - nontraumatic
4273	Subdural haemorrhage - nontraumatic
17734	Subdural haematoma - nontraumatic
18912	Subdural haemorrhage NOS
20284	Intracranial haemorrhage NOS
45781	Precerebral arterial occlusion
57495	Infarction - precerebral
32447	Basilar artery occlusion
4240	Carotid artery occlusion
2156	Stenosis, carotid artery
4152	Thrombosis, carotid artery

40847	Vertebral artery occlusion
2652	Carotid artery stenosis
23671	Cerebral infarct due to thrombosis of precerebral arteries
24446	Cerebral infarction due to embolism of precerebral arteries
8837	Cerebral arterial occlusion
5363	CVA - cerebral artery occlusion
569	Infarction - cerebral
6155	Stroke due to cerebral arterial occlusion
16517	Cerebral thrombosis
36717	Cerebral infarction due to thrombosis of cerebral arteries
15019	Cerebral embolism
34758	Cerebral embolus
27975	Cerebral infarction due to embolism of cerebral arteries
3149	Cerebral infarction NOS
15252	Brainstem infarction NOS
5602	Cerebellar infarction
25615	Brainstem infarction
5185	Lateral medullary syndrome
9985	Left sided cerebral infarction
10504	Right sided cerebral infarction
26424	Infarction of basal ganglia
504	Transient cerebral ischaemia
3132	Drop attack
1433	Transient ischaemic attack
2417	Vertebro-basilar insufficiency
23942	Basilar artery syndrome
5268	Insufficiency - basilar artery
33377	Vertebral artery syndrome
21118	Vertebro-basilar artery syndrome
23465	Subclavian steal syndrome
44765	Carotid artery syndrome hemispheric
6489	Transient global amnesia
10794	Vertebrobasilar insufficiency
19354	Other transient cerebral ischaemia
1895	Transient cerebral ischaemia NOS
15788	Transient cerebral ischaemia NOS
1469	Stroke and cerebrovascular accident unspecified
1298	CVA unspecified
6253	Stroke unspecified
6116	CVA - Cerebrovascular accident unspecified
18689	Middle cerebral artery syndrome
19280	Anterior cerebral artery syndrome
19260	Posterior cerebral artery syndrome

8443	Brain stem stroke syndrome
17322	Cerebellar stroke syndrome
33499	Pure motor lacunar syndrome
51767	Pure sensory lacunar syndrome
7780	Left sided CVA
12833	Right sided CVA
16956	Cerebral palsy, not congenital or infantile, acute
13577	Other cerebrovascular disease
11171	Cerebral atherosclerosis
5184	Precerebral atherosclerosis
40053	Generalised ischaemic cerebrovascular disease NOS
24385	Chronic cerebral ischaemia
12555	Generalised ischaemic cerebrovascular disease NOS
3979	Hypertensive encephalopathy
31816	Hypertensive crisis
4635	Cerebral aneurysm, nonruptured
22018	Dissection of cerebral arteries, nonruptured
35059	Carotico-cavernous sinus fistula
22400	Cerebral arteritis
10189	Cerebral amyloid angiopathy
37947	Nonpyogenic venous sinus thrombosis
39344	Cereb infarct due cerebral venous thrombosis, nonpyogenic
51759	Occlusion and stenosis of middle cerebral artery
37493	Other cerebrovascular disease NOS
23361	Late effects of cerebrovascular disease
48149	Sequelae of intracerebral haemorrhage
43451	Sequelae of other nontraumatic intracranial haemorrhage
39403	Sequelae of cerebral infarction
51138	Sequelae/other + unspecified cerebrovascular diseases
6228	Sequelae of stroke,not specfd as h'morrhage or infarction
40758	Cereb infarct due unsp occlus/stenos precerebr arteries
33543	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
51311	Other specified cerebrovascular disease
10062	Cerebrovascular disease NOS
2075	Arterial, arteriole and capillary disease
21321	Capillary disease
5640	Atherosclerosis
996	Arteriosclerosis
1318	Aortic atherosclerosis
19155	Aorto-iliac disease
16284	Renal artery atherosclerosis
14797	Extremity artery atheroma
16260	Extremity artery atheroma NOS

12888	Acquired renal artery stenosis
5168	Other specified artery atheroma
37199	Carotid artery atherosclerosis
22677	Carotid artery disease
3995	Arteriosclerotic vascular disease NOS
1735	Aortic aneurysm
16521	Dissecting aortic aneurysm
27563	Thoracic aortic aneurysm which has ruptured
16800	Ruptured thoracic aortic aneurysm
23532	Thoracic aortic aneurysm without mention of rupture
17767	Abdominal aortic aneurysm which has ruptured
13572	Ruptured abdominal aortic aneurysm
63920	Ruptured suprarenal aortic aneurysm
1867	Abdominal aortic aneurysm without mention of rupture
17345	AAA - Abdominal aortic aneurysm without mention of rupture
45521	Juxtarenal aortic aneurysm
28109	Inflammatory abdominal aortic aneurysm
15304	Ruptured aortic aneurysm NOS
16034	Aortic aneurysm without mention of rupture NOS
40787	Thoracoabdominal aortic aneurysm, without mention of rupture
9759	Leaking abdominal aortic aneurysm
6872	Aortic aneurysm NOS
9454	Other aneurysm
33613	Aneurysm of brachial artery
25438	Aneurysm of radial artery
18478	Aneurysm of renal artery
17560	Aneurysm of iliac artery
16395	Aneurysm of common iliac artery
58794	Aneurysm of internal iliac artery
59671	Aneurysm of iliac artery NOS
45000	Aneurysm of leg artery
6684	Aneurysm of femoral artery
16366	Aneurysm of popliteal artery
28573	Arterial false aneurysm
18012	False aneurysm
41171	Aneurysm of other artery
31876	Aneurysm of common carotid art
50678	Aneurysm of external carotid artery
36390	Aneurysm of internal carotid artery
38732	Aneurysm of splenic artery
27389	Aneurysm of hepatic artery
16068	Other aneurysm NOS
3588	Aneurysm NOS

5943	Other peripheral vascular disease
5702	Peripheral ischaemic vascular disease
1826	Ischaemia of legs
6827	Peripheral ischaemia
1231	Raynaud's syndrome
1002	Raynaud's disease
5595	Raynaud's phenomenon
23880	Vibratory white finger
39097	Raynaud's syndrome NOS
34638	Thromboangiitis obliterans
23497	Buerger's disease
9204	Peripheral gangrene
5414	Gangrene of toe
12735	Gangrene of foot
39949	Gangrene of finger
38907	Other specified peripheral vascular disease
34152	Diabetic peripheral angiopathy
4317	Acrocyanosis
22834	Acroparaesthesia - Schultze's type
3715	Acroparaesthesia - unspecified
15272	Erythrocyanosis
10500	Erythromelalgia
4325	Other specified peripheral vascular disease NOS
3530	Peripheral vascular disease NOS
1517	Intermittent claudication
6853	Claudication
15863	Spasm of peripheral artery
2760	Peripheral vascular disease NOS
4289	Arterial embolism and thrombosis
8998	Arterial embolus and thrombosis
9364	Thrombosis - arterial
28004	Arterial embolic and thrombotic occlusion
15253	Embolism and thrombosis of the abdominal aorta
31900	Aortic bifurcation syndrome
5650	Aortoiliac obstruction
51574	Leriche's syndrome
23477	Saddle embolus
45645	Embolism and thrombosis of the thoracic aorta
44085	Embolism and thrombosis of an arm or leg artery
34159	Embolism and thrombosis of the brachial artery
29372	Embolism and thrombosis of the radial artery
62368	Embolism and thrombosis of the ulnar artery
30495	Embolism and thrombosis of an arm artery NOS

2065	Embolism and thrombosis of the femoral artery
4539	Embolism and thrombosis of the popliteal artery
44835	Embolism and thrombosis of a leg artery NOS
15302	Peripheral arterial embolism and thrombosis NOS
32235	Embolism and thrombosis of other specified artery
54865	Embolism and/or thrombosis of the common iliac artery
27494	Embolism and thrombosis of the iliac artery unspecified
6900	Embolism and thrombosis of the subclavian artery
66981	Embolism and thrombosis of the splenic artery
31460	Embolism and thrombosis of the axillary artery
41597	Embolism and thrombosis of other arteries NOS
3714	Arterial embolism and thrombosis NOS
1471	Polyarteritis nodosa
6157	Kawasaki disease
20509	Hypersensitivity angiitis
62277	Hypersensitivity arteritis
26860	Goodpasture's syndrome
23569	Hypersensitivity angiitis NOS
4810	Wegener's granulomatosis
10432	Giant cell arteritis
9843	Cranial arteritis
3275	Temporal arteritis
49149	Horton's disease
68403	Giant cell arteritis NOS
21697	Thrombotic thrombocytopenic purpura
37640	Takayasu's disease
21602	Churg-Strauss vasculitis
18380	Juvenile polyarteritis
30532	Necrotising vasculopathy, unspecified
68136	Polyarteritis nodosa and allied conditions NOS
41225	Other disorders of arteries and arterioles
2995	Acquired arteriovenous fistula
3005	Stricture of artery
28742	Rupture of artery
44709	Aorto-duodenal fistula
4649	Arteritis unspecified
23533	Aortitis
56024	Other disorders of arteries and arterioles
33513	Fibromuscular hyperplasia of arteries NOS
26877	Other disorders of arteries and arterioles NOS
50241	Anterior spinal and vertebral artery compression syndromes
18423	Arterial insufficiency
1470	Vasculitis

8610	Iliac artery occlusion
7694	Femoral artery occlusion
9554	Popliteal artery occlusion
4550	Diseases of capillaries
4942	Hereditary haemorrhagic telangiectasia
35157	Rendu - Osler - Weber disease
20361	Non-neoplastic naevus
2217	Spider naevus
66897	Araneus naevus
24332	Senile naevus
93385	Telangiectasia
3226	Other and unspecified diseases of capillaries
22651	Capillary haemorrhage
40276	Capillary hyperpermeability
9374	Capillaritis
38602	Other specified arterial, arteriole or capillary disease
8323	Arterial, arteriole and capillary diseases NOS
1641	Oesophageal varices
11972	Varices - other
24989	Oesophageal varices with bleeding
30655	Oesophageal varices without bleeding
26319	Oesophageal varices in cirrhosis of the liver
8363	Oesophageal varices in alcoholic cirrhosis of the liver
28929	Gastric varices
10797	Oesophageal varices NOS
1001	Chronic obstructive pulmonary disease
998	Chronic obstructive airways disease
148	Bronchitis unspecified
17359	Chest infection - unspecified bronchitis
7092	Recurrent wheezy bronchitis
3163	Tracheobronchitis NOS
1934	Laryngotracheobronchitis
152	Wheezy bronchitis
3480	Bronchitis NOS
3243	Chronic bronchitis
25603	Simple chronic bronchitis
15626	Chronic catarrhal bronchitis
16717	Smokers' cough
11150	Mucopurulent chronic bronchitis
40159	Purulent chronic bronchitis
61513	Mucopurulent chronic bronchitis NOS
27819	Obstructive chronic bronchitis
5798	Chronic asthmatic bronchitis

5909	Chronic wheezy bronchitis
14798	Emphysematous bronchitis
1446	Acute exacerbation of chronic obstructive airways disease
24248	Mixed simple and mucopurulent chronic bronchitis
23618	Chronic tracheitis
45089	Chronic tracheobronchitis
15157	Chronic bronchitis NOS
794	Emphysema
26306	Chronic bullous emphysema
68662	Zonal bullous emphysema
99536	Bullous emphysema with collapse
23492	Chronic bullous emphysema NOS
10980	Centrilobular emphysema
40788	Other emphysema
16410	Other emphysema NOS
33450	Emphysema NOS
2195	Bronchiectasis
20364	Recurrent bronchiectasis
41491	Post-infective bronchiectasis
32679	Bronchiectasis NOS
11312	Extrinsic allergic alveolitis
15588	Farmers' lung
27345	Bird-fancier's lung
31447	Pigeon-fanciers' lung
26278	pneumonitis
51858	Other allergic alveolitis
11833	Hypersensitivity pneumonitis NOS
10863	Mild chronic obstructive pulmonary disease
10802	Moderate chronic obstructive pulmonary disease
9876	Severe chronic obstructive pulmonary disease
12166	Other specified chronic obstructive airways disease
21061	Chronic obstruct pulmonary dis with acute lower resp infectn
7884	Chron obstruct pulmonary dis wth acute exacerbation, unspec
5710	Chronic obstructive airways disease NOS
37247	Chronic obstructive pulmonary disease NOS
21973	Lung disease due to external agents
25013	Pneumoconioses
21257	Occupational lung disease
19492	Coal workers' pneumoconiosis
8303	Asbestosis
5005	Pleural plaque disease due to asbestosis
51410	Asbestosis NOS
46460	Silica and silicate pneumoconiosis

62233	Simple silicosis
71853	Complicated silicosis
89206	Massive silicotic fibrosis
23446	Silica pneumoconiosis NOS
30235	Siderosis
23461	Pneumoconiosis due to inorganic dust NOS
37365	Byssinosis
26442	Cannabinosis
31423	Pneumoconiosis NOS
31722	Respiratory disease due to chemical fumes and vapours
54830	Acute bronchitis due to chemical fumes
49025	Acute pneumonitis due to chemical fumes
20448	Upper respiratory inflammation due to chemical fumes
47142	Chronic respiratory conditions due to chemical fumes
64721	Chronic emphysema due to chemical fumes
47782	Chronic pulmonary fibrosis due to chemical fumes
9711	Pneumonitis due to inhalation of solids or liquids
10992	Aspiration pneumonitis
3847	Pneumonitis due to inhalation of food or vomitus
41781	Pneumonitis due to inhalation of regurgitated food
45948	Pneumonitis due to inhalation of vomitus
56385	Vomit inhalation pneumonitis
25054	Aspiration pneumonia due to vomit
56647	Pneumonitis due to inhalation of oil or essence
54252	Pneumonitis due to inhalation of solid or liquid NOS
46066	Pneumonitis due to inhalation of solid or liquid NOS
43285	Progressive massive fibrosis
18130	Acute radiation pneumonitis
22536	Chronic pulmonary fibrosis following radiation
44015	Drug-induced interstitial lung disorders
53205	Acute drug-induced interstitial lung disorders
34001	Lung disease due to external agents NOS
11494	Other respiratory system diseases
978	Pleurisy
23482	Pleurisy without effusion or active tuberculosis
15024	Adhesion of pleura or lung
3409	Thickening of pleura
4428	Calcification of pleura
19207	Acute dry pleurisy
40819	Diaphragmatic pleurisy
37599	Basal pleurisy
47354	Fibrinous pleurisy
31645	Pleurisy without effusion or active tuberculosis NOS

57092	Encysted pleurisy
4493	Haemopneumothorax
6830	Haemothorax
29188	Hydropneumothorax
33577	Hydrothorax
7593	Malignant pleural effusion
18081	Other pleural effusion
947	Pleural effusion NOS
60142	Exudative pleurisy NOS
9559	Pleural effusion NOS
1550	Pneumothorax
27821	Spontaneous tension pneumothorax
23766	Other spontaneous pneumothorax
36017	Acute pneumothorax NOS
2486	Other spontaneous pneumothorax NOS
9101	Spontaneous pneumothorax NOS
28695	Pneumothorax NOS
30214	Pulmonary congestion and hypostasis
1585	Pulmonary congestion
26082	Chronic pulmonary oedema
7321	Pulmonary oedema NOS
7791	Postinflammatory pulmonary fibrosis
31806	Other alveolar and parietoalveolar disease
68814	Pulmonary alveolar microlithiasis
6837	Idiopathic fibrosing alveolitis
5519	Cryptogenic fibrosing alveolitis
6051	Diffuse pulmonary fibrosis
28229	Idiopathic fibrosing alveolitis NOS
22835	Bronchiolitis obliterans organising pneumonia
54308	Other alveolar and parietoalveolar disease
4910	Interstitial pneumonia
15815	Alveolar and parietoalveolar disease NOS
9954	Rheumatoid lung
64799	Rheumatic pneumonia
42940	Lung disease with polymyositis
3859	Pulmonary sarcoidosis
47364	Lung disease with Sjogren's disease
31564	Lung disease with systemic lupus erythematosus
6563	Other diseases of lung
3094	Pulmonary collapse with atelectasis
7324	Atelectasis
8370	Collapse of lung
30406	Post operative atelectasis

22905	Interstitial emphysema
35432	Pneumomediastinum
22915	Pulmonary eosinophilia
31319	Loeffler's syndrome
16439	Tropical eosinophilia
20269	Pulmonary eosinophilia NOS
558	Acute pulmonary oedema unspecified
5293	Acute pulmonary oedema NOS
57678	Adult respiratory distress syndrome
24848	Adult respiratory distress syndrome
24466	Broncholithiasis
36706	Calcification of lung
8317	Interstitial lung disease NEC
1813	Lung disease NOS
11665	Pleural condition, unspecified
37944	Other diseases of trachea and bronchus NEC
35218	Other bronchus disease
2911	Other trachea disease
29172	Stenosis of trachea
15572	Stenosis of bronchus
9653	Bronchospasm
28862	Mediastinitis
46447	Other diseases of mediastinum, NEC
49709	Fibrosis of mediastinum
14914	Diseases of mediastinum, NEC NOS
18052	Disorders of diaphragm
10832	Paralysis of diaphragm
42188	Disorders of diaphragm NOS
16080	Other diseases of respiratory system NEC
4492	Other diseases of respiratory system NOS
17928	Respiratory system diseases NOS
65733	[X]Other specified chronic obstructive pulmonary disease
65060	[X]Other interstitial pulmonary diseases with fibrosis
73095	[X]Other specified pleural conditions
66460	[X]Other specified respiratory disorders
4506	Alcoholic gastritis
13266	Liver, biliary, pancreas + gastrointestinal diseases NEC
48488	Acute and subacute liver necrosis
41480	Acute necrosis of liver
6690	Acute hepatic failure
15855	Acute hepatitis - noninfective
53704	Acute yellow atrophy
55637	Acute necrosis of liver NOS

26490	Subacute hepatic failure
22168	Subacute hepatitis - noninfective
65067	Acute and subacute liver necrosis NOS
6863	Cirrhosis and chronic liver disease
10691	Alcoholic fatty liver
3216	Acute alcoholic hepatitis
4743	Alcoholic cirrhosis of liver
68376	Florid cirrhosis
21713	Alcoholic fibrosis and sclerosis of liver
7885	Alcoholic liver damage unspecified
17330	Alcoholic hepatic failure
1754	Chronic hepatitis
23578	Chronic persistent hepatitis
9029	Chronic active hepatitis
7957	Autoimmune chronic active hepatitis
1755	Chronic aggressive hepatitis
66534	Chronic lobular hepatitis
53877	Chronic hepatitis unspecified
15489	Chronic hepatitis NOS
16725	Cirrhosis - non alcoholic
3450	Diffuse nodular cirrhosis
27438	Cardiac portal cirrhosis
58184	Indian childhood cirrhosis
55454	Portal cirrhosis unspecified
16455	Non-alcoholic cirrhosis NOS
22841	Macronodular cirrhosis of liver
18739	Cryptogenic cirrhosis of liver
1638	Cirrhosis of liver NOS
9494	Biliary cirrhosis
5638	Primary biliary cirrhosis
7943	Alcoholic hepatitis
7602	Chronic alcoholic hepatitis
42843	Other non-alcoholic chronic liver disease
10234	Non-alcoholic fatty liver
1780	Hepatosplenomegaly
25383	Hepatic fibrosis
10572	Steatosis of liver
33597	Other non-alcoholic chronic liver disease NOS
10539	Chronic liver disease NOS
31897	Liver abscess and sequelae of chronic liver disease
46023	Liver abscess - excluding amoebic liver abscess
70524	Liver abscess via umbilicus
4454	Liver abscess NOS

46278	Phlebitis of portal vein
23511	Hepatic coma
22411	Encephalopathy - hepatic
5129	Portal hypertension
10636	Hepatorenal syndrome
24901	[X] Hepatic failure
21769	[X] Liver failure
23775	Liver failure NOS
16062	Hepatic failure
1640	Other liver disorders
31008	Chronic passive liver congestion
41237	Hepatitis in viral diseases EC
71785	Hepatitis in coxsackie virus
4406	Hepatitis in cytomegalic inclusion virus
7947	Hepatitis in infectious mononucleosis
58876	Hepatitis in other viral disease
899	Hepatitis unspecified
15562	Toxic hepatitis
5219	Hepatitis unspecified NOS
49042	Hepatic infarction
36727	Toxic liver disease
22766	Toxic liver disease with cholestasis
36107	Toxic liver disease with hepatic necrosis
41104	Toxic liver disease with acute hepatitis
17219	Toxic liver disease with chronic persistent hepatitis
39351	Toxic liver disease with chronic active hepatitis
44120	Toxic liver disease with fibrosis and cirrhosis of liver
41673	Toxic liver disease, unspecified
48879	Hepatic veno-occlusive disease
18652	Autoimmune hepatitis
27663	Granulomatous hepatitis, not elsewhere classified
25869	Other specified liver disorder
28798	Nonspecific reactive hepatitis
3256	Liver cyst
5037	Other specified liver disorder NOS
15360	Liver disorder NOS
3097	Gastrointestinal haemorrhage
1188	Haematemesis
2712	Vomiting of blood
397	Melaena
27862	Altered blood in stools
20859	Blood in stools altered
12471	Gastrointestinal haemorrhage unspecified

1642	GIB - Gastrointestinal bleeding
15517	Gastric haemorrhage NOS
2150	Intestinal haemorrhage NOS
4354	Upper gastrointestinal haemorrhage
4636	Gastrointestinal tract haemorrhage NOS
2773	Nephritis, nephrosis and nephrotic syndrome
2088	Acute glomerulonephritis
5417	Acute nephritis
20074	Bright's disease
29384	Acute proliferative glomerulonephritis
48261	Acute focal nephritis
20129	Acute glomerulonephritis NOS
2999	Nephrotic syndrome
9840	Nephrotic syndrome with proliferative glomerulonephritis
1803	Nephrotic syndrome with membranous glomerulonephritis
29634	Nephrotic syndrome with minimal change glomerulonephritis
40349	Lipoid nephrosis
23913	Nephrotic syndrome, minor glomerular abnormality
22852	Nephrotic syndrome, focal and segmental glomerular lesions
19316	Nephrotic syndrome, diffuse membranous glomerulonephritis
21947	Nephrotic syn difus mesangial prolifertiv glomerulonephritis
21989	Nephrotic syn,diffuse mesangiocapillary glomerulonephritis
17365	Nephrotic syndrome, diffuse crescentic glomerulonephritis
2471	Nephrotic syndrome in diabetes mellitus
45499	Kimmelstiel - Wilson disease
47672	Nephrotic syndrome in systemic lupus erythematosus
22205	Lupus nephritis
94373	Nephrotic syndrome with other pathological kidney lesions
27427	Nephrotic syndrome NOS
7804	Chronic glomerulonephritis
10647	Nephritis - chronic
11875	Nephropathy - chronic
10809	Chronic membranous glomerulonephritis
65064	Chronic rapidly progressive glomerulonephritis
4669	Chronic focal glomerulonephritis
63615	Other chronic glomerulonephritis NOS
15097	Chronic glomerulonephritis NOS
33580	Nephritis and nephropathy unspecified
4850	Nephritis and nephropathy unspecified
11873	Nephropathy, unspecified
16008	Proliferative nephritis unspecified
5291	Membranous nephritis unspecified
12465	Membranoproliferative nephritis unspecified

7164	Recurrent benign haematuria syndrome
24384	Familial glomerulonephritis in Alport's syndrome
21423	Berger's IgA or IgG nephropathy
50305	Hypocomplementaemic persistent glomerulonephritis NEC
36342	Mesangioproliferative glomerulonephritis NEC
41881	Mesangiocapillary glomerulonephritis NEC
45867	Renal medullary necrosis unspecified
23990	Tubulo-interstit nephritis, not specif as acute or chron
36125	Unspecif nephr synd, diff concentric glomerulonephritis
62520	Unsp nephrit synd, diff endocap prolif glomerulonephritis
30301	Unsp nephrit synd, diff mesang prolif glomerulonephritis
27335	Other nephritis and nephrosis in diseases EC
34669	Other interstitial nephritis
44055	Other nephritis and nephrosis NOS
5182	Unspecified glomerulonephritis NOS
2266	Acute renal failure
10837	Acute renal tubular necrosis
31369	Acute renal medullary necrosis
31402	Necrotising renal papillitis
57919	Acute drug-induced renal failure
25582	Acute renal failure NOS
512	Chronic renal failure
350	Renal failure unspecified
11787	Renal impairment
6842	Impaired renal function
26220	Renal sclerosis unspecified
2304	Atrophy of kidney
7190	Glomerulosclerosis
4480	Renal sclerosis NOS
8919	Impaired renal function disorder
29638	Renal osteodystrophy
66062	Renal rickets
34637	Renal osteodystrophy NOS
30310	Nephrogenic diabetes insipidus
39840	Other impaired renal function disorder
56939	Hypokalaemic nephropathy
17339	Secondary hyperparathyroidism
5072	Renal tubular acidosis
9379	Acute interstitial nephritis
50804	Other impaired renal function disorder NOS
25980	Impaired renal function disorder NOS
7154	Small kidney of unknown cause
43919	Unilateral small kidney

38774	Bilateral small kidneys
38768	Small kidneys unspecified
8668	Glomerular disease
31581	Acute nephritic syndrome
66136	Acute nephritic syndrome, focal+segmental glomerular lesions
17060	Recurrent and persistent haematuria
60856	Recur+persist haematuria difus crescentic glomerulonephritis
85659	IgA nephropathy
21297	Chronic nephritic syndrome
61811	Isoltd prteinur+specfd morph les df mesangiocap glomnephr
59992	Isolated proteinuria, with unspecified morpholog changes
8607	Analgesic nephropathy
41159	Nephropathy induced by other drugs meds and biologl substncs
49150	Other specified nephritis, nephrosis or nephrotic syndrome
15780	Nephritis, nephrosis and nephrotic syndrome NOS
29881	Neuropathic bladder
47607	CVA - cerebrovascular accident in the puerperium
671	Chromosomal anomalies
1543	Down's syndrome - trisomy 21
23489	Mongolism
18415	Trisomy 21
10759	Down's syndrome NOS
35665	Patau's syndrome - trisomy 13
43565	Trisomy 13, mosaicism
19038	Trisomy 13 NOS
33642	Edward's syndrome - trisomy 18
31795	Cri-du-chat syndrome
33948	Wolff - Hirschorn syndrome
12840	Velocardiofacial syndrome
49391	Other condition due to autosomal anomaly
19062	Partial trisomy syndromes
54377	Trisomies of autosomes NEC
34913	Triploidy
18017	Polyploidy
22451	Balanced translocations
24383	Gonadal dysgenesis
4943	Turner's syndrome
51868	Turner's phenotype, mosaicism 45X/46XX or 45X/46XY
34681	Gonadal dysgenesis NOS
15846	Klinefelter's syndrome
54490	Klinefelter's phenotype, karyotype 47XXY
68109	Klinefelter's syndrome, XY/XXY mosaic
4376	Sex chromosome abnormality, male phenotype, unspecified

32782	XXX syndrome
11948	XXY syndrome
37484	Male with structurally abnormal sex chromosome
10628	Fragile X chromosome
9768	Karyotype 47,XYY
32603	Fragile X syndrome
20231	Chromosomal anomalies NOS
26140	Mosaicism NOS
41461	Prader-Willi Syndrome
31426	Laurence-Moon-Biedl syndrome
936	Marfan's syndrome
16087	William syndrome
36679	Waardenburg's syndrome
5550	Gorlin-Chaudhry-Moss syndrome
32441	Usher's syndrome
36477	Trichorhinophalangeal syndrome
37855	Treacher Collins syndrome
44866	Branchio-otorenal dysplasia
32868	Russell - Silver syndrome
33522	Smith - Lemli - Opitz syndrome
21966	Holt - Oram syndrome
10491	Klippel - Trenaunay - Weber syndrome
43325	Rubenstein - Tayi syndrome
43396	Arachnodactyly
26136	Caudal dysplasia sequence
16711	Stickler syndrome
10068	Noonan's syndrome
24395	Alport's syndrome
12357	Beckwith's syndrome
10956	Prader - Willi syndrome
31942	VATER association
25306	Angelman syndrome
31853	Congenital hemihypertrophy
15729	Other anomalies NOS
18041	Anomalies of umbilicus
8112	Burns
1570	Scalds
5080	Burn confined to eye and adnexa
30265	Conjunctival burns
28325	Corneal burns
25946	Eyelid burns
28304	Chemical burn of eyelids and periocular area
41650	Other burns of eyelids and periocular area

12645	Alkaline chemical burn of cornea and conjunctival sac
38387	Acid chemical burn of cornea and conjunctival sac
33523	Other chemical burn of cornea and conjunctival sac
22443	Burn of eyelid NOS
37815	Burn of cornea NOS
9475	Burn of the face, head or neck
11999	Face burns
50509	Head burns
357	Unspecified thickness burn of unspecified part of face/head
40419	Unspecified thickness burn of the eye
14963	Unspecified thickness burn of the lip(s)
35276	Unspecified thickness burn of the nose
50154	Unspecified thickness burn of the scalp
37575	Unspecified thickness burn of the forehead
29128	Unspecified thickness burn of the cheek
29086	Superficial burn of the face, head or neck
37399	Erythema of head or neck, first degree burn
21816	Superficial burn of unspecified part of the face or head
12112	Superficial burn of the ear
39306	Superficial burn of the eye
48916	Superficial burn of the lip(s)
9107	Superficial burn of the scalp
30561	Superficial burn of the cheek
50473	Superficial burn of the neck
50492	Superficial burn of the face, head or neck NOS
35145	Partial thickness burn of the face, head or neck
61517	Superficial part. thickness burn unspecified part face/head
73322	Superficial partial thickness burn of the eye
88998	Lip - 2nd degree burn
70684	Deep partial thickness burn of the ear
38013	Partial thickness burn of the face, head or neck NOS
61254	Full thickness burn of the face, head or neck
35240	Full thickness burn of the scalp
68347	Deep full thickness burn of scalp without loss of body part
10304	Burn of the face, head or neck NOS
4846	Burn of the trunk
5507	Unspecified thickness burn of unspecified part of the trunk
49906	Unspecified thickness burn of the breast
4707	Unspecified thickness burn of the chest wall
1852	Unspecified thickness burn of the abdominal wall
4884	Unspecified thickness burn of the back (excluding buttock)
4379	Unspecified thickness burn of the buttock
27431	Unspecified thickness burn of the genitalia

48930	Unspecified thickness burn of the trunk NOS
60463	Superficial burn of the trunk
51037	Erythema of trunk, 1st degree burn
56523	Superficial burn of unspecified part of the trunk
18958	Superficial burn of the chest wall
47783	Superficial burn of the back (excluding buttock)
37107	Superficial burn of the buttock
33412	Partial thickness burn of the trunk
71545	Superficial partial thickness burn unspecified part of trunk
41902	Superficial partial thickness burn of the abdominal wall
54238	Superficial partial thickness burn of the buttock
60531	Deep partial thickness burn of the buttock
73072	Full thickness burn of the trunk, unspecified
24686	Full thickness burn of the breast
51950	Deep full thickness burn of buttock, with loss of body part
6969	Burn of the trunk NOS
6189	Burn of the arm (excluding wrist and hand)
4352	Unspecified thickness burn of the arm
29636	Unspecified thickness burn of the arm, unspecified
24010	Unspecified thickness burn of the forearm
50356	Unspecified thickness burn of the upper arm
51009	Unspecified thickness burn of the axilla
5659	Unspecified thickness burn of the shoulder
57192	Unspecified thickness burn of the arm NOS
47856	Superficial burn of the arm
41893	Superficial burn of the arm, unspecified
20848	Superficial burn of the forearm
47886	Superficial burn of the upper arm
38855	Superficial burn of the axilla
52353	Superficial burn of the arm NOS
33937	Partial thickness burn of the arm
69010	Superficial partial thickness burn of the arm, unspecified
23842	Superficial partial thickness burn of the forearm
57058	Superficial partial thickness burn of the upper arm
36074	Partial thickness burn of the arm NOS
48279	Full thickness burn of the arm
71411	Full thickness burn of the arm, unspecified
28841	Full thickness burn of the forearm
7099	Burn of the arm (excluding wrist and hand) NOS
6808	Burn of the wrist(s) and hand(s)
27976	Unspecified thickness burn of the wrist and hand
12275	Unspecified degree burn of finger
10618	Unspecified degree burn of hand

12754	Unspecified degree burn of thumb
1922	Unspecified thickness burn of the hand, unspecified
25129	Unspecified thickness burn of a single finger
15260	Unspecified thickness burn of more than one finger
25461	Unspecified thickness burn of the back of hand
54590	Unspecified thickness burn of the wrist
25539	Unspecified thickness burn of the wrist or hand NOS
44868	Superficial burn of the wrist and hand
37801	First degree burn of finger
30390	First degree burn of hand
33931	Superficial burn of the hand, unspecified
32218	Superficial burn of a single finger
43735	Superficial burn of the thumb
40485	Superficial burn of more than one finger
41824	Superficial burn of the thumb and finger(s)
41914	Superficial burn of the palm of hand
32210	Superficial burn of the back of hand
28376	Superficial burn of the wrist
58822	Superficial burn of the wrist or hand NOS
21040	Partial thickness burn of the wrist and hand
51566	Second degree burn of finger
46522	Second degree burn of hand
39961	Superficial partial thickness burn of hand, unspecified
29913	Superficial partial thickness burn of a single finger
44800	Superficial partial thickness burn of the thumb
30324	Superficial partial thickness burn of more than one finger
52441	Superficial partial thickness burn of palm of hand
58074	Superficial partial thickness burn of the wrist
52845	Deep partial thickness burn of a single finger
67346	Deep partial thickness burn of the thumb
54766	Full thickness burn of the back of hand
6388	Burn of wrist or hand NOS
9309	Burn of lower limbs
22856	Leg burns
35035	Unspecified thickness burn of the leg
2206	Unspecified degree burn of the leg, unspecified
3513	Unspecified thickness burn of the foot
36709	Unspecified thickness burn of the ankle
17993	Unspecified thickness burn of the lower leg
33824	Unspecified thickness burn of the knee
14677	Unspecified thickness burn of the thigh
29165	Unspecified thickness burn of the leg NOS
40325	Superficial burn of the leg

39714	Erythema of leg, first degree burn
37407	Superficial burn of the foot
17514	Superficial burn of the ankle
41890	Superficial burn of the knee
17765	Superficial burn of the thigh
33414	Partial thickness burn of the leg
31031	Blister of leg, second degree burn
40596	Superficial partial thickness burn of the foot
52724	Superficial partial thickness burn of the lower leg
60619	Deep partial thickness burn of the thigh
44732	Partial thickness burn of multiple sites of the leg
44861	Partial thickness burn of the leg NOS
44619	Full thickness burn of the leg
48176	Full thickness burn of the foot
55106	Full thickness burn of the thigh
8774	Burn of the lower limb NOS
21763	Burn of multiple specified sites
37469	Unspecified thickness burn of multiple specified sites
25698	Superficial burn of multiple specified sites
52075	Burn of internal organs
22574	Burn of the mouth, unspecified
37116	Burn of the gum
46867	Burn of the oesophagus
71073	Burn of the vagina and uterus
8601	Burns as a percentage of body surface (BS) involved
33411	Burn involving <10% of body surface (BS)
45835	Burn involving 10-19% of body surface (BS)
56883	Burn: 20-29% of body surface NOS
24631	Corrosions involving 30-39% of body surface
48941	Burn involving 40-49% of body surface (BS)
35973	Corrosions involving 40-49% of body surface
17193	Corrosions involving 50-59% of body surface
19906	Corrosions involving 60-69% of body surface
39698	Corrosions involving 70-79% of body surface
31003	Corrosions involving 80-89% of body surface
9202	Burn - unspecified
2215	Unspecified degree of burn NOS
7265	Superficial burn NOS
383	First degree burn
7129	Partial thickness burn NOS
23860	Second degree burn
42205	Deep partial thickness burn NOS
20249	Full thickness burn NOS

24253	Third degree burn
14725	Burn - unspecified
28203	Burns NOS
32760	Opiate poisoning
72893	Unspecified opium poisoning
20458	Heroin poisoning
40317	Methadone poisoning
50661	Sedative and hypnotic drug poisoning
15279	Barbiturate poisoning
97845	Barbiturate poisoning NOS
31082	Chloral hydrate poisoning
23367	Sedative and hypnotic drug poisoning NOS
29288	Sleeping drug poisoning
66559	Ether poisoning
54406	Benzodiazepine poisoning
52966	Diazepam poisoning
71455	Nitrazepam poisoning
42433	Poisoning by temazepam
36231	Cannabis poisoning
31754	Amfetamine poisoning
37544	Ecstasy poisoning
102064	Opiate antagonist poisoning NOS
4340	Nonmedicinal agent causing toxic effects
19217	Alcohol causing toxic effect
8984	Ethyl alcohol causing toxic effect
36714	Ethanol causing toxic effect
102321	Butyl alcohol causing toxic effect
36499	Alcohol causing toxic effect NOS
59055	Petroleum ether causing toxic effect
25290	Toxic effect of homologues of benzene
23855	Other solvents causing toxic effect
42557	Carbon tetrachloride causing toxic effect
56381	Toxic effect of chloroform
51374	Other solvents causing toxic effect
37459	Anoxic brain damage complication
19688	Cerebral anoxia complication
20488	Post operative CSF leak
16148	Peripheral vascular complications of care
17222	Liver failure as a complication of care
10721	Hepatorenal syndrome as a complication of care
11554	Renal failure as a complication of care
39598	Kidney failure as a complication of care
24292	Post operative renal failure

62515 [X]Toxic effects of substances chiefly nonmedicinal source