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An investigation into the association between asthma, osteoporosis, and fractures using electronic health records

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To my parents,
Panayiota and Vasilis

Στους γονείς μου,
Παναγιώτα και Βασίλη

"If I have seen further, it is by standing on the shoulders of giants"

-Isaac Newton

DECLARATION

I, Christos Chalitsios, hereby declare that the work presented in this thesis is my own. Where information has been obtained from other sources, it has been clearly indicated in the thesis.

Signature

Christos Chalitsios

FOREWORD

Christos Chalitsios designed the research protocols, obtained the ethical approvals and the data, and performed the data management, analysis, and interpretation. Christos Chalitsios wrote the first draft of the manuscripts, and the final draft after incorporating the advice and comments from Profs Dominick E. Shaw and Tricia M. McKeever. For each research article, Christos Chalitsios was the first and corresponding author. The inclusion and bias assessment of the studies in the systematic review was simultaneously carried out by the author of this thesis and Prof. Tricia M. McKeever as a second reviewer. The list of codes used in this thesis were developed by the author or, in the case of asthma and corticosteroids medication by collaborating with Prof. Dominick E. Shaw with the help of and in the case of osteoporosis and fractures by collaborating with Prof. Opinder Sahota.

ABSTRACT

Background: Asthma is one of the most common chronic medical condition; however, little is known about patients' bone health.

Methods: Four observational studies were conducted to investigate (i) the incidence of osteoporosis and fragility fractures in people with asthma compared to the general population, (ii) the risk of osteoporosis and fragility fractures due to corticosteroids in asthma, (iii) the prescribing patterns of oral corticosteroids and bisphosphonates as well as the factors associated with their prescribing, and (iv) the risk of subtrochanteric (ST) and femoral shaft (FS) fractures due to bisphosphonates in asthma. Analyses relied on data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES). OpenPrescribing.net was also used to extract prescribing data to answer the 3rd objective. A systematic review and a series of meta-analyses were also performed assessing the current evidence of the impact of corticosteroids on bone health in patients with asthma.

Results: Analysis of incidence showed that patients with asthma had a higher risk of osteoporosis (adjusted hazard ratio (aHR) 1.18, 95% CI 1.13 to 1.23) and were 12% (aHR 1.12, 95% CI 1.07 to 1.16) more likely to sustain fragility fractures than the general population. Age modified the effect of asthma on osteoporosis and fragility fractures, such that the effect was stronger in younger people ($p_{interaction}<0.0001$). The vertebra (aHR 1.40, 95% CI 1.33–1.48) and forearm/wrist (aHR 1.27, 95% CI 1.22–1.32) were the sites linked with a significant risk. The study of corticosteroids effect on bone health found a dose–response relationship between both cumulative dose and number of oral (OCS) and inhaled (ICS) corticosteroids prescriptions and risk of osteoporosis or fragility fractures. After adjusting for confounders, people receiving more OCS prescriptions (≥9 vs 0) had a 4.50 (95% CI 3.21 to 6.11) and 2.16 (95% CI 1.56 to 3.32) increased odds of osteoporosis and fragility fractures, respectively. For ICS (≥11 vs 0)

the odds were 1.60 (95% CI 1.22 to 2.10) and 1.31 (95% CI 1.02 to 1.68). The cumulative dose had a similar impact, with those receiving more OCS or ICS being at greater risk. Our meta-analysis confirmed the above results. There was no effect of ICS on bone loss both at spine and femoral neck in asthma. However, people with asthma receiving OCS were at greater risk of osteoporosis than nonexposed people with asthma (pooled HR = 1.76; 95%CI: 1.48 to 2.09; $I^2 = 68\%$). Similarly, higher ICS exposure was associated with higher odds of osteoporosis (OR=1.20; 95%CI: 1.08 to 1.42) and fractures (pooled OR=1.19; 95%CI: 1.05 to 1.35; $I^2 = 0\%$) when comparing people with asthma receiving ICS and not. When the prescribing of bisphosphonates and OCS was examined, although OCS use was positively associated with bisphosphonates prescribing, variation among practices and Clinical Commissioning Groups (CCG) existed. Of the patients with asthma sustained a ST/FS fracture, 40.3% had received bisphosphonates as compared with 14.2% of the controls corresponding to an aOR of 4.42 (95%CI, 2.98 to 8.53). The duration of use influenced the risk with long-term users to be at a greater risk (> 5 yrs. vs no exposure; aOR= 7.67; 95%CI, 1.75 to 33.91). Drug withdrawal was associated with diminished odds of ST/FS fractures.

Conclusions: These findings have important implications for clinical practice, health policy and future research. Most importantly, results highlight the need to develop an asthma specific bone protection guidance to ensure safer asthma management reducing bone comorbidities and improving patients' quality of life.

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LIST OF PUBLICATIONS

Peer-reviewed publications contributing to my PhD thesis

1. Chalitsios CV, McKeever TM, Shaw DE. Incidence of osteoporosis and fragility fractures in asthma: a UK population-based matched cohort study. ***European Respiratory Journal*** 57, 2001251 (2021). doi.org/10.1183/13993003.01251-2020. (Chapter 5)

2. Chalitsios CV, Shaw DE, McKeever TM. Risk of osteoporosis and fragility fractures in asthma due to oral and inhaled corticosteroids: two population-based nested case-control studies. ***Thorax*** 76,1:21-28 (2021). doi.org/10.1136/thoraxjnl-2020-215664. (Chapter 6)

3. Chalitsios CV, Shaw DE, McKeever TM. Corticosteroids and bone health in patients with asthma: A systematic review and meta-analysis. ***Respiratory Medicine*** 181, 106374 (2021). doi.org/10.1016/j.rmed.2021.106374 (Chapter 7)

4. Chalitsios CV, Shaw DE, McKeever TM. A retrospective database study of oral corticosteroid and bisphosphonate prescribing patterns in England. ***NPJ Primary Care Respiratory Medicine***. 30**,** 5 (2020). doi.org/10.1038/s41533-020-0162-6 (Chapter 8)

5. Chalitsios CV, Shaw DE, McKeever TM. Risk of subtrochanteric and femoral shaft fractures due to bisphosphonate therapy in asthma: A population based nested case-control study. ***Osteoporosis International.*** (2021). doi.org/10.1007/s00198-021-06197-7 (Chapter 9)

Other peer-reviewed publication during my PhD project

6. Chalitsios CV, McKeever TM, Langley TE, Shaw DE. Impact of COVID-19 on corticosteroids and antibiotics prescribing in England: an interrupted time series analysis. ***Journal of Public Health***. fdab017 (2021). doi.org/10.1093/pubmed/fdab017.

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LIST OF ABBREVIATIONS

AFF	Atypical Femoral Fractures
APC	Admitted Patient Care
BMI	Body Mass Index
BNF	British National Formulary
BTS	British Thoracic Society
CCG	Clinical Commissioning Groups
CCI	Charlson Comorbidity Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
DEXA	Dual Energy X-ray Absorptiometry
EHR	Electronic Health Records
FCE	Finished Consultant Episode
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FRAX	Fracture Risk Assessment Tool
FS	Femoral Shaft
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GP	General Practice
HES	Hospital Episode Statistics
(a)HR	(adjusted) Hazard Ratio
HRT	Hormone Replacement Therapy
ICD	International Classification of Diseases
ICS	Inhaled Corticosteroids
IMD	Index of Multiple Deprivation
IQR	Interquartile Range

LABA	Long-Acting Beta$_2$ Agonist
NICE	National Institute for Health Excellence
NHS	National Health System
OCS	Oral Corticosteroids
ONS	Office of National Statistics
(a)OR	(adjusted) Odds Ratio
QOF	Quality and Outcomes Framework
SABA	Short-Acting Beta$_2$ Agonist
SD	Standard Deviation
ST	Subtrochanteric
UK	United Kingdom
USA	United States of America
UTS	Up to Standard
WHO	World Health Organization

1 INTRODUCTION

1.1 Aim

This doctoral thesis aims to understand the current burden and risk of osteoporosis and fragility fractures in asthma and as related to asthma treatment as well as the association between the use of bisphosphonates (medications that reduce the risk of osteoporosis) and the risk of subtrochanteric (ST) and femoral shaft (FS) fractures in asthma to provide bone protection guidance for clinicians and policy makers improving patients' quality of life.

1.2 Motivation

Asthma is one of the most common noncommunicable chronic disease. Although asthma itself can have a major effect on a person's health and wellbeing, paradoxically asthma treatments can also have important and detrimental side effects. Asthma treatments include inhaled (ICS) and oral (OCS) corticosteroids both of which can lead to osteoporosis and fragility fractures. Despite the high prevalence of asthma little is known about these side effects in asthma; in particular, data on osteoporosis are scarce and there are no asthma specific bone protection guidelines either nationally or internationally. This has become more pertinent with the realisation that bisphosphonates might be associated with side effects including atypical femoral fractures (AFF) in the subtrochanteric and femoral shaft regions.

1.3 Objectives

To this end, my research addresses the following objectives:

- To describe the incidence of osteoporosis and fragility fractures in asthma compared to the general population.
- To estimate the risk of osteoporosis and fragility fractures due to OCS and ICS comparing exposed and non-exposed people with asthma.

- To perform a systematic review and meta-analysis quantifying the impact of OCS and ICS on bone mineral density (BMD), and risk of osteoporosis and fractures in asthma.
- To assess OCS and bisphosphonates prescribing patterns at practice level and investigate factors associated with their prescribing.
- To estimate the risk of ST/FS fractures due to bisphosphonate therapy comparing exposed and non-exposed people with asthma.

1.4 Structure

- Chapter 1 provides the aim, rationale, objectives, and structure of the thesis.
- Chapter 2 provides the background to the thesis.
- Chapter 3 describes the databases used in this project.
- Chapter 4 provides basic details of data management.
- Chapter 5 quantifies the incidence of osteoporosis and fragility fractures in asthma compared to the general population.
- Chapter 6 quantifies the risk of osteoporosis and fragility fractures due to corticosteroids in asthma.
- Chapter 7 provides current and comprehensive evidence of the impact of corticosteroids on bone health in asthma.
- Chapter 8 describes the prescribing patterns of OCS and bisphosphonates and investigates factors associated with their prescribing.
- Chapter 9 quantifies the risk of ST/FS fractures due to bisphosphonates in asthma.
- Chapter 10 summarises and discusses the overall findings of this PhD project.

2 BACKGROUND

2.1 Asthma

2.1.1 A brief history of asthma

The word "asthma" originates from the Greek noun "ἅσθμα" which comes from the verb "ἀάζειν (aazein)" meaning "to breathe out with open mouth, to breathe sharply". This word appears in Homer's Iliad about 2700 years ago (in 800 B.C.); but it was Hippocrates who introduced the term "asthma" in medicine at his book entitled "Corpus Hippocraticum". However, the term "asthma" was probably used as a symptom and not as a disease which we know today. In Greek antiquity, the person who presented the first accurate clinical description of asthma was Aretaeus and it was Claudius Galen who described the asthma as an obstruction of bronchial tubes (1).

The term "asthma" appeared in English in A.D. 1600 approximately (2). In 65 A.D. Seneca published a work in which he provided a picturesque description of asthma pointing out its sudden attacks characterized by very brief duration (3,4). It was Henry Hyde Salter, the author of the magnum opus called "On asthma: Its pathology and treatment" (1859), stated that asthma is a "*Paroxysmal dyspnoea of a peculiar character, generally periodic with intervals of healthy respiration between attacks*" (5,6). 33 years later, Sir William Osler, a pioneer of the contemporary medicine presented asthma as following (7):

- *Bronchial spasm.*
- *Oedema of the nasal or respiratory mucosa.*
- *Hay fever and asthma are shared same characteristics.*
- *The sputum is distinctive, and it consists of round gelatinous masses called "perles."*
- *It might begin in early childhood lasting into old age.*
- *A specific type of inflammation of the smaller airways called bronchioles.*

- *Cold infection, diet, emotional disturbances, and climate may induce a paroxysm.*
- *The illness might run in families.*

In 1905, von Pirquet and his student called Schick made the first clinical observation of allergic reaction in children due to intolerance to animal antiserum (8). The next year, Pirquet introduced the term "allergy" in order to describe how the skin react after an injection of tuberculin in sensitised people (9). In 1910, some of the Auer's surveys prompted Meltzer that asthma was an indication of anaphylaxis (10). In 1923, Arthur Coca established the term "atopy" which was a milestone in terms of the better understanding of allergic phenomena (11). As a result, there was a better knowledge about the early and late phase reaction in asthma by the 1980s, whilst the effectiveness of the ICS use (especially of beclomethasone dipropionate) was established by a series of clinical trials in the 70s (12).

2.1.2 Definition of asthma

The Global Initiative for Asthma (GINA) report defined asthma as follows: "*Asthma is a chronic airway inflammation. It is characterised by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation"* (13).

Asthma is one of the most prevalent non-communicable diseases in adults. The main symptoms (cough, wheeze, breathlessness and chest tightness) (14) are non-specific, and asthma is characterised by the pattern of its symptoms and their timings, the response to treatment, asthma triggers, and a variable expiratory airflow limitation which is generally reversible. The disease severity ranges from milder attacks which can interrupt daily life and work productivity, to more severe and life-threatening attacks (13) in which case it can greatly hinder the patient's life and ability to perform regular activities and can even cause death. The few signs of asthma are also non-

specific; the clinician can look for expiratory wheezing and comorbidities such as obesity, bronchiectasis, eczema, and allergic rhinitis to aid with the diagnosis of asthma. Asthma is inherently variable, and therefore asthma patients can experience fluctuating symptoms.

2.1.3 Diagnosis of asthma

The diagnosis of asthma is a combination of identifying a pattern of symptoms (wheezing, dyspnoea, chest tightness, or cough), a variable expiratory airflow limitation and no alternative explanation for these (15), however there is no gold-standard method for its diagnosis (16). A questionnaire about symptoms and what triggers them, any personal or family history of allergies, disorders, or asthma should be included at the initial clinical assessment. Additionally, a range of lung function tests can help a physician's decision, but no one can warrant a diagnosis of asthma as their false positive and negative rates are substantial (17).

A spirometry test can be offered in adults if a diagnosis of asthma is considered. This test should be regarded as positive if the ratio of forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) is less than 70% (13,16,17). In adults, a bronchodilator reversibility test is recommended as an indication of asthma when an increase by more than 12% or 200ml in FEV_1 10-15 min after exposure to β_2-agonists or corticosteroids is presented (13,16,17). An improvement more than 400ml in FEV_1 is a strong predictor of asthma (16). It should be mentioned that a normal spirometry does not rule out a diagnosis of asthma and an obstructive spirometry with positive bronchodilator reversibility test increases the probability of asthma (16). Another type of test is the direct challenge test which measures any change in FEV_1 a set time after inhaling histamine or methacholine (16,17). A provocative concentration of 8 mg/ml or less can be considered as positive (16,17). Indirect challenges such as exercise challenge are other potentially helpful tests, but these tests are less sensitive than the direct challenge tests and cannot be done correctly within a primary care setting (18).

Moreover, variable exploratory airflow can be investigated by average within-day variability of peak expiratory flow (PEF), expressed as amplitude percent mean, of more than 10% in adults (13). The implication of the fractional exhaled nitric oxide (FeNO) test is controversial. Both the British Thoracic Society (BTS) and GINA do not support the use of FeNO for diagnosing asthma (16,19), whereas the National Institute for Health Care and Excellence (NICE) guidelines recommend it (17). The larger the variability or the more times variability is noticed, the greater the probability of asthma (20). It is more likely to document airflow limitation during or after symptoms as it is not always presented, however airflow limitation on its own is not adequate to confirm an asthma diagnosis, as it might be presented in patients with chronic obstructive pulmonary disease (COPD) (20).

Accurate diagnosis of asthma is essential as correct treatment of asthma can reduce the frequency and severity of exacerbations and improve overall quality of life (21). However, the existence of both asthma and COPD in the same does occur (22), the differential diagnosis of COPD and asthma rests on differences in clinical presentation, triggering factors, and on demonstration of reversibility of airflow obstruction. This airflow obstruction is not fully reversible in COPD, whereas it is in asthma. The Dutch hypothesis suggests that both diseases are manifestations of the same disease process, with asthma preceding COPD. The overlap syndrome is then called "Asthma COPD Overlap Syndrome" (ACOS). The other school of thought, sometimes called the British hypothesis, proposes asthma and COPD are distinct disease entities with different causal mechanisms. Asthma and COPD can coexist independently in the same patient according to this hypothesis. The group of individuals with a concomitant diagnosis merits attention, as patients with both asthma and COPD have more frequent exacerbations, increased morbidity and mortality, faster lung function decline and a poorer quality of life than patients with only asthma.

2.1.4 Pathophysiology of asthma

Asthma is a result of a chronic inflammation narrowing and swelling the airways and may produce extra mucus (Figure 2-1). This can make breathing difficult and trigger coughing, wheezing, and shortness of breath. Essentially, the asthma is a result of immune response in the bronchial airways (23). Bronchospasm may be resolved immediately in 1 to 2 hours, or in about 50% of subjects, may become part of a 'late' response, where this initial insult is followed 3 to 12 hours later with further bronchoconstriction and inflammation (24). Asthma symptoms can be different from person to person and over time. Some people may experience an asthma exacerbation when they are exposed to a trigger (e.g. tobacco, smoke, dust mites, and pollen) (16), however there is no single cause of asthma. Certain factors can increase the probability of developing asthma and they can be categorised as genetic and environmental factors (e.g. air pollution) (25).

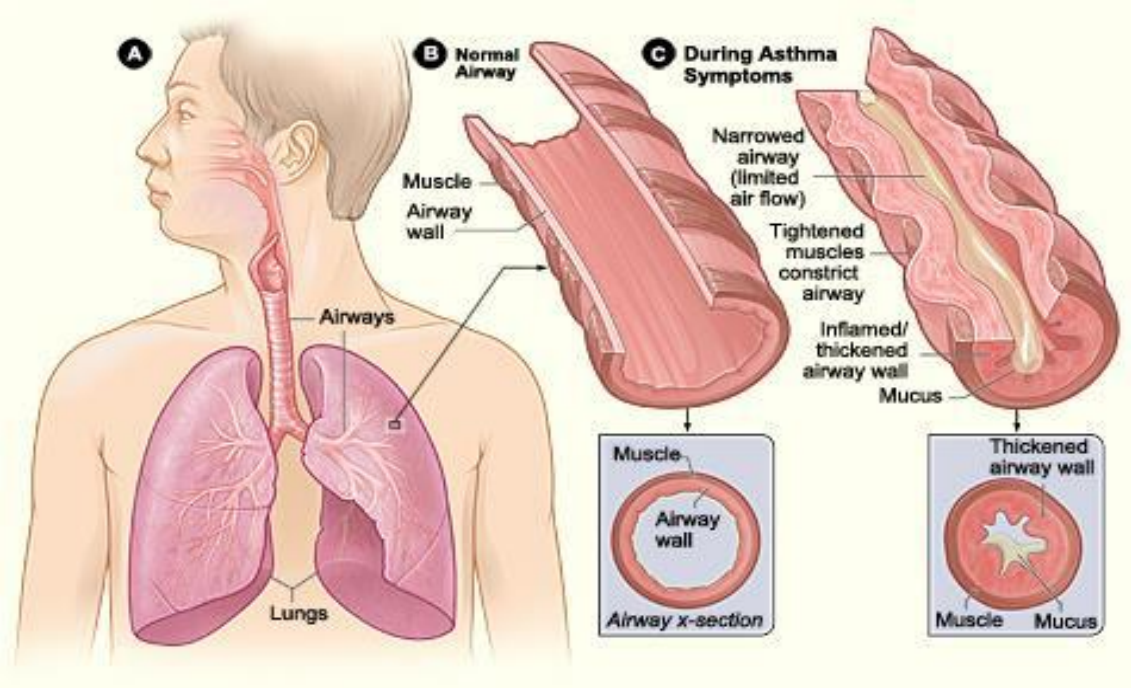

Figure 2-1. *Asthma pathophysiology. A) shows the location of the lungs and airways in the body. B) shows a cross-section of a normal airway. C) shows a cross-section of an airway during asthma*

symptoms. www.nhlbi.nih.gov/health-topics/asthma. Work of the US Federal government; (public domain; free from copyright restriction).

2.1.5 The burden of asthma

Asthma is one of the most common chronic disease affecting 334 million people all over the world (26). It is projected that this figure will increase to 400 million by 2025 (27). In adults, the global prevalence of doctor diagnosed asthma is 4.3% (95% CI 4.2 to 4.4) with a great fluctuation between the developing and developed countries, ranging from 0.2% in China to 21.0% in Australia (28). However, the prevalence of asthma in developing countries is probably underestimated as many people have difficulties accessing in health care and asthma medication is not available (20). The prevalence of asthma in developed countries can be characterized as stable or decreased, whereas in developing countries there is a rapid increase as these countries adopt the western lifestyle (20).

The World Health organisation (WHO) states that 417,918 deaths were asthma-related globally in 2016, with the majority of them to occur in low- and lower-middle income countries (29). Nevertheless, the mortality rates have decreased over time suggesting better asthma management and systematic use of asthma medication (27). In the United States of America (USA), asthma mortality rates reveal a gradual decrease from 1999 to 2015, falling from 2.1 to 1.2 deaths per 100,000 persons (30). Similarly, in Europe, the death rates have also significantly decreased from 6,287 deaths in 1985 to 1,164 in 2012 (31).

Apart from the profound impact on health, asthma has additionally a considerable financial cost for each country. The economic burden of asthma is a combination of its prevalence; the direct costs (e.g. hospital services, doctor visits) and indirect costs (e.g. loss of work productivity). A recent review on the economic burden of asthma demonstrated wide variations in costs across countries (32). Annual direct costs varied

from less than US$150 per patient (Abu Dhabi, United Arab Emirates) to more than US$3,000 per patient in USA (32). All combined, the total cost of asthma in the USA based on the pooled sample amounted to $81.9 billion in 2013 (33). In the EU, the total annual costs of asthma were €33.9 billion, of whom €19.5 and €14.4 billion accounted for the direct and indirect costs, respectively (34).

Asthma is also a major public health issue in the United Kingdom (UK) and has a profound impact on patients, on healthcare resources, and on the wider economy. In the UK, 5.4 million people are currently receiving treatment for asthma of whom 4.3 million are adults (35), and each year 12.7 million working days are lost due to illness. The direct National Health System (NHS) expenditure on asthma is more than £1 billion annually (36), and each day three people die in the UK due to their asthma (35).

2.1.6 Pharmacological treatment of asthma

The main goals of asthma treatment are to minimise the burden of the disease (e.g. activity limitation, sleep disruption) and the risk of adverse events (e.g. exacerbations, death) (20). Asthma treatment is a combination of self-education, asthma management plan, inhaler training (37), minimisation of risk factors, and pharmacological treatment (13). Treatment assessment and adjustment is essential according to each patient symptoms, comorbidities, adverse effects, and satisfaction. The decision-making process should be shared with the patient to improve outcomes (38). Both the BTS/SIGN and GINA asthma guidelines recommend a stepwise approach of pharmacological treatment of asthma (13,16). The approach of each guideline is slightly different; however, the BTS/SIGN approach will be presented as this thesis is based on UK data.

2.1.6.1 British Thoracic Society / Scottish Intercollegiate Guideline Network stepwise approach

In adults, treatment step 1 is defined by either no maintenance treatment or nonregular treatment with low-dose ICS (Figure 2-2). Step 2 includes regular low-dose ICS, step 3 adds an inhaled long-acting β_2 agonist. Step 4 increases the ICS dose to medium and introduces a trial of leukotriene receptor antagonists. Step 5 includes the administration of OCS, which should be minimised due to their systemic side effects. Additional treatment that can be considered in step 5 are add-on antiimmunoglobulin E (anti-IgE) treatment such as omalizumab, anti-interleukin-5 (anti-IL5) treatment such as mepolizumab/reslizumab, or bronchial thermoplasty.

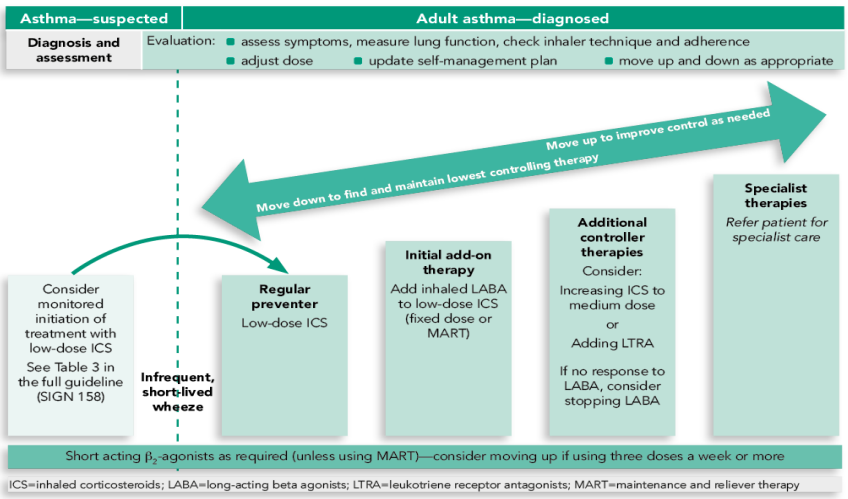

***Figure 2-2**. Summary of asthma management in adults. This figure is reproduced from BTS/SIGN British Guideline on the management of asthma by kind permission of the British Thoracic Society. British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN). British Guideline on the management of asthma. Edinburgh: SIGN; 2019. Available from URL: http://www.sign.ac.uk*

2.1.6.2 Classes of pharmacological treatment of asthma

Inhaled corticosteroids and β_2-agonists are the basis of the pharmacological treatment of asthma. Bronchial inflammation is managed by ICS to prevent exacerbations and breathlessness is relieved by β-agonists through bronchodilatation. Prescribed β-agonists are either short-acting (SABA) or long-acting (LABA). SABA use is for quick relief and is not included in the maintenance treatment steps. On the other hand,

LABA tend to act slower and are included in these treatment steps. Leukotriene receptor antagonists or theophylline can be considered before OCS, although evidence for their efficacy in severe asthma is lacking (20). Long-acting muscarinic antagonists can be used as an add-on therapy in patients at risk of exacerbations, as it modestly improves lung function and increases time to severe exacerbation (39). Omalizumab, an anti-IgE or anti-IL5 treatment, is reserved for patients with moderate to severe asthma as it reduced exacerbations (40) and hospitalisations (41). OCS may be effective for adults with severe asthma (42), but often have severe side-effects (43–45). Other immunosuppressant medications including ciclosporin or methotrexate are not recommended due to adverse effects and limited evidence on the effectiveness of bronchial thermoplasty (42). The roles of macrolide antibiotics and antifungal therapy in asthma remain unclear, as there is no conclusive evidence (42,46). There are some promising emerging therapies including benralizumab (an anti-IL5 antibody) (47) and fevipiprant, a prostaglandin D2 type 2 receptor antagonist (48). Studies on IL-13 antibodies have been discouraging (49,50), but a monoclonal antibody targeting both IL-4 and IL-13 (dupilumab) has shown potential in a clinical trial (51).

2.1.6.2.1 Corticosteroids in management of asthma

Corticosteroids are hormones which modify the expression of nearly 10% of our genes and influence the activity of almost every cell in our body (52). Cortisol is an essential steroid hormone secreted by the adrenal gland and like many other physiological processes in the body has a circadian rhythm. Glucocorticoids are also discharged after a psychological trauma or a serious injury to the body (52). The biologically active form of the glucocorticoid is cortisol which is turned to cortisone and vice versa by the type 2 11-b-hydroxysteroid dehydrogenase and 1 11-b-hydroxysteroid dehydrogenase, respectively (53). Up to now, corticosteroids are a milestone in asthma treatment as they are able to diminish the airway inflammation and hyper-responsiveness controlling asthma symptoms (54).

The effectiveness of ICS in managing symptoms, diminishing exacerbations, and improving the health of people with asthma is well-established. Thus, ICS is the first line for patients who have to use a β_2-agonist inhaler for more than once a day. Furthermore, evidence demonstrates that the early use of ICS might prevent the airways from any irreversible pathological changes (55). Adult asthma patients can be benefitted by ICS at relatively low doses equivalent to 400μg/day of budesonide (56). By increasing ICS doses, patients can observe more benefit, however the risk of side-effects goes up as well (56). Nevertheless, it has been shown that when asthma patients discontinue ICS, then airway responsiveness comes back to baseline values and patients experience aggravated symptoms.

While the majority of patients respond positively to ICS dose, there are some people with severe asthma who do not appear the expected results in terms of their asthma symptoms. It is estimated that 10% of patients have severe asthma (57) out of which 30 to 40% are on regular use of OCS in order to control their asthma (58–60). Oral corticosteroids (also known as systemic corticosteroids) are used to manage asthma exacerbations and difficult asthma. From time to time, longer-term exposure to OCS is inevitable so as difficult-to-treat asthma to be manageable. Oral prednisolone is the most commonly used (61). A plethora of studies have been conducted evaluating the use of OCS control during asthma exacerbations. They show that OCS courses of 5-10 days are efficient in regaining asthma control when an exacerbation occurs (62–64). Furthermore, a study reveals that after an acute asthma exacerbation, a short OCS course can benefit the patient reducing the risk of a relapse and hospital admission (65).

Despite the crucial role of corticosteroids in the management of asthma, there are some recognised side-effects in the general population including osteoporosis and fragility fractures (66,67).

2.2 Osteoporosis

2.2.1 Definition and epidemiology of osteoporosis

The term "osteoporosis" (osteo + porosis) derives from the Greek words (οστέο = osteo = bone + πόρος = poros = pore) and means "porous" bone. Osteoporosis is defined as follows: *"Osteoporosis is characterised by low bone mass, deterioration of microarchitectural bone structure and cortical porosity leading to increased risk of fractures particularly at hip, spine and lower forearm"* (Figure 2-3) (68).

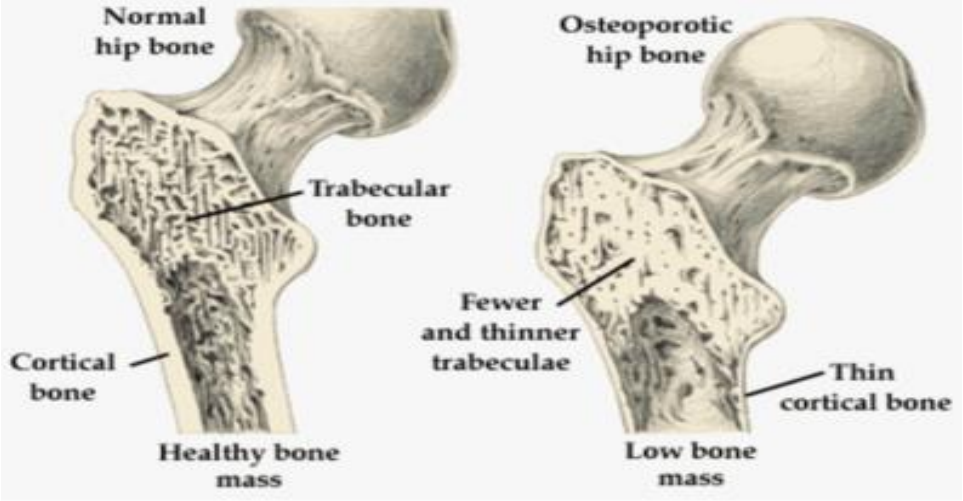

Figure 2-3*. Trabecular and cortical bone tissue in a healthy adult and a patient with osteoporosis.*

The above definition highlights four essential aspects. Firstly, osteoporosis affects the entire body bones (systemic disease). Secondly, low BMD or bone mass is not the only defining feature. Third, it is crucial to emphasize on micro-architectural deterioration of bone as 50% of patients sustained fragility fractures have not been diagnosed with osteoporosis based on BMD measurements. The last one is that osteoporosis is linked to increased risk of fracture (69).

Many factors can lead to osteoporosis. Bone loss and fragility are usually caused as a combination of: (i) inadequate production of bone mass and strength until adolescence (70), (ii) increased bone resorption leading to bone loss, and (iii) insufficient formation

response to bone resorption (71). The bone mass of an individual reaches a peak from 20 to 45 years old and is affected by various factors including genetics (e.g. gender, age) and environmental (70). Taking into account the factors that affect bone metabolism osteoporosis can be categorized into two categories: (i) primary and (ii) secondary osteoporosis (72). The primary is further divided into two sub-categories: a) involutional osteoporosis type I (or postmenopausal osteoporosis) caused by deficiency of oestrogen after the menopause and b) osteoporosis type II (senile osteoporosis) which is associated with bone reduction due to aging. On the other hand, different diseases, medication (e.g. glucocorticoids) and life style can cause secondary osteoporosis (72).

The actual number of people with osteoporosis is usually hard to be identified because of the silent development of the disease. There were 20 million people with a diagnosis of osteoporosis in six countries in Europe including UK in 2015 (73). The vast majority of osteoporosis cases were females reaching 15.8 million whereas there were 4.2 million males. The number of women with osteoporosis elevated significantly with age. Thus, the prevalence of osteoporosis in people aged 50 years old or more was 7% in men and 23% in women. This percentage in the UK was 7% and 22%, respectively.

2.2.2 Diagnosis of osteoporosis

The gold standard method for the diagnosis of osteoporosis is based on a specific type of x-ray scan called dual energy x-ray absorptiometry (DEXA). This scan is a non-invasive and quick procedure measuring the bone mineral density. Its introduction took place in 1987 and immediately became acceptable from the medical community (74,75). During the BMD scanning the energy which comes from the x-ray passes through the bones and is absorbed, whereas the amount of energy which is not absorbed can be detected on the other side of the body. The absorbed energy depends on the bones dense. In other words, if a bone is dense then a larger amount of energy

will be absorbed compared with a thinner bone. Afterwards, the radiation is converted into surface density which is measured in g/cm^2. Thus, it is possible to estimate the BMD for specific region of the human body. The amount of radiation which gives is equal to a chest radiography, however if the whole body is being examined then this amount is equal to 1.5 chest radiography (76).

BMD scanning is recommended for individuals who belong in one of the following categories (77):

- *In women aged 65 yrs. and older and men aged 70 yrs. and older.*
- *In postmenopausal women and men above age 50–69 yrs., based on risk factor profile.*
- *In postmenopausal women and men aged 50 yrs. and older who have had an adult age fracture.*
- *Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose ≥5 mg prednisone or equivalent for ≥3 months) associated with low bone mass or bone loss.*

The WHO has established a widespread acceptable score for the diagnosis of osteoporosis defined as a T-score ≤ 2.5 (Table 2-1). The T-score is the units of standards deviation from the average bone density of a healthy person 30-year-old of the same sex and is calculated as following (78):

$$T - score = \frac{\text{patient's BMD} - \text{population peak BMD}}{\text{SD of population peak BMD}}$$

Table 2-1. Diagnostic Criteria for Osteoporosis and Osteopenia in Postmenopausal Women and Men Older than 50 Years (Data adapted with permission of the World Health Organisation).

Category	BMD derived from DEXA measurements
Normal	T-score ≤ -1
Osteopenia	T-score between -1 and -2.5
Osteoporosis	T-score ≤ -2.5
Severe Osteoporosis	Patients with a fragility fracture and a T-score ≤ -2.5

2.2.3 Glucocorticoids-induced osteoporosis

The corticosteroids use is extremely popular in the management of inflammatory diseases including asthma. However, as it was mentioned, they are associated with some serious side effects and one organ system that can be directly affected is the skeleton. Osteoporosis is among the most devastating adverse effects of corticosteroids and was first described by Cushing in 1932 (79). Exposure to corticosteroids is the most frequent reason of secondary osteoporosis. The deleterious impact of corticosteroids on bones results from direct effects on osteoblasts, osteocytes, and osteoclasts. Corticosteroids increase bone resorption and reduce bone formation (80,81). The risk of bone loss is most intense during the first months (6% to 12% the first year) of exposure, but the following months is slower and more stable (81–83). Most hormones that increase bone loss expedite not only resorption of bone tissue but also the ossification (84). With chronic use, osteoclast, which plays a vital role in bone resorption, slows and suppression of bone development becomes the most common skeletal effect.

2.2.4 Fragility fractures as a complication of osteoporosis

2.2.4.1 Definition of fragility fractures

The clinical consequence of osteoporosis is that it is a condition in which bone mass is reduced and bone structure is damaged to the extent that bone becomes fragile leading to fractures called fragility fractures. Generally, a bone fracture is: *"An abnormal*

disruption (partial or complete) in the continuity of a bone and is often referred to as a broken bone". A bone fracture can occur due to a high-energy impact (e.g. vehicle accident) or low-energy injury as a result of a certain medical condition (e.g. osteoporosis) that weaken the bones. The WHO has specified a low-energy injury equivalent to a fall from a standing height or less (85). A fragility fracture is defined as: *"A fracture that results from mechanical forces that would not ordinarily result in fracture, known as low-level or low-energy or minimal trauma fractures"* (86). NICE reports that the most common sites where a fragility fracture occurs is at the hip, spine and wrist. They may also occur at the humerus, pelvis, and other bones (87).

2.2.4.2 Burden of fragility fractures

In 2017, there were 2.7 million fragility fractures in six large countries in Europe. The majority of fractures occurred in women (66%) than men (34%) (73). In the UK, the number of a new fragility fracture was 22 per 1,000 population with the lifetime risk of a hip fracture to be 8% and 18% for men and women aged 50 years old or more, respectively. The number of fractures varies among countries (88) due to several reasons including low calcium administration, limited sunlight exposure, and low socioeconomic status. Nevertheless, the number of fragility fractures in all of them will increase as the life expectancy increases. It is projected that all fragility fractures will be elevated from 2.7 million in 2017 to 3.3 million in 2030. Apart from the impact on patient's daily life, fragility fractures also carry a financial impact. Given the increase of the population and longevity the cost of fragility fractures will follow an upward trend over the next years. Specifically, the fracture-related costs in six European countries was estimated at €37.5 million in 2017 which will increase to €47.4 million in 2030 (89). Similarly, the UK follows the same pattern projecting an increase from €5.2 million in 2017 to €6.8 million in 2030 (73). Loss of productivity and the impact on a person's independence are two additional substantial fracture-related burdens (73).

2.2.4.3 Risk factors for fragility fractures

Fragility fractures usually occur in people with osteoporosis; however, it is not solely explained by low bone mass but by a variety of factors. They can be categorised into fixed and modifiable risk factors. Fixed risk factors (e.g. age, gender etc) cannot be modified but they are important in order to identify people at greater risk (Table 2-2). Common modifiable factors are BMD, glucocorticoid exposure, smoking etc. Some of them are analysed further below.

Table 2-2. Risk factors for fragility fractures.

Nonmodifiable	**Modifiable**
Age	Low body weight
Sex	Calcium/vitamin D deficiency
Asian or white ethnicity	Inadequate physical activity
Previous fragility fracture	Excessive alcohol intake
Parental history of hip fracture or osteoporosis	Smoking
Small frame	Glucocorticoids
	Menopause-related oestrogen deficiency

Age is a fixed risk factors which has been confirmed to exponentially increase the risk of fragility fractures irrespective of sex, race, or region. Each 5-year increase was associated with increased risk of hip fracture in Caucasian women (RR = 1.4; 95%CI 1.2 to 1.6) (90). Greater age in men was also associated with higher risk of hip fractures (91). Similarly, patients from 70 to 79 years old had 5 times greater risk of vertebral fracture than those aged 60 years old or less (92). Women are more likely to be diagnosed with osteoporosis than men with the lifetime risk to be ranged from 40 to 50% being around 3 times higher than men (13 to 20%) (93). Greater bone size and muscle mass as well as lower loss of bone mass could be some explanations for that (94). The higher risk in women can be partially explained by the higher odds of falls (OR = 1.49; 95%CI 1.02 to 2.19) (95).

Low BMD increases the risk of fragility fractures (91,96). A meta-analysis of cohort studies showed that the risk of fractures goes up from 1.5 to 3 times for each SD decrease in BMD (97). Similarly, another study which examined 40,000 men and women from 12 cohorts for 170,000 person-years confirmed the importance of BMD as risk factor for fractures highlighting that it is similar in both genders (98). In a 2-year investigation, 31 men who had experienced a fragility fracture were matched with healthy controls. The results shown that BMD was significantly lower in patients compared to control group at all regions (99). Nevertheless, there is no assurance that a fracture will not occur because of a normal BMD score, but it is less likely. Both age and gender interact with bone mineral density for fracture prediction. For any BMD risk of fracture is substantially higher in older people compared to younger (100). The same BMD score with the same technique at any one site has a different significance at different ages as age contributes to risk independently of BMD.

Prior fragility fracture is a well-documented major risk factor for future fragility fracture (77,101–104). On average, the presence of a previous fracture can double the risk of a future fracture (105,106). In the Reykjavik study of 30,795 men and women, the risk of a next fragility fracture within the year following the first fracture was 2.7-fold higher than the risk seen in the whole of the study population (107). Furthermore, a substantial number of patients who experience a hip or wrist fracture have a history of up to three previous fractures (108).

The negative effect of OCS on fracture risk is better documented than that of ICS. van Staa et al. found that the adjusted relative rate of non-vertebral fracture during OCS exposure was 1.33 (95%CI 1.29 to 1.38), that of hip fracture 1.61 (95%CI 1.47 to 1.76), and that of spine fracture 2.60 (95%CI 2.31 to 2.92) compared to controls. Even short-term exposure (5 to 30 days) can deteriorate patients bone health (66). A meta-analysis consisting of more than 42,000 exposed and nonexposed to OCS reported a relative

risk for fragility fracture equal to 2.63 (95%CI 1.68 to 4.13) at the age of 50 years (109). The impact of ICS on bones is still debated, but it is believed that the higher doses can be deleterious. Hubbard et al. found significant increased risk of hip fracture for ICS exposure more than 201μg/d. ICS dose between 201μg/d and 400μg/d was associated with 1.23 times (95%CI 1.06 to 1.44) increased risk of hip fractures than nonexposed (110). The relationship between ICS use and the first occurrence of a fracture was also examined in a cohort of 1,671 patients with COPD or asthma. The rate ratio of fractures for participants receiving a mean ICS dose 602 μg/d or more but never exposed to OCS was equal to 4.21 (95%CI 2.19 to 8.13) compared to nonexposed to ICS patients. There was no found a significant risk with lower ICS doses (111). However, van Staa et al. reported increased risk of nonvertebral fractures even with low ICS doses (300 μg/d or less) (RR = 1.11; 95%CI 1.03 to 1.20) (112).

2.2.4.4 Fracture risk assessment

Although BMD is a crucial factor for evaluating risk of fractures there are several BMD independent characteristics that contribute and need to be considered when diagnosing osteoporosis and making treatment decisions.

Fracture Risk Assessment Tool (FRAX®) is widely used in medicine to predict fractures guiding treatment decisions. The WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield, UK developed this fracture risk tool based on a variety of risk factors such as gender, age, glucocorticoids exposure and several other factors combined with BMD or not (113,114). These risk factors were identified examining meta-analyses assessing risk factors for fractures (91,113,115). FRAX used baseline and follow-up data from nine population-based cohort studies (46,000 participants with 4,000 fragility fractures including 850 hip fractures) (116). Then, the contribution of each risk factor to the overall fracture risk was assessed using multivariate regression models within each cohort (115). Based on this analysis four model exist giving the 10-

year percentage probability of fracture at the region of hip, proximal humerus, spine and forearm (116). FRAX was designed for postmenopausal women and men aged 50 or more and now is available for 68 countries in 5 continents and will be in several others in the future (114,117). When a country is not represented a surrogate can be chosen. Some limitations of FRAX are the unknown algorithm which would be useful for external validation of this tool as well as the limited option of binary data entry.

QFractue is another prediction tool in UK which has been developed incorporating primary care databases from England and Wales using a cohort of 2.2 million people in order to estimate the fracture risk (118). This score was externally validated from another cohort with the same number of participants (119). Risk of major fragility fractures including spine, hip, and wrist can be estimated. Compared to FRAX it can be used for a wider age range (30 to 100 years) but it does not take into account BMD measurements which is a main limitation.

2.2.5 Bisphosphonates as bone protection treatment

Bisphosphonates are recommended as the first line therapy to prevent osteoporosis (and glucocorticoid-induced osteoporosis) and reduce the risk of fragility fractures (120–123). The primary aims of pharmacological therapy are (i) to increase bone strength in order to decreased the risk of falls and consequently the risk of fragility fractures, (ii) to relieve symptoms of fractures, and (iii) maintain physical function (72). According to the National Osteoporosis Guideline Group the following three bisphosphonates have been approved as protection therapy during glucocorticoid exposure: (i) alendronate, (ii) risedronate, and (iii) zoledronic acid (124). It is recommended that adults with a previous fragility fracture or taking ≥7.5 mg of prednisolone or women and men ≥70 years old are eligible for bone protection pharmacologic intervention with bisphosphonates (124). Randomised control trials have reported an increased bone mineral density in exposed patients to corticosteroids

(125–127). A Cochrane review including twelve randomised clinical trials shown that individuals receiving bisphosphonates had a 44% (95%CI 9 to 65) lower risk of a new spine fracture compared to individuals taking vitamin D and/or calcium (128). Further randomised trials demonstrated a reduction in the risk of hip and spine fractures ranging from 40 to 70% (129). Despite bisphosphonate effectiveness of decreasing fragility fracture risk, unusual (or atypical) fractures at the subtrochanteric (ST) and femoral shaft (FS) regions reported in people treated with bisphosphonates 15 years ago (130,131).

2.2.5.1 Atypical femoral fractures and bisphosphonates

A definition of atypical femoral fractures which helps to distinguish them from typical fragility fractures is the following: "*A fracture to satisfy the case definition of an AFF should be located at the subtrochanteric or femoral shaft region*" (Figure 2-4) (132).

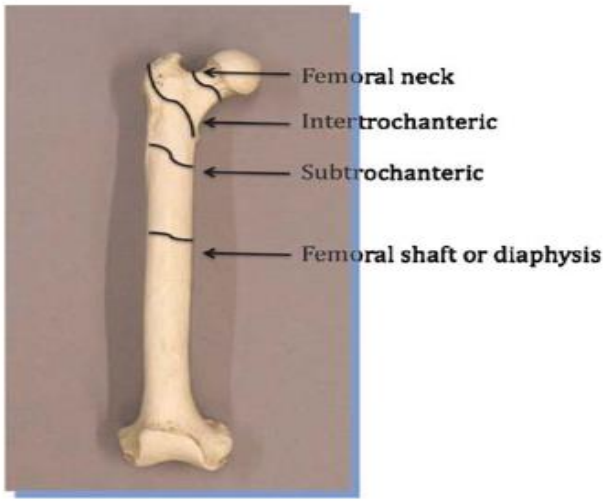

***Figure 2-4**. Location of subtrochanteric and femoral shaft.*

In addition, at least four out of five major characteristics must be presented.

- *The fracture is associated with minimal or no trauma, as in fall from a standing height or less.*
- *The fracture line originates at the lateral cortex and is substantially transverse (a fracture that is at a right angle with the bone's long axis) in its orientation, although it*

may become oblique (a fracture that is diagonal (>30°) to the bone's long axis) as it progresses medially across the femur.

- *Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.*
- *The fracture is non-comminuted or minimally comminuted (a fracture in which the bone has broken into several pieces).*
- *Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site.*

Moreover, there are four minor features that have been sometimes associated with AFF, but it is not a requirement.

- *Generalized increase in cortical thickness of the femoral diaphysis.*
- *Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh.*
- *Bilateral incomplete or complete femoral diaphysis fractures.*
- *Delayed fracture healing*

The epidemiological studies of AFF related to bisphosphonates can be divided into two categories. The first research approach is the use of large databases in which each diagnosis of AFF is based on a coding system (e.g. International Classification of Diseases (ICD-10)) in order to identify subtrochanteric and femoral shaft fractures. This approach does not involve a radiography review to ascertain whether the fractures have atypical characteristics. A limitation with this approach is the misclassification of fracture location as the diagnosis of an AFF is based on specific characteristic in order an AFF to be distinguished from a fragility fracture at the subtrochanteric or femoral shaft region. A study found that 104 ST/FS fractures occurred among 33,815 patients and the estimated incidence rate was 1.46 (95%CI 1.11 to 1.88) per 1,000 person-years. There was no significant association between ST/FS and bisphosphonates (HR = 1.03; 95%CI 0.7 to 1.52). A double rise in risk for patients

treated with bisphosphonates for more than 5 years was observed (HR = 2.02; 95% CI 0.41 to 10.00), however the rarity of the fractures may explain the non-significant outcome (133). Abrahamsen et al. found no difference in risk of ST/FS fractures among patients receiving bisphosphonate than non-exposed controls (134). Conversely, Park et al. conducted a nested case-control study recruiting data of 205,466 women with at least one bisphosphonate prescription from 2002 to 2008 following-up them until 2009. They reported a higher risk of ST/FS fractures among them received bisphosphonates for ≥ 5 years (OR = 2.74, 95%CI 1.25 to 6.02) (135).

The second study design includes assessment of a radiography in order an AFF to be confirmed. Drawbacks with this design may be the small sample size. The percentage of ST/FS fractures with atypical characteristics ranged between 1% and 48% (136–143). An Australian study reviewed 152 patients with ST/FT fractures finding 20 patients with AFF and 17 were current on bisphosphonates whereas just 3 of 132 patients with typical ST/FS fractures were on bisphosphonates (136). The relative risk of an AFF patient being on bisphosphonate was 37.4 (95%CI 12.9 to 113.3) The radiographs of 1,234 women with a ST/FS fracture were evaluated. The researchers found 47 AFF, 12 probably AFF and 263 controls with ST/FS without atypical characteristics. The age-adjusted relative risk of AFF with any bisphosphonate use was 47.3 (95%CI 25.6 to 87.3), nevertheless the rise in absolute risk was just 5 AFF per 10,000 person-years (142). Black et al. did not shown any significant increase of risk of AFF related to bisphosphonates. They assessed 284 cases of hip or femur fractures among 14,195 women. 12 fractures in 10 participants were assessed as ST/FS atypical fractures, giving a rate of 2.3 per 10,000 person-years. The relative hazard in treatment group was 1.03 (95%CI 0.06 to 16.46) in comparison to the placebo group (144).

2.3 The data gap in the literature

There is a well-recognised association between asthma, corticosteroids (especially OCS) which are widely used in asthma, and glucocorticoids-induced osteoporosis (145), leading to a higher incidence of fragility fractures. Despite the clear link between corticosteroids and osteoporosis, and the high prevalence of both asthma (28) and osteoporosis (146), there are no asthma specific bone protection guidelines and very little data on the risk of osteoporosis and fractures related to treatment in asthma. This lack of data is reflected in the guidance. For example, the recent BTS/SIGN guidelines on asthma management cover specific co-morbidities including osteoporosis and bone protection. They just state *"bone mineral density should be monitored in adults. When a significant reduction occurs, treatment with a bisphosphonate should be offered"* (147). No specific guidance is given here on the management of osteoporosis and this aspect of the guidance has not changed in the last 15 years. No evidence grade is given for this recommendation. The latest NICE asthma guidelines (148) do not mention osteoporosis in 372 pages. This lack of guidance is also reflected in the literature. Despite there being a wealth of data on the potential risk of OCS and ICS for inducing osteoporosis and fragility fractures there are very few studies specific to asthma. Studies investigating the adverse effects of corticosteroids on bone health in patients with asthma have contradictory findings (149–154). However, these studies have been limited by their small size and/or focus on severe asthma.

Bisphosphonates are the most prescribed class of drugs for the treatment of glucocorticoid-induced osteoporosis and reducing risk of fragility fractures. The latest BTS/SIGN guidelines on asthma management suggest bisphosphonate therapy if the BMD significantly reduced (147). However, there is a potential for some serious adverse effects including atypical femoral fractures. Evidence of epidemiological studies with radiography review report that the risk of atypical femoral fractures is now thought to be higher than previously realised and bone protection "holidays"

after three to five years of bisphosphonate therapy are advised. Data investigating any adverse event such as AFF in order to make a balanced treatment decision with respect to prevention of bone health is needed. This evidence lacuna around the risks and benefits of bisphosphonates is particularly pertinent in asthma as patients are younger and more likely to be female and receive long term steroid treatment. There is a limited number of studies about the association between bisphosphonate exposure and AFF (142,144,155), however they are not asthma-specific in order to provide evidence for balanced and beneficial disease specific bone protection guidance.

3 DATA SOURCES

3.1 Electronic health records in the United Kingdom

Electronic health records (EHR) databases have been widely used as a means of answering research questions over the last decades. There are several EHR databases available in the UK, and multiple front-end software systems that manage and upload the data into them.

The Clinical Practice Research Datalink (CPRD) GOLD is one of the oldest research databases of primary care EHR in the UK and generating the highest number of peer-reviewed publications (156). There are several different software systems available in the UK to record clinical data, for example Vision or EMIS (Egerton Medical Information System), which are used by general practices to record the information that is subsequently uploaded to their respective databases. This thesis may refer to the CPRD GOLD as "CPRD". Q-research and THIN (The Health Improvement Network) are some other primary care databases in the UK. The data content of these databases is generally comparable with the CPRD GOLD, but their size and linkage availabilities can differ. Data on secondary care are available in Hospital Episode Statistics (HES), while data on mortality and an area-based socio-economic status are made available by the Office of National Statistics (ONS).

The CPRD GOLD was the main data source for this PhD project and is supported by the Vision software system. The next sections describe also the other sources used for this PhD project, namely the HES and OpenPrescribing.net.

The studies were approved by the Independent Scientific Advisory Group of the CPRD (ISAC protocol number 19_041RA) (Appendix 1).

3.2 Clinical Practice Research Datalink GOLD

3.2.1 Background

Clinical Practice Research Datalink, previously called GPRD (General Practice Research Database), is a real-world research service supporting retrospective and prospective public health and clinical studies established (as Value Added Medical Products) in London in 1987 (157). CPRD is jointly sponsored by the Medicines and Healthcare products Regulatory Agency and the National Institute for Health Research, as part of the Department of Health and Social Care. CPRD collects de-identified patient data from a network of primary practices across the UK using the Vision computer system (157). Primary care data are linked to a range of other health related data to provide a longitudinal, representative UK population health dataset (158). The data encompass 50 million patients, including 15 million currently registered patients of whom 4.4 million were active (alive) and currently registered in 2015 (158). The CPRD includes information on patients' demographics, clinical diagnoses, prescriptions, and referrals made by practitioners (158).

3.2.2 The health care system in the United Kingdom

In the UK, healthcare is provided by the National Health System (NHS) and is free at the point of delivery for all residents (159). The system relies on general practitioners (GP) as the cornerstone of health care. GP act as the first point of contact for any non-urgent case providing primary healthcare and coordinate referrals to further services, when necessary. Hospitals then provide specialist services, as well as direct access to Accident and Emergency care. Secondary care teams feedback information to GP about their patients, including diagnoses and prescribed medications. Community pharmacies are privately owned but have contracts with the relevant health service to supply prescription drugs. Over 98% of the UK population are registered with a primary care GP (158). Patient data are routinely recorded onto computers by practice staff, against a unique patient NHS number (158). Thus, prospective follow up of

individuals is possible via the healthcare records of the GP, and this reason why primary care databases offer such opportunities for research.

3.2.3 Structure of CPRD data

CPRD is structured in several different files, the main dataset that contains patients' medical diagnoses as recorded by their primary care provider during routine clinical encounters. Any patient-identifiable information (e.g. name or address) and any free text notes which are removed for privacy reasons. For those primary care practices that participate in the CPRD linkage scheme, data are linked at patient-level to further health-related information, such as secondary healthcare records, the national death registry, or socioeconomic status data.

Clinical information in the CPRD is structured in a relational format and organises data in different tables, which each refer to one set of information and can be linked with each other via unique identifiers (Table 3-1, Figure 3-1). For instance, the "patient" table includes patient' demographics and consists of rows with each row to represent an individual patient, and columns listed individual characteristic such as year of birth. In a table, each row has a unique number called "patient id" in order a row to be linked with a row in another table using this identified key number. In the "patient" table there is another identifier called "practice id" providing the possibility to be linked with the "practice" table retrieving information about the practice.

Table 3-1. An overview of data files in the CPRD.

CPRD files	Description
Patient	Contains basic patient demographics and patient registration details
Practice	Contains details of each practice, including region and collection information.
Staff	Contains practice staff details, with one record per member of staff.
Consultation	Contains information relating to the type of consultation as entered by the GP from a pre-determined list. Consultations can be linked to the events that occur as part of the consultation via the consultation identifier (consid).
Clinical	Contains medical history events. This file contains all the medical history data entered on the GP system, including symptoms, signs and diagnoses. This can be used to identify any clinical diagnoses, and deaths. Patients may have more than one row of data. The data is coded using Read codes, which allow linkage of codes to the medical terms provided.
Additional clinical details	Contains information entered in the structured data areas in the GP's software including smoking status, BMI, alcohol consumption, bold pressure etc. Patients may have more than one row of data. Data in this file is linked to events in the clinical file through the additional details identifier (adid).
Referral	Contains referral details recorded on the GP system. These files contain information involving patient referrals to external care centres (normally to secondary care locations such as hospitals for inpatient or outpatient care) and include speciality and referral type.
Immunisation	Contains details of immunisation records on the GP system.
Test	Contains records of test data on the GP system. The data is coded using a Read code, chosen by the GP, which will generally identify the type of test used. The test name is identified via the *Entity Type*, a numerical code, which is determined by the test result item chosen by the GP at source. There are three types of test records, involving 4, 7 or 8 data fields (data1 - data8). The data must be managed according to which sort of test record it is. Data can denote either qualitative text-based results (for example 'Normal' or Abnormal') or quantitative results involving a numeric value.
Therapy	Contains details of all prescriptions on the GP system. This file contains data relating to all prescriptions (for drugs and appliances) issued by the GP. Patients may have more than one row of data. Drug products and appliances are recorded by the GP using the product code system.

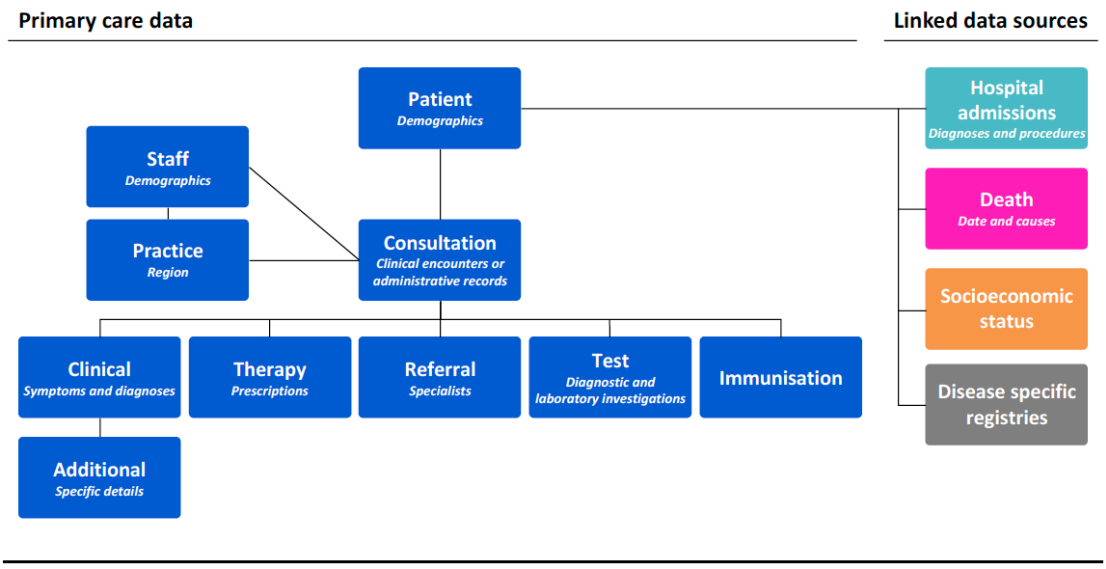

Figure 3-1. *Simplified overview of the relational data structure of CPRD and linked data sources. Patients consult with practice staff, where clinical, therapy, referral, test and immunisation information are recorded. Adapted with permission from Herrett et al* (158).

Data are recorded via a standard clinical terminology system, called "Read" coding system after its creator Dr. James Read. Read codes allow the recording of diagnoses, similarly to diagnosis coding systems such as the ICD, as well as a wide range of patients' characteristics and clinical concepts including: social circumstances; ethnicity and religion; clinical signs, symptoms and observations; laboratory tests and results; diagnostic, therapeutic or surgical procedures performed; and a variety of administrative items (160). Therapeutic information includes prescriptions using codes from the Prescription Pricing Authority, with the corresponding date, dosage, and method of administration. Additional information is provided on vaccinations, weight and blood pressure measurements, laboratory test results and on some aspects of lifestyle (160). All information is entered by practice staff and is anonymised prior to central collection (158).

3.2.4 Strengths and limitations

A key strength of this database is its size; the CPRD holds data from 738 practices in the UK (January 2018 dataset). This allows epidemiological associations to be

investigated in more detail and estimated with a higher level of statistical precision than is possible with smaller data sources, which is of particular importance for the study of rare exposures and diseases (158). For individual patients, there is a long follow-up period with a median of 11.72 years IQR (4.34 to 22.91) for current patients (i.e. registered at currently contributing practices, excluding transferred out and deceased patients) and 5.46 years IQR (1.96 to 12.89) overall, enabling research into diseases with long latency and long-term outcomes. The CPRD has a wide range of variables available that provide information on patients' demographic, clinical and social characteristics. This has made it possible to establish a comprehensive patient profile, including smoking status, BMI, alcohol status and prevalent comorbidities. Particularly the combination of clinical and socioeconomic data is a distinctive feature of the linked datasets that is rarely available in other research cohorts. Patients including in CPRD are broadly representative of the UK population in terms of age and sex (158) and also comparable in terms of ethnicity (161). Validation studies of some diagnoses within the CPRD have shown high positive predictive value (162–164). The quality of the data entered into the CPRD can be variable as the main purpose of existence of the database is not for research; however, there are two key criteria to ensure data quality within the database (158). The first one is acceptability of patients taking into account the registration status, recording of events in the patient record, and valid age and gender and the second one up to standard (UTS) time for practices considering the continuity of recording and the number of recorded deaths (158).

On the other hand, CPRD has also some limitations that should be mentioned. The missing data across patient and time should be seriously considered as restriction as it can lead to biased analyses. Misclassification of diagnoses might be another issue. This arises due to patient failing to present to the GP with the disease and from variation in coding diagnoses among GP (158). The extent of misclassification bias is different between diseases (164). Finally, as there no standard definition for diagnoses

and other information, Read codes should be developed from each research team for each study resulting in inconsistent results between studies using the same data (158). In addition, information is not available relate to over-the-counter medications or patients' adherence to medication.

3.2.5 Linkage with databases

The CPRD has established a linkage program enabling access to a broad range of additional healthcare-related information (160). The CPRD can link patients' primary with secondary care records (HES), and socioeconomic data (Index of Multiple Deprivation (IMD)). It is also linked to mortality data from national death registry (ONS) and disease-specific registries such as the Myocardial Infarction National Audit Project, that have not been used in this thesis. Linkage is only available for English practices, due to the differences in NHS admission datasets created in Wales, Scotland and Northern Ireland (157). In the dataset provided by CPRD for use in this thesis, linkage was available for 75% of English practices covering approximately 60% of all patients in CPRD.

3.2.5.1 The Hospital Episode Statistics dataset

3.2.5.1.1 Background

The Hospital Episode Statistics dataset contains details of all admissions to English NHS health care providers, including acute hospital trusts, primary care trusts and mental health trusts (165). HES also covers admissions to independent sector providers (private or charitable hospitals) paid for by the NHS, and it is estimated that 98–99% of hospital activity in England is funded by the NHS (165). The dataset used in the current thesis was the HES Admitted Patient Care (APC) including any secondary-based activity requiring a hospital bed. HES APC does not cover accident and emergency attendances or outpatient bookings, which are held in separate HES databases (165).

3.2.5.1.2 Structure of HES data

HES APC data files are structured according to financial years. Each row in HES APC indicates a 'Finished Consultant Episode' (FCE). An FCE represents a continuous period of care under one consultant, and each is specified with a start and an end date. Episodes are labelled as 'finished' and entered in HES APC according to the financial year in which they end. Consequently, episodes that start in one financial year and end in another are classified as unfinished in the starting financial year and finished in the ending financial year. Unfinished episodes need to be removed before analysis to prevent double counting (165). A hospital admission in HES APC is referred to as a 'spell', defined as an uninterrupted inpatient stay at one hospital. A spell may include several FCE if the patient was seen by multiple consultants during the same stay but does not include transfers between hospitals. If a patient is transferred to a different hospital, a new spell begins. In order to identify and measure continuous hospital stays, which include transfers to other hospitals, continuous inpatient spells (CIP) need to be derived (165).

HES APC provides detailed clinical, demographic, and organisational information for each FCE (Table 3-2). Apart from data on diagnoses and procedures, HES APC contains information on dates of admission, operations and discharge, admission method (e.g. emergency or planned), care provider and many geographical variables mapped from a patient's postcode (165). Diagnoses are coded using (ICD-10). Each FCE has one primary diagnosis, which accounts for the majority of the length of stay of the FCE. The other diagnoses are referred to as comorbidities.

Table 3-2. key data fields available for each finished consultant episode (FCE) in HES APC data.

Patient	Admission/FCE	Clinical	Geography	Provider	Maternity
HESID	Episode start date	Diagnoses (up to 20)	Government office region	Care provider (hospital)	Gestational age
Age at admission	Episode end date	Operations (up to 24)	Local authority	General practice of patient	Number of previous births
Age at discharge	Date of admission	Operation dates	Clinical commissioning group		Birth weight
Sex	Date of discharge	Consultant specialty	IMD		Maternal age
Ethnicity	Admission method				Mode of delivery
	Discharge method				Baby number (for multiple births)
	Discharge destination				
	Admission source				
	Waiting time (date of decision to admission)				

3.2.5.1.3 Strengths and limitations

The main strengths of using the HES database for epidemiological research are its global coverage providing an unselected samples of hospitals, its possibility to be linked with other datasets, and standardised ICD-10 codes (165). However, there are some limitations that should be mentioned. These include the variation of coding between different hospitals, the sensitivity to admission thresholds (if this differs between hospitals or guidelines) and the patients that opt out of data recording for research purposes (2.3% of episodes) (165). Clinical coders rely on discharge summaries in order to enter data correctly, and as such, data quality can vary between hospitals. In addition, financial incentives exist in order to improve coding. Some conditions have a higher remuneration than others, so hospitals have an incentive to code multiple and specific comorbidities (165).

3.2.5.2 Index of multiple deprivation

Index of Multiple Deprivation is the official measure of relative deprivation for small residential areas (or neighbourhoods) in England (166). IMD is a composite measure based on various social and economic characteristics of neighbourhoods and is used as a proxy for the socioeconomic status of individuals who live there. The index ranks every small area in England from 1 (most deprived area) to 32,844 (least deprived area). Quintiles are calculated by ranking the 32,844 small areas in England from most deprived to least deprived and dividing them into five equal groups. These small areas, also known as lower-layer super output areas, contain an average population of 1,500 people, and their boundaries remain fixed over time allowing the study of temporal trends. The linkage provided by CPRD is established by matching the patient's postcode to the neighbourhood it refers to. To ensure patient anonymity, CPRD provides information about deprivation quintiles, but not the ranks themselves. IMD scores are updated every few years, and the dataset used in this thesis relied on the 2015 version (167).

3.3 OpenPrescribing.net project

OpenPrescribing.net is a project built by the EBM DataLab at the University of Oxford, to help make complex medical and scientific data more accessible and more impactful in real world. OpenPrescribing.net is currently funded by NHS England and Oxford NIHR Biomedical Research Centre. It was previously supported by the Health Foundation and the National Institute for Health Research School for Primary Care Research.

It provides a search interface onto the raw prescribing data files published by NHS Business Service Authority. The provided prescribing data is two months behind, so for example January's prescribing data is published on OpenPrescribing in March. The website has data from the past 5 years without containing any patient information as

well as it does not provide any indication or length of treatment. The data covers prescriptions that are prescribed in England by GP and non-medical prescribers and that are dispensed anywhere in the UK (e.g. at pharmacists). Namely, prescriptions written in England but dispensed outside England are included. However, the data does not cover private prescriptions. For each general practice in England, and for each medicine (by presentation), dressing and appliance, the information provided is the number of prescribed items that are dispensed, the quantity of tablets, capsules, liquid dispensed, the net ingredient cost (the basic price of a drug), and the actual cost (the estimated cost to the NHS). GP practices are identified only by their national code, so an additional data file (linked to the first by the practice code) provides the name and address of each practice. Each presentation is identified by the British National Formulary (BNF) Code. An additional data file (linked to the main data file by the BNF code) provides the chemical name for each presentation. Practice prescribing data is based on information about prescriptions written and dispensed and does not include any information about the number of patients who have been given prescriptions. One limitation can be that it does not provide the indication for each prescription, whereas a key strength is that it covers all prescribed items dispensed in England and not just a sample.

4 DATA PROCESSING

4.1 Data extraction and processing

4.1.1 Introduction

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

Except for the most common demographic information, variables are generally not readily available and need to be extracted from the longitudinal data. For example, typical study data will provide a list of study participants, with their baseline date and baseline measurements, such as smoking, body mass index (BMI). When working with CPRD, researchers will first need to identify the relevant study population (e.g. identify all patients with a new diagnosis of asthma) and extract individual characteristics (e.g. age, sex, smoking status, comorbidities, etc.). Relevant measurements may or may not be recorded. Also, most records will not coincide with the baseline date and some measurements may have been recorded several times in the months before/after baseline, so that an algorithm needs to be defined to extract, select and/or combine the different measurements. This chapter aims to define some of the variable which were used across the studies including CPRD linked to HES data. The management of OpenPrescibing.net data is analysed in the Chapter 8, as only one study used these data, and they did not require any complex management.

4.1.2 Diagnostic codes

In UK primary care, clinical concepts are represented by 'Read' codes (in the CPRD, Read codes are mapped to 'medcodes'), and in secondary care settings (including HES data linked to CPRD), ICD-10 codes are used. To extract disease-specific diagnostic codes, a previously published and accepted approach was taken into account (168).

4.1.3 Demographic characteristics

Patients' year of birth is listed in primary care records' patient table. Age at baseline was calculated by subtracting patients' year of birth from the year of interest for each study. In some analyses age was further categorised into groups. Sex was extracted from primary care records patient table, with 1 = male, 2 = female. No patients with indeterminate gender in the data used in this PhD thesis. The IMD were provided in linked socioeconomic data table (patient_imd2015.txt) at patient level. The dataset used in this thesis refers to the 2015 version of IMD scores, and 1 = least deprived and 5 = most deprived.

4.1.4Clinical measurements

Baseline clinical measurements were extracted from patient primary care records, as part of the 'additional' and 'clinical' tables. If no measurement took place within that time frame, the measure was considered missing. Below the phrase "index date" will be used, but it is not possible to define it here as it is not the same for each study, so there is a definition for that date in the corresponding chapter.

4.1.4.1 Body Mass Index

Initially, the BMI was calculated using weights and heights recorded data (weight in kg and height in m) from the additional CPRD file. Weights less than 20 kg or more than 450kg and heights less than 1.21m or above 2.14m set to missing data. The

measurement remained the same in case of only one weight and height measurement per day, otherwise the difference between multiple measurements on the same date was calculated getting the mean weight and height of the day. Then, the median height was used as least affected by outliers. The weight difference between visits was calculated. Random intercepts model was fitted regressing weight on time, adjusting for age and gender (grouping: patient) and calculate standardised residuals. Any weight measurements where the residuals are outliers unless the data point is within 10 kg of the preceding (n-1) or subsequent (n+1) measurement by date, was dropped. The modelling process was repeated using the cleaned data (once or twice more until no extras are removed) to ensure outlier residuals are removed. Measurements with an inter-date weight change of > 5 kg per day was removed if patient only has weight measurements for two visits. The BMI was calculated based on the WHO classification. Any BMI less than 10 set to missing data. Additionally, BMI status was extracted using Read codes for patients with a missing BMI status.

4.1.4.2 Smoking status

Smoking status was defined as the CPRD record of smoking status using the nearest measurement ever prior to the index date and categorised as never-smoker, former-smoker, or current-smoker. Smoking status was determined from the CPRD datasets based on Read codes, additional clinical information, and prescriptions for smoking cessation therapy. If never-smokers had a previous record indicating smoking in their entire CPRD history, they were counted as a former-smoker.

4.1.4.3 Alcohol consumption

Self-reported alcohol consumption was collected prospectively and coded by general practitioners or practice nurses on the consultation date in CPRD. The most recent alcohol consumption record prior to the index date was used to classify participants drinking behaviour. Four categories were defined including: (1) non-drinkers (Read

codes such as "Non-drinker alcohol"), (2) former drinkers (Read codes such as "stopped drinking alcohol"), (3) occasional drinkers (Read codes such as "drinks rarely"), and (4) current drinkers (Read codes such as “drinks wine”, and “alcohol misuse”). Data based on the alcohol status and the alcohol units per week from the additional file of CPRD were also extracted to define patients in the above categories, where available. The information about the alcohol status helped to include more patients as “non-drinkers” or “former-drinkers”, and if a patient had more than 0 alcohol units per week classified as “current drinker”. Non-drinkers were reclassified as former drinkers if they had any record of drinking recorded in their entire clinical record entered on CPRD prior to study entry, otherwise their category remained the same.

4.1.4.4 Drug prescriptions

Information relating to drug prescription data is provided in primary care records ‘therapy’ table. Each prescription relates to one drug (described with a ‘prodcode’ number), a quantity (‘qty’, or the number of tablets or canisters prescribed), a numeric daily dose (‘ndd’), and drug strength (the active dose contained in each tablet or each inhalation). Other parameters are also given but they have not been used in this thesis (e.g. pack size or type of the prescribed product). A product dictionary details the specific formulation of each drug and alongside the BNF classification, the pharmaceutical reference book in the UK. The following algorithm was also used to deal with missing or implausible values of oral and inhaled corticosteroids.

Once all possible values about the quantity, prescribed number of tablets and inhalations per day of each prescription had been estimated using the data provided by the CPRD, the method to check for implausible results and fill in missing data was as follows.

- Define implausible number of tablets/puffs prescribed per day and quantity to these were defined using the 99th centile for each value
- Identify prescriptions with implausible quantity
- Replace those with implausible quantity with mean of patient for that specific drug, or if not available mean of all patients for that specific drug
- Identify prescriptions with implausible number of tablets prescribed per day
- Replace those with implausible number of tablets prescribed per day with mean of patient for that specific drug, or if not available mean of all patients for that specific drug.
- Calculate prednisolone for OCS and beclomethasone for ICS equivalent dose per day of all prescriptions.

4.1.4.5 Comorbidities

The comorbidities were also summarised using the Charlson Comorbidity Index score (169). The Charlson index includes 17 categories of comorbid disease weighted from 1 (e.g. peripheral vascular disease) to 6 (e.g. metastatic cancer) based on their association with 1-year all-cause mortality (Table 4-1). So, for each patient any of these diseases for each participant was obtained from the "clinical" file of CPRD.

Table 4-1. Comorbidities used to calculate the Charlson comorbidity score, and weighting used.

Charlson disease category	Charlson score weight
AIDS	6
Metastatic tumour	6
Mod liver disease	3
Diabetes with complications	2
Renal disease	2
Hemiplegia	2
Cancer	2
Cerebrovascular disease	1
Chronic pulmonary disease	1
Congestive heart disease	1
Dementia	1
Diabetes	1
Mild liver disease	1
Myocardial infarction	1
Peptic ulcer disease	1
Peripheral vascular disease	1
Rheumatological disease	1

5 INCIDENCE OF OSTEOPOROSIS AND FRAGILITY FRACTURES IN ASTHMA: A UK POPULATION-BASED MATCHED COHORT STUDY

5.1 Introduction

ICS are considered the gold-standard treatment in asthma, with OCS to be used in people with difficult asthma, or for exacerbations (16). Asthma is amongst the most common indications for prolonged (≥ 3 months) OCS therapy (170). Additionally, 17% of people with asthma have difficult-to-treat asthma (171) and 30% of them receive up to the equivalent of 20mg prednisolone equivalent and almost half of them receive up to over 2000 μg of ICS per day (59). Although corticosteroids are the main asthma treatment, there are well-recognised deleterious effects (45,66,172,173).

Osteoporosis which can result in fragility fractures is the most common severe and preventable side effect of steroid use (174). Fragility fractures are associated with substantially increased health care costs, morbidity, and mortality (175,176). In the general population, studies suggest an increased fragility fracture risk in patients exposed to both short (≤ 3 months) and prolonged OCS use (66,67). Vertebral fracture risk increases by 55% with exposure at doses as low as prednisone 2.5mg per day, whereas hip fracture risk increases by 77% in patients exposed to 2.5 - 7.5mg per day (67). ICS also carry risk; compared to controls, people with an airway disease exposed to ICS have a higher fracture risk ranging from 15% to 51% depending on the fracture location (112).

Although there is a clear link between OCS and ICS use, and the risk of osteoporosis and fragility fractures, less is known about the relationship between asthma and these bone diseases. Some studies have examined this relationship, but they have used as outcome any change in the bone mineral density with conflicting findings (149,150,177–179). A high prevalence of fractures in patients with steroid dependent

asthma has been also reported (152,154). However, knowledge is limited due to small sample size (152,154) or focus on specific asthma groups (153).

The aim of this study was to estimate the incidence and risk of osteoporosis and fragility fractures among patients with asthma, when compared to the general population. The impact of age, gender, glucocorticoids, and the risk of specific fractures were reported.

5.2 Methods

5.2.1 Study population

A matched cohort study was conducted utilising the Clinical Practice Research Datalink. The study population included all adult patients (≥18 years old) with a new Read code for asthma between 1st April 2004 (activation of Quality and Outcomes Framework score (QOF)) to 31th December 2017, with at least 1 year of data collection prior to the index date (Appendix 2) (180). An index date equal to a new Read coded asthma diagnosis to each patient was assigned. Each patient with asthma was matched up to four randomly selected patients without asthma (not any record of Read coded asthma diagnosis) by age (±1 year), gender and practice generating a matched cohort. To each patient without asthma the same index date as his/her matched patient was assigned. Only patients classed as "acceptable" research quality data and registered to an UTS practice according to CPRD's recommendations included.

5.2.2 Definition of outcomes

The outcomes of interest were the time from the index date to the first Read coded 1) osteoporosis and 2) fragility fractures diagnoses, separately (Appendix 2). Patients with a previous history of osteoporosis and the specific fracture outcome under

investigation before the index date were excluded. Fragility fractures were defined as composite of vertebral, hip, forearm-wrist and humerus fractures. An additional category called "unspecified" was generated including fractures classified as fragility fractures without specifying the exact fracture location. These locations were selected as they are considered major fragility fractures sites and are associated with morbidity and mortality (176,181). Any fracture described as an "open fracture" was excluded, since this type usually occurs via a high-energy event, and is not associated with frailty.

5.2.3 Follow-up

The index date was the start date of the follow-up, and the end date was defined as the date of the patient's death, the date of the last collection of the practice, the date of the patient transferred out of the practice, the date of the first Read coded outcome of interest or the end of the dataset, whichever came earliest.

5.2.4 Potential confounders

For each participant in this study, information on the following variables was retrieved, all of which are well-established risk fractures or thought to have an impact on osteoporosis or fracture risk and are also likely to be recorded within the database: age at the index date; sex, including only those clearly classified as male or female; body mass index (BMI) using the nearest measurement prior to the index date and categorised according to the WHO; smoking and alcohol status using the nearest measurement prior to the index date; socioeconomic status measured by using the patient-level IMD 2015 in quintiles (with quintile 1 being the least deprived and quintile 5 being the most deprived; history of any fracture (not those considered as an outcome), fall or COPD prior to the index date; at least one prescription of opioids, vitamin D and calcium, and hormone replacement therapy (HRT) in the year prior to

the index date. The comorbidities were also summarised using the Charlson Comorbidity Index score (169).

Exposure to OCS, ICS was calculated in two ways. The OCS and ICS prescriptions were extracted the year prior the index date as well as rates per patient per year of follow-up by dividing the total number of prescriptions of each patient during the follow-up period to the corresponding person-time of each one patient. If there was no record for a medication or diagnosis, we assumed that the patient did not have the exposure.

5.2.5 Statistical analysis

All continuous demographic and lifestyle variables were summarised using mean and standard deviation or median and interquartile range for those following normal or skewed distribution, respectively. Categorical variables were summarised by frequency and percentages. The baseline characteristics between asthma and non-asthma patients was compared by performing a conditional logistic regression analysis using the matched set as the strata variable. Absolute incidence rates of osteoporosis and fragility fractures were calculated by dividing the number of incident diagnosis by follow-up person-years for both groups. The probability of experiencing fragility fractures during the follow-up time was presented with a plot using the Kaplan-Meier method and the log-rank test examined any difference between the groups. Performing a Cox regression analysis, stratified by matched set, the HR estimates and 95% CI were calculated comparing the risk of osteoporosis and fragility fractures between asthma and non-asthma patients. Then, the model was adjusted for potential confounders listed above. Each of the potential confounding variables were added into the model, one at a time, and were included in the model if they altered the age-gender adjusted HR by 5% or more. The Cox model assumption was tested using Schoenfeld residuals. Missing data for BMI, smoking status, and

alcohol status were assumed as missing at random and imputed using chained equations. Ten imputations were generated, and the imputed model consisted of age, gender, outcome, and all confounders. Missing data for IMD were assigned a new category. A subgroup analysis by gender, age group, and fracture location was performed. To test whether age or gender modified the effect of asthma on osteoporosis and fragility fractures, the likelihood ratio test to examine for statistical evidence of effect modification. To test the robustness of the findings and determine whether the overall risk of fragility fractures was similar in different patient populations two sensitivity analyses were conducted. Therefore, the main analysis was repeated (a) including patients with a history of osteoporosis before the index date, and (b) excluding patients with any fracture before the index date. When the outcome was the occurrence of a fragility fracture, the approach of the main analysis, in which we only excluded those with a previous history of the specific fracture outcome under investigation, assumes that a fracture will only affect subsequent fracture probability in the same bone. However, a fracture in one bone can affect fracture risk in another bone. To test this, the main analysis was conducted again after additionally excluding those with a history of any previous fracture. Similarly, osteoporosis affects the fracture risk, so those with a history of osteoporosis were included. Finally, after excluding the patients without asthma, we investigated the effect on osteoporosis and fragility fractures of some well-known risk factors within asthma group, including ICS and OCS prescriptions during the follow-up, by estimating aHR. All statistical analyses were performed using Stata v16.

5.3 Results

5.3.1 Baseline characteristics

The study included 138,123 patients with asthma and 520,626 age-, sex- and practice-matched non-asthma patients. The mean age of people with and without asthma was 52.0±17.9 and 51.7±17.8, respectively (Table 5-1). Patients with asthma compared to

non-asthma were more likely to be obese (26.7% vs 16.6%, $p < .0001$) and ex- or current smokers (52.9% vs 39.7%, $p < .0001$) (Table 5-1). Furthermore, patients had had more comorbidities than controls ($p < .0001$). More patients with asthma had at least one prescription of opioids (10.4% vs 6.1%, $p < .0001$) before the index date than the non-asthma.

Table 5-1. Baseline characteristics of asthma and non-asthma patients.

	Asthma patients		Non asthma patients		
Descriptor	**n=138,123**	**%***	**n=520,626**	**%***	***p*-value****
Age y, mean ± SD	52.0±17.9		51.7±17.8		
<40	39,043	28.3	149,685	28.7	
40-49	24,998	18.1	95,308	18.3	
50-59	23,974	17.4	90,549	17.4	
60-69	24,774	17.9	92,478	17.8	
70-79	17,417	12.6	64,307	12.3	
≥80	7,917	5.7	28,299	5.4	
Gender					
Male	56,538	40.9	213,635	41.0	
Female	82,585	59.1	306,991	59.0	
Follow-up y, median (IQR)[a]	4.50 (2.1-7.9)		4.58 (2.1-8.0)		
Follow-up y, median (IQR)[b]	4.51 (2.1-7.9)		4.60 (2.1-8.0)		
IMD					<.0001
Least Deprived	16,026	11.6	62,026	11.9	
-	16,439	11.9	61,102	11.7	
-	16,030	11.6	58,013	11.1	
-	15,341	11.1	52,752	10.1	
Most deprived	14,612	10.5	46,284	8.8	
Missing status	59,675	43.2	240,339	46.1	
CCI score					<.0001
0-1	113,950	82.5	447,602	86.0	
2	11,796	8.5	38,310	7.4	
3	6,452	4.7	18,572	3.6	
4	2,855	2.1	7,790	1.5	
≥5	3,070	2.2	8,352	1.6	
BMI (kg/m^2)					<.0001
Underweight (<18.5)	2,214	1.6	6,676	1.3	
Normal (18.5 - 24.9)	31,486	22.8	111,417	21.4	
Overweight (25 - 29.9)	37,110	26.9	109,519	21.0	
Obese (≥30)	36,890	26.7	86,361	16.6	
Missing status	30,423	22.0	206,653	39.7	
Smoking status					<.0001
Never	62,095	45.0	254,418	48.9	
Former	42,307	30.6	103,230	19.8	
Current	30,760	22.3	103,729	19.9	
Missing status	2,961	2.1	59,249	11.4	
Alcohol consumption					<.0001
Never	13,759	10.0	46,968	9.1	
Former	11,734	8.5	33,039	6.3	
Occasional	18,102	13.1	60,005	11.5	
Current	74,419	53.9	261,961	50.3	
Missing status	20,109	14.6	118,653	22.8	
At least one prescription of					
Bisphosphonates	3,923	2.8	11,628	2.2	<.0001
Opioids	14,321	10.4	31,781	6.1	<.0001
Vitamin D and/or Calcium intake	4,386	3.2	12,308	2.4	<.0001

HRT	11,237	8.1	34,460	6.6	<.0001
ICS	70,024	50.7	23,136	4.4	<.0001
OCS	34,221	24.8	18,799	3.6	<.0001
History of					
Falls	11,758	8.5	33,169	6.4	<.0001
Any fracture	29,139	21.1	95,523	18.3	<.0001
COPD	15,365	11.1	11,345	2.2	<.0001

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; HRT, hormone replacement therapy; ICS, inhaled corticosteroids; IMD, index of multiple deprivation; OCS, oral corticosteroids.

[a] The outcome was a fragility fracture diagnosis.

[b] The outcome was an osteoporosis diagnosis.

**Percentages have been rounded and might not total 100.*

***P-values based on likelihood ratio test.*

5.3.2 Osteoporosis risk

During the whole study period the incidence of osteoporosis was higher in asthma than non-asthma group. The incidence rates were 5.26 (95% CI 5.09 to 5.42) and 3.23 (95% CI 3.16 to 3.29) per 1,000 person-years for patients with and without asthma, respectively (Table 5-2). An association between asthma and osteoporosis was observed (aHR = 1.18; 95% CI 1.13 to 1.23). Age and gender modified the effect of asthma on osteoporosis, such that effect to be stronger in younger people ($p_{interaction}$ < .0001) and slightly larger in men with asthma ($p_{interaction}$ < .0001), respectively. The stratified risk by age groups and sex shows that men from 50 to 79 years old was the most vulnerable population to osteoporosis and women with asthma from 18 to 79 years old were also at greater risk compared to women of the general population (Table 5-3).

Table 5-2. Incidence rates and hazard ratios (HR) for associations of osteoporosis with exposure to asthma.

	Asthma patients		Nonasthma patients				
Variables	**Number with osteoporosis**	**Rate per 1000 person-years**	**Number with osteoporosis**	**Rate per 1000 person-years**	**Unadjusted HR (95%CI)**	**Adjusted HR[b] (95%CI)**	***p*-value**
Overall	3,767	5.26	9,911	3.23	1.45 (1.40-1.51)	1.18 (1.13-1.23)	<.0001
Gender							
Male	768	2.60	1,431	1.27	2.05 (1.88-2.24)	1.35 (1.22-1.50)	<.0001
Female	2,999	7.11	8,480	4.37	1.35 (1.29-1.41)	1.14 (1.09-1.20)	<.0001
Age[a]							
<40	55	0.28	126	0.17	1.67 (1.22-2.30)	1.54 (1.04-2.29)	.032
40-49	208	1.48	496	0.93	1.59 (1.35-1.87)	1.29 (1.06-1.57)	.013
50-59	678	5.06	1,697	3.01	1.51 (1.38-1.65)	1.24 (1.12-1.39)	<.0001
60-69	1,195	8.97	3,049	6.02	1.49 (1.39-1.59)	1.20 (1.10-1.29)	<.0001
70-79	1,182	15.04	3,269	6.19	1.42 (1.33-1.52	1.17 (1.08-1.26)	<.0001
≥80	449	15.99	1,274	5.81	1.36 (1.22-1.52)	1.16 (1.02-1.32)	.022

[a] *Age at the index date.*

[b] *Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, and previous: COPD, fractures; when not stratified by those.*

Table 5-3. Incidence rates and hazard ratios (HR) for associations of osteoporosis with exposure to asthma stratified by gender and age groups.

	Asthma patients		Nonasthma patients				
Variables	**Number with osteoporosis**	**Rate per 1000 person-years**	**Number with osteoporosis**	**Rate per 1000 person-years**	**Unadjusted HR (95%CI)**	**Adjusted HR[b] (95%CI)**	***p*-value**
			Men				
Age[a]							
<40	15	0.20	28	0.10	2.06 (1.10-3.86)	1.01 (0.42-2.39)	.995
40-49	39	0.72	64	0.31	2.31 (1.55-3.45)	1.36 (0.81-2.27)	.238
50-59	142	2.49	176	0.82	3.04 (2.43-3.79)	1.76 (1.33-2.33)	<.0001
60-69	252	4.19	455	1.99	2.11 (1.81-2.46)	1.31 (1.10-1.57)	<.0001
70-79	236	6.53	508	3.60	1.82 (1.56-2.13)	1.24 (1.04-1.48)	.02
≥80	84	7.54	200	4.71	1.60 (1.24-2.07)	1.20 (0.89-1.63)	.226
			Women				
Age[a]							
<40	40	0.33	98	0.21	1.57 (1.08-2.26)	1.73 (1.10-2.71)	.016
40-49	169	1.97	432	1.33	1.48 (1.24-1.77)	1.26 (1.01-1.58)	.033
50-59	536	6.95	1,521	4.37	1.34 (1.21-1.48)	1.16 (1.03-1.31)	.012
60-69	943	12.89	2,594	9.34	1.38 (1.28-1.49)	1.16 (1.06-1.21)	.001
70-79	946	19.88	2,761	7.94	1.32 (1.23-1.43)	1.15 (1.06-1.28)	.001
≥80	365	21.53	1,074	6.07	1.33 (1.18-1.49)	1.14 (0.98-1.31)	.072

[a] *Age at the index date.*

[b] *Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures, when not stratified by those*

5.3.3 Osteoporosis risk among patients with asthma

Increasing OCS prescriptions raised the risk with patients exposed to nine or more prescriptions per year of follow-up to be at higher risk than non-exposed (aHR = 6.11; 95% CI 5.31 to 7.02) (Table 5-4). Risk of osteoporosis increased with regular use of ICS prescription per year, however a substantial increase was observed after the 17th prescription per year of follow-up (aHR = 10.66; 95% CI 8.20 to 12.05). The risk of osteoporosis was greater in most deprived patients with asthma in relation to least deprived patients (aHR = 1.21; 95% CI 1.08 to 1.35)

Table 5-4. Risk of osteoporosis within asthma patient stratified by well-known risk factors.

	Asthma patients (n=138,123)				
Predictive variables	**Osteoporosis**	**Rate per 1000 person-years**	**Unadjusted HR (95%CI)**	**Adjusted HR[a] (95%CI)**	**p-value**
OCS prescriptions per person-year (n)					<.0001
0 (120,761)	2,341	3.67	Reference	Reference	
1-2 (8,489)	434	9.29	2.57 (2.31-2.86)	1.75 (1.57-1.95)	
3-5 (5,797)	463	15.79	4.41 (3.97-4.89)	2.49 (2.24-2.77)	
6-8 (1,652)	234	28.33	7.91 (6.92-9.18)	3.82 (3.28-4.44)	
≥9 (1,424)	295	54.03	15.36 (13.48-17.50)	6.11 (5.31-7.02)	
ICS prescriptions per person-year (n)					<.0001
0 (50,199)	1,234	4.87	Reference	Reference	
1-8 (79,430)	1,663	3.72	0.76 (0.70-0.81)	0.98 (0.92-1.05)	
9-13 (7,068)	429	11.51	2.51 (2.22-2.85)	1.72 (1.52-1.94)	
14-16 (980)	254	41.41	9.94 (7.99-12.35)	5.48 (4.41-6.82)	
≥17 (446)	187	79.11	16.24 (12.70-18.12)	10.66 (8.20-12.05)	
Gender					<.0001
Male	768	2.61	Reference	Reference	
Female	2,999	7.11	2.73 (2.52-2.95)	3.03 (2.80-3.28)	
Age					<.0001
≤40	55	0.28	Reference	Reference	
40-49	208	1.48	5.29 (3.93-7.13)	5.43 (4.03-7.32)	
50-59	678	5.05	18.06 (13.72-23.78)	18.00 (13.66-23.73)	
60-69	1,195	8.97	32.31 (24.65-42.34)	31.27 (23.79-41.10)	
70-79	1,182	14.12	51.71 (39.46-67.76)	45.34 (34.43-59.72)	
≥80	449	15.99	60.66 (45.83-80.29)	47.13 (35.36-62.79)	
Smoking					<.0001
Never	1,435	4.37	Reference	Reference	
Former	1,381	6.39	1.10 (1.01-1.20)	1.14 (1.06-1.24)	
Current	949	5.79	1.40 (1.27-1.55)	1.46 (1.34-1.59)	
BMI (kg/m^2)					<.0001
Underweight (<18.5)	253	14.18	1.48 (1.23-1.87)	1.50 (1.25-1.80)	
Normal (18.5 - 24.9)	1,340	6.94	Reference	Reference	
Overweight (25 - 29.9)	1,195	4.83	0.67 (0.62-0.73)	0.68 (0.63-0.74)	
Obese (≥30)	880	3.21	0.49 (0.44-0.53)	0.50 (0.46-0.55)	
IMD					<.0001
Least deprived	381	4.61	Reference	Reference	
-	401	4.96	1.08 (0.94-1.25)	1.01 (0.87-1.15)	
-	381	4.84	1.06 (0.92-1.22)	0.99 (0.86-1.14)	
-	370	4.95	1.08 (0.93-1.25)	1.02 (0.88-1.17)	
Most deprived	429	6.17	1.35 (1.17-1.55)	1.36 (1.18-1.56)	
Not known IMD	1,805	5.47	1.18 (1.05-1.31)	1.21 (1.08-1.35)	

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ICS, Inhaled Corticosteroids; IMD, Index of Multiple Deprivation; OCS, Oral corticosteroids.

[a] *Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures.*

5.3.4 Fragility fracture risk

A total of 4,286 (3.1%) patients with asthma and 13,040 (2.5%) without asthma sustained fragility fracture. The incidence rates were 5.99 (95% CI 5.81 to 6.17) in asthma and 4.77 (95% CI 4.69 to 4.85) in non-asthma group per 1,000 person-years (Table 5-5). After adjusting for confounders, the risk of fragility fractures was 12% higher in patients with asthma than those without asthma (aHR = 1.12; 95% CI 1.07 to 1.16). The Kaplan-Meier graph also displayed a significantly higher probability of fracture during the follow-up between the patients with and without asthma (Log-rank test, $p < .0001$) (Figure 5-1). The effect of asthma on risk of fragility fractures was modified by age ($p_{interaction} < .0001$), but not gender ($p_{interaction} = .9972$). Men from 40 to 59 and women from 18 to 49 and 60 to 69 years old had larger risk of fragility fractures in comparison to the corresponding general population (Table 5-6). Forearm-wrist (aHR = 1.21; 95% CI 1.13 to 1.30) and vertebral (aHR = 1.19; 95% CI 1.10 to 1.28) were the sites with a higher risk (Table 5-7). The risk of site-specific fragility fractures stratified by gender and age groups is summarised in Table 5-8.

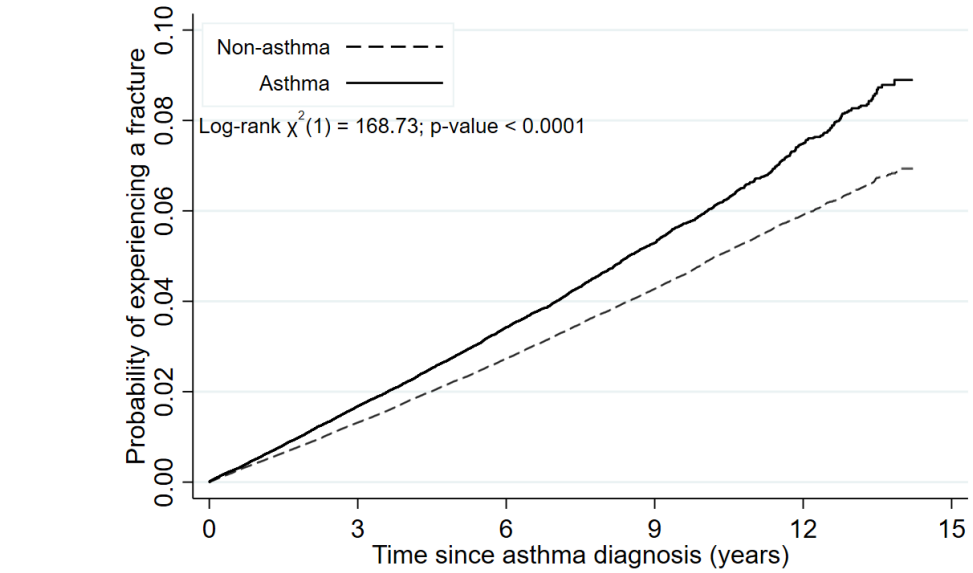

Figure 5-1. *Kaplan-Meier plot showing the probability of experiencing a fracture during the follow-up between asthma and non-asthma patients. The long-rank test is also presented.*

Table 5-5. Incidence rates and hazard ratios (HR) for associations of fracture with exposure to asthma.

	Asthma patients		Nonasthma patients				
Variables	**Number with fractures**	**Rate per 1000 person-years**	**Number with fractures**	**Rate per 1000 person-years**	**Unadjusted HR (95%CI)**	**Adjusted HR[b] (95%CI)**	***p*-value**
Overall	4,286	5.99	13,040	4.77	1.26 (1.21-1.30)	1.12 (1.07-1.16)	<.0001
Gender							
Male	1,107	3.76	3,287	2.93	1.29 (1.21-1.39)	1.11 (1.02-1.20)	.011
Female	3,179	7.54	9,753	6.06	1.25 (1.20-1.30)	1.11 (1.06-1.16)	<.0001
Age[a]							
<40	388	1.98	1,079	1.43	1.38 (1.23-1.55)	1.24 (1.07-1.44)	.005
40-49	428	3.07	1,171	2.21	1.39 (1.24-1.55)	1.33 (1.15-1.51)	<.0001
50-59	636	4.74	1,945	3.84	1.24 (1.13-1.35)	1.16 (1.04-1.28)	.009
60-69	1,052	7.87	3,021	5.96	1.33 (1.24-1.42)	1.15 (1.05-1.25)	.001
70-79	1,128	13.36	3,629	11.14	1.21 (1.13-1.29)	1.02 (0.95-1.11)	.541
≥80	654	23.41	2,195	20.30	1.15 (1.06-1.26)	1.00 (0.90-1.10)	.964

[a] *Age at the index date.*

[b] *Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, and previous: COPD, fractures; when not stratified by those.*

Table 5-6. Incidence rates and hazard ratios (HR) for associations of fragility fractures with exposure to asthma stratified by gender and age groups.

Variables	Asthma patients		Nonasthma patients		Unadjusted HR (95%CI)	Adjusted HR[b] (95%CI)	*p*-value
	Number with fractures	Rate per 1000 person-years	Number with fractures	Rate per 1000 person-years			
Men							
Age[a]							
<40	136	1.79	467	1.60	1.12 (0.92-1.35)	0.94 (0.73-1.20)	.632
40-49	145	2.68	360	1.74	1.53 (1.26-1.86)	1.53 (1.21-1.95)	<.0001
50-59	155	2.72	423	1.97	1.38 (1.14-1.65)	1.28 (1.03-1.61)	.032
60-69	252	4.19	728	3.19	1.32 (1.14-1.52)	1.06 (0.89-1.25)	.501
70-79	265	7.34	831	5.91	1.26 (1.10-1.44)	1.00 (0.85-1.17)	.999
≥80	154	13.99	478	11.37	1.25 (1.04-1.50)	1.01 (0.81-1.26)	.892
Women							
Age[a]							
<40	252	2.09	612	1.32	1.58 (1.25-1.83)	1.47 (1.22-1.78)	<.0001
40-49	283	3.31	811	2.50	1.32 (1.15-1.51)	1.25 (1.06-1.47)	.010
50-59	481	6.23	1,522	5.19	1.20 (1.08-1.33)	1.12 (0.98-1.26)	.079
60-69	800	10.87	2,293	8.20	1.33 (1.22-1.44)	1.17 (1.06-1.29)	.001
70-79	863	17.86	2,798	15.10	1.19 (1.10-1.28)	1.03 (0.94-1.12)	.526
≥80	500	29.53	1,717	25.97	1.13 (1.03-1.25)	0.99 (0.89-1.13)	.989

[a] *Age at the index date.*

[b] *Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures, when not stratified by those.*

Table 5-7. Overall incidence rates and hazard ratios (HR) for associations of site-specific fracture with exposure to asthma.

	Asthma patients		Nonasthma patients				
Fracture location	**Number with a fracture**	**Rate per 1000 person-years**	**Number with a fracture**	**Rate per 1000 person-years**	**Unadjusted HR (95%CI)**	**Adjusted HR[b] (95%CI)**	***p*-value**
Forearm-Wrist	1,463	2.04	4,363	1.59	1.28 (1.20-1.35)	1.21 (1.13-1.30)	<.0001
Vertebra	685	0.96	1,845	0.67	1.42 (1.30-1.55)	1.19 (1.10-1.28)	<.0001
Hip	873	1.22	2,954	1.08	1.13 (1.05-1.22)	1.01 (0.92-1.08)	.905
Humerus	598	0.83	1,842	0.67	1.24 (1.13-1.35)	1.05 (0.94-1.17)	.371
Unspecified[a]	667	0.93	2,036	0.74	1.26 (1.16-1.38)	1.06 (0.95-1.17)	.267

[a] *Just a mention that it was a fragility fracture without specifying the exact fracture location.*

[b] *Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures.*

Table 5-8. Adjusted Hazard ratios (HR) for associations of site-specific fracture with exposure to asthma stratified by gender and age groups.

		Adjusted HR[a] (95% CI)				
Variables		**Vertebral fractures**	**Forearm-wrist fractures**	**Hip fractures**	**Humerus fractures**	**Unspecified[b] fractures**
Gender						
	Male	1.16 (1.04-1.39)	1.12 (1.02-1.24)	1.08 (0.92-1.26)	1.14 (0.92-1.41)	1.16 (0.89-1.51)
	Female	1.13 (1.02-1.29)	1.24 (1.15-1.35)	0.96 (0.87-1.08)	1.02 (0.89-1.16)	1.03 (0.93-1.16)
Age[a]						
	<40	1.58 (1.15-2.17)	1.30 (1.09-1.55)	1.27 (0.62-2.60)	0.90 (0.58-1.40)	0.80 (0.22-2.88)
	40-49	1.59 (1.10-2.34)	1.31 (1.08-1.59)	1.26 (0.76-2.09)	1.21 (0.88-1.67)	1.39 (0.93-2.08)
	50-59	1.26 (0.92-1.71)	1.12 (0.94-1.33)	1.35 (0.98-1.86)	1.15 (0.89-1.48)	1.05 (0.79-1.39)
	60-69	1.16 (0.94-1.44)	1.31 (1.13-1.52)	0.91 (0.75-1.13)	1.22 (1.00-1.50)	1.05 (0.87-1.27)
	70-79	1.07 (0.89-1.28)	1.06 (0.90-1.25)	0.94 (0.82-1.09)	0.95 (0.76-1.20)	1.09 (0.91-1.31)
	≥80	1.02 (0.79-1.31)	1.12 (0.87-1.45)	1.02 (0.88-1.20)	0.65 (0.45-0.93)	1.05 (0.80-1.37)

[a] *Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures.*

[b] *Just a mention that it was a fragility fracture without specifying the exact fracture location.*

[c] *Age at the index date.*

5.3.5 Fracture risk among asthma patients

There were 17,233 (12.5%) and 87,675 (64%) distinct users with at least one OCS and ICS prescription per year of follow-up, respectively. The median OCS and ICS prescriptions per year of follow-up were 2 (IQR 1 to 4) and 5 (IQR 2 to 7), respectively. The fragility fracture risk increased from the sixth OCS course per year of follow-up (6 to 8 courses; aHR = 1.35; 95% CI 1.10 to 1.64). A larger risk due to ICS appeared after the 17th prescription per year of follow-up (aHR = 6.15; 95% CI 2.37 to 13.21) (Table 5-9).

Table 5-9. Risk of fragility fracture within asthma patients stratified by well-known risk factors.

	Asthma patients (n=138,123)				
Predictive variables	**Fractures**	**Rate per 1000 person-years**	**Unadjusted HR (95%CI)**	**Adjusted HR[a] (95%CI)**	**p-value**
OCS prescriptions per person-year (n)					<.0001
0 (120,890)	3,515	5.54	Reference	Reference	
1-2 (8,557)	326	7.62	1.37 (1.22-1.54)	0.97 (0.86-1.09)	
3-5 (5,795)	251	9.23	1.66 (1.46-1.89)	1.00 (0.88-1.14)	
6-8 (1,599)	105	14.28	2.60 (2.12-3.19)	1.35 (1.10-1.64)	
≥9 (1,282)	89	18.41	3.38 (2.71-4.21)	1.46 (1.16-1.83)	
ICS prescriptions per person-year (n)					<.0001
0 (50,448)	1,766	7.05	Reference	Reference	
1-8 (79,692)	2,174	4.99	0.70 (0.66-0.75)	0.92 (0.85-1.01)	
9-13 (6,982)	252	9.43	1.34 (1.18-1.53)	0.95 (0.83-1.08)	
14-16 (812)	56	27.87	4.15 (3.17-5.41)	2.45 (1.93-3.20)	
≥17 (189)	20	67.26	10.01 (5.41-18.81)	6.15 (2.37-13.21)	
Gender					<.0001
Male	1,107	3.76	Reference	Reference	
Female	3,179	7.54	2.00 (1.86-2.14)	2.13 (1.98-2.28)	
Age					<.0001
≤40	388	1.98	Reference	Reference	
40-49	428	3.06	1.54 (1.34-1.77)	1.58 (1.38-1.81)	
50-59	636	4.74	2.34 (2.09-2.70)	2.46 (2.17-2.80)	
60-69	1,052	7.87	3.98 (3.55-4.47)	4.13 (3.66-4.65)	
70-79	1,128	13.36	6.88 (6.12-7.72)	6.72 (5.95-7.59)	
≥80	654	23.41	12.58 (11.09-14.27)	11.34 (9.91-12.98)	
Smoking					<.0001
Never	1,736	5.29	Reference	Reference	
Former	1,517	7.04	1.34 (1.25-1.43)	1.09 (1.02-1.18)	
Current	1,033	6.19	1.17 (1.08-1.26)	1.35 (1.25-1.47)	
BMI (kg/m^2)					<.0001
Underweight (<18.5)	588	11.89	1.83 (1.51-2.21)	1.46 (1.19-1.79)	
Normal (18.5 - 24.9)	1,257	6.34	Reference	Reference	
Overweight (25 - 29.9)	1,296	5.80	0.92 (0.85-0.99)	0.83 (0.76-0.89)	
Obese (≥30)	1,145	5.08	0.82 (0.75-0.89)	0.71 (0.65-0.77)	
IMD					<.0001
Least deprived	417	5.04	Reference	Reference	
-	479	5.93	1.18 (1.04-1.35)	1.11 (0.98-1.27)	
-	480	6.12	1.22 (1.07-1.39)	1.17 (1.03-1.33)	
-	394	5.28	1.05 (0.91-1.20)	1.02 (0.88-1.16)	
Most deprived	409	5.87	1.17 (1.02-1.34)	1.15 (1.02-1.31)	
Not known IMD	2,107	6.39	1.25 (1.13-1.39)	1.27 (1.14-1.41)	

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ICS, Inhaled Corticosteroids; IMD, Index of Multiple Deprivation; OCS, Oral corticosteroids.

[a] *Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures*

5.3.6 Sensitivity analyses

The results remained consistent in the sensitivity analyses (Table 5-10).

Table 5-10. Incidence rates and hazard ratios (HR) for associations of fragility fractures with exposure to asthma after conducting sensitivity analyses.

	Unadjusted HR (95%CI)	Adjusted HR[c] (95%CI)	*p*-value
Overall[a]	1.26 (1.21-1.30)	1.12 (1.07-1.17)	<.0001
Overall[b]	1.28 (1.23-1.33)	1.14 (1.08-1.20)	<.0001

[a] *Patients with an osteoporosis diagnosis prior the asthma diagnosis have been included.*

[b] *Patients with an any fracture diagnosis prior the asthma diagnosis have been excluded.*

[c] *Adjusted for age, gender, smoking, BMI, Charlson score, ICS, OCS, IMD, previous: COPD, fractures osteoporosis, when not stratified by those.*

5.4 Discussion

Overall, this study shows that asthma is associated with an increased risk of osteoporosis and fragility fractures. This association was stronger in the younger age groups. Among patients with asthma, a single OCS course raised the osteoporosis risk, and greater use of ICS increased the risk of both bone diseases.

To the best of my knowledge, this is the largest study reporting the incidence and risk of osteoporosis and fragility fractures in asthma using a primary care database. Other strength is the population-based setting that means the findings are generalizable to the wider population. Osteoporosis and fragility fracture diagnoses were captured for the general population of asthma and not just for a specific one such as people with severe asthma. It was able to adjust for a wide range of potentially confounding factors. The results were also robust to sensitivity analyses. The limitations of matching include the need for a large sample size to identify matched subjects and selection of suitable/appropriate variables for matching. In cohort studies, matching may not increase statistical power (efficiency), but it does not introduce bias (as it does in case-control studies). With large databases such as CPRD linked to HES any small loss in efficiency may be unimportant, and the similarity of the exposed and

unexposed cohorts at the start is a gain, as this prevented the possible association between the matching factors and asthma at the start of the study reducing confounding (182).

The data use from primary care databases has some limitations. Firstly, there may be misclassification of asthma, osteoporosis, and fragility fractures diagnoses, as we were reliant on how accurately general practitioners record these conditions. However, these diagnoses have been previously validated in the database demonstrating a positive predictive value around 90%; therefore, the existence of any diagnosis misclassification in our study should be very unlikely (163,183). In addition, most fractures are painful and medical treatment would be sought for it and it be recorded, however, vertebral fractures or osteoporosis often do not come to clinical attention, and people might not be aware of these conditions (184); this may result in the underestimation of their coding and as a result of their risk. Nevertheless, this underestimation should not be different in people with asthma than people who do not have asthma. As in all health care datasets, prescriptions were based on issued prescriptions without knowing whether they were dispensed.

The absolute incidence rate of each fragility fractures site in my general population is in accordance with another CPRD cohort study (185), and the incidence of hip fractures is additionally identical to population statistics in the UK (10.8 vs 10.3 per 10,000 person-years) (186). The observed rate is consistent with the limited published studies examining the osteoporosis and fracture risk in asthma. However, these studies were small (e.g. 105 patients vs 133 controls), lacked data on important confounders such as BMI, socioeconomic status, or focused on specific asthma group providing a little information about the risk in asthma (153,154,187). Sweeney et al. found a higher risk of osteoporosis and fracture compared to our study which probably reflects the more severe asthma population (153). There was a greater risk of spine and forearm fractures in accordance with reports shown a lower BMD at these

sites in patients with asthma (173,178,188), but not a significant risk of hip fractures in agreement with a meta-analysis (189) which did not find a reduced BMD at femur/hip between patients with asthma and controls.

This study found the effect of asthma on osteoporosis is stronger in younger people and males and on fragility fractures in younger people. This observation may be due to other factors such as previous fractures, low oestrogen level, comorbidities, and other medications which have a bigger impact on the risk of osteoporosis and fragility fracture and are more likely in older people or women. Therefore, at younger ages and in men the main risk factor for osteoporosis will be steroids, hence the stronger relationship. Lastly, men and youngers generally receive osteoporosis treatment less frequently than women and older people (35). Knowledge that the effect of asthma on osteoporosis and fragility fractures is stronger in younger people is crucial in daily asthma practice in terms of the management of corticosteroid therapy minimising the side effects in subpopulation being at higher risk. Furthermore, as the effect of asthma on osteoporosis is stronger in males a high awareness is recommended not only in female but in male patients with asthma

Previous studies have reported an increase in fracture risk in relation to daily and cumulative OCS use, and this study shows that even one prescription per year increases the risk (67,153,190). Concerns about the negative impact of ICS on bones are recognised with long-term use (≥0.7mg/day) (112), with these findings confirming the negative effects on bone of ICS within asthma population at regular use of ICS. It is best practice to review OCS and ICS dose and use the lowest dose possible to maintain asthma control (191). Although there is clear guidance on OCS and bisphosphonate therapy in the general population, there is no current recommendation for bisphosphonate therapy for ICS users, despite evidence supporting fractures-related to ICS (111,112).

Current UK guidelines on asthma do not cover the management of these bone comorbidities appropriately due to the very few studies specific to asthma. Specifically, the BTS/SIGN guideline on asthma management cover specific co-morbidities including osteoporosis, but not specific bone protection guidance is given (16), and the NICE asthma guideline does not mention osteoporosis at all (17). The results suggest that osteoporosis and fragility fractures should be addressed explicitly in future guideline updates.

5.5 Conclusion

Patients with asthma have an increased osteoporosis and fragility fractures risk compared to the general population, in particular vertebral and humerus fractures. An increased awareness of these bone disease comorbidities in asthma, particularly in the younger population, is needed. Reviewing corticosteroid dose and using the lowest dose possible minimising the risk of these bone conditions in asthma is recommended.

6 RISK OF OSTEOPOROSIS AND FRAGILITY FRACTURES IN ASTHMA DUE TO ORAL AND INHALED CORTICOSTEROIDS: TWO POPULATION-BASED NESTED CASE-CONTROL STUDIES

6.1 Introduction

The Global Initiative for Asthma (GINA) guidelines suggest a stepwise approach with low to high-dose ICS alone or in combination with long-acting-β_2-agonists as the first line treatment for patients with moderate to severe asthma, and use of OCS for patients experiencing exacerbations or having severe asthma.(13) Both ICS and OCS are known to cause well-recognised side effects (66,172,192,193).

One of the most frequent adverse effects is osteoporosis which can lead to fragility fractures (111,174,194). Fragility fracture are associated with substantial increased health care costs, morbidity, and mortality.(89,176) Studies investigating the adverse effects of corticosteroids on bone health based on change in bone mineral density (BMD) in patients with asthma have contradictory findings. Laatikainen et al. did not find statistically significant differences in BMD between three groups of patients with asthma (ICS; n = 26 vs OCS; n = 65 vs non-exposed; n = 28) (149). Similarly, a 4-year longitudinal study assessing lumbar spine BMD in people with asthma receiving low (n = 26) and high (n = 9) ICS doses as well as sporadic (n = 26) and frequent (n = 9) OCS did not reveal any change in BMD ($p > .05$) (150). This might be a result due to small sample size in both studies. In contrast, Wong et al. showed that cumulative dose of ICS (median = 876 mg) was negatively associated with BMD ($p < 0.05$) in young patients with asthma (151). Sivri et al. also found a significantly lower BMD in female patients with asthma exposed to regular use of ICS (750 to 1500μg/d for at least 3 months) (195). Few studies have quantified the risk between corticosteroids and bone health in patients with asthma, mostly examining the effects of OCS (152–154). However, these studies have been limited by their small size and focus on severe asthma.

Given that the use of ICS in asthma is likely to increase with the recent change in GINA guidance recommending combined long-acting-β_2-agonists with ICS at step 1 (13) and OCS are still prescribed for severe asthma or exacerbations, I sought to clarify the link between steroids, osteoporosis and fragility fractures in patients with asthma stratifying the risk by dose, number of courses, and type of steroids.

6.2 Methods

6.2.1 Source population

Two population-based nested case-control studies were conducted utilising the Clinical Practice Research Datalink GOLD (158) linked to the Hospital Episode Statistics database (196). The study population included all adult patients (≥18 years old) with a Read code for asthma between 1st April 2004 (activation of Quality and Outcomes Framework score) to 31th December 2017, with at least 1 year of data collection prior to the Read coded diagnosis of asthma date ensuring that only 'incident' cases were picked (180). Patients classed as "acceptable" research quality data and registered to an up-to standard practice according to CPRD's recommendations were included.

6.2.2 Cases, controls, and outcomes definition

Cases were defined by the first-recorded diagnosis of 1) osteoporosis and 2) fragility fracture (as separate outcomes). The databases were linked using an identifier variable (same in both databases) called "patid", and then the earliest diagnosis was defined in both databases by using either the Read or ICD-10 code, depending on the database. The date of the first diagnosis of 1) osteoporosis and 2) fragility fracture served as the index date for the cases. Each case was matched with up to four randomly selected

patients from the remaining patients with asthma by age (±1 year), gender and practice. The same index date to controls and cases was assigned.

Vertebral, hip, forearm-wrist, and humeral fractures are considered common sites of fragility fractures, and are associated with morbidity and mortality (176,181). A composite of these fracture sites was used to define the presence of fragility fractures. Any fracture described as an "open fracture" was excluded, since this type usually occurs via a high-energy event, and is not related to frailty. The code list was reviewed by a clinician to identify appropriate fractures that were unlikely to be osteoporotic in nature.

6.2.3 Potential confounders

For each participant in this study, information on the following variables was retrieved which are well-established risk for fracture or thought to have an impact on osteoporosis or fracture risk and are also likely to be recorded within the databases: age at the index date; sex, including only those clearly classified as male or female; body mass index using the nearest measurement prior the index date and categorised according to the WHO; smoking and alcohol status using the nearest measurement ever prior to the index date; socioeconomic status measured by using the patient-level Index of Multiple Deprivation 2015 in quintiles, with quintile 1 being the least and quintile 5 the most deprived; osteoporosis (only when the outcome was fragility fractures), any fracture (not those considered as an outcome) or falls prior the index date; bisphosphonates, Vitamin D and Calcium supplements the year prior the index date. The comorbidities were also summarised using the Charlson comorbidity index score (169). If there was no record for a medication or diagnosis, patients were assumed to have not had the exposure.

6.2.4 Exposure assessment

Corticosteroid use was categorised in a number of ways. Initially, a 1-year period prior to index date was used to identify the exposure status. OCS and ICS use were examined as the number of prescriptions filled. It was not possible to categorise the OCS use by type since 97% of individuals received prednisolone. ICS was grouped according to type as follows: beclomethasone dipropionate, budesonide, fluticasone propionate, and ciclesonide. Where the type of ICS was changed during the year, we considered the most frequently prescribed. The OCS and ICS as cumulative dose in milligrams (mg) over the previous year was also assessed. To calculate the cumulative OCS and ICS dose using information from tablet strength (e.g. 5mg) or the dose of drug delivered with each inhalation (e.g. 0.1mg) and prescribed quantity, multiplying the quantity by strength for each prescription, and then all doses per patient were summed. Missing or implausible values were dealt with using a recognised algorithm (197). I additionally looked for the exposure in different time periods. Thus, the cumulative dose and number of OCS and ICS prescriptions were calculated as a rate per year, identifying prescriptions up to 10 years prior the index date (median patients' record time prior the index date), as well as from the asthma to the index date. The reference category for all analyses was no steroid exposure. To account for differences in potency of different types of corticosteroids, dosages were converted into prednisolone and beclomethasone equivalent for OCS and ICS, respectively (Table 6-1).

Table 6-1. Equivalent doses to prednisolone and beclomethasone for oral and inhaled corticosteroids.

Oral corticosteroids	
Prednisolone 5mg	Betamethasone 0,75mg
	Deflazacort 6mg
	Dexamethasone 0,75mg
	Hydrocortisone 20mg
	Methylprednisolone 4mg
	Prednisone 5mg
Inhaled corticosteroids	
Beclomethasone 0.4mg	Budesonide 0.4mg
	Fluticasone 0.2mg
	Ciclesonide 0.16mg

6.2.5 Statistical analysis

Descriptive statistics were used to summarise the characteristics of the cases and controls. To account for the matched design, conditional logistic regression was used deriving unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) assessing the effect of OCS and ICS exposure on the first osteoporosis and fragility fracture diagnosis after the asthma date, separately. Firstly, a univariate analysis between the exposure and outcome of interest to establish the unadjusted OR was performed. The *a priori* confounders were BMI and smoking status. The next step was to fit the conditional logistic regression model including the exposure of interest and the *a priori* confounders. Each of the other potential confounding variables were added into the model, one at a time, removing this potential confounder before adding the next. If the inclusion of the confounder changed the effect of the exposure of interest by more than 5% then it was an important confounder and should be placed in the fully adjusted model. Missing data for BMI and smoking status were assumed as missing at random and imputed using chained equations. 10 imputations were generated, and the imputed model consisted of all listed confounders, OCS and ICS exposure, and the case-control indicator. Missing data for IMD were assigned a new

category. The prevalence of those receiving at least one bisphosphonate prescription per steroid prescription category after their initiation the year prior to the index dates was also calculated. Sensitivity analyses was also conducted including only the patients with at least one ICS prescription the year prior to the index dates as a stricter definition of asthma as well as only the individuals not in receipt of OCS within the database records examining the relationship between ICS and bone comorbidities eliminating any confounding due to OCS. All analyses were performed in Stata v16.

6.3 Results

6.3.1 Characteristics of the study populations

This study identified 1,564 patients with asthma and osteoporosis, and 3,313 control subjects as well as 2,131 patients with asthma and fractures and 4,421 control subjects from a cohort of 69,074 people with asthma (Table 6-2 & 6-3). The vast majority were women, and the mean age were 69.4 years (range 26-95 years) for osteoporosis and 66.4 years (range 18-94 years) for fractures. Patients with asthma and both osteoporosis and fracture were more likely to smoke, had more comorbid illness, and were from a lower social class compared with control subjects. The cases were more likely to have a previous diagnosis of fall or fracture and had more prescriptions of bisphosphonates in the previous year than their controls.

Table 6-2. Characteristics of patients with osteoporosis and control subjects

Characteristic	Cases (N=1564)	Controls (N=3313)	Unadjusted OR (95%CI)
	n (%)	n (%)	
Age[a] (mean±SD), y	69.4±10.7	68.1±10.4	-
Sex			
Male	303 (19.4)	619 (18.7)	-
Female	1,261 (80.6)	2,694 (81.3)	-
Smoking status			
Never	584 (37.3)	1,438 (43.4)	1.00
Former	584 (37.3)	1,267 (38.3)	1.17 (1.02-1.35)
Current	381 (24.4)	574 (17.3)	1.95 (1.62-2.33)
Missing status	15 (01.0)	34 (1.0)	0.93 (0.37-2.32)
BMI status			
Underweight (<18.5)	76 (04.9)	48 (01.5)	2.25 (1.50-3.36)
Normal (18.5 - 24.9)	481 (30.7)	654 (19.7)	1.00
Overweight (25 - 29.9)	435 (27.8)	990 (29.9)	0.56 (0.47-0.67)
Obese (≥30)	322 (20.6)	1,099 (33.2)	0.39 (0.32-0.46)
Missing status	250 (16.0)	522 (15.8)	0.63 (0.51-0.79)
Alcohol status			
Non-drinker	187 (12.0)	323 (09.8)	1.00
Ex-drinker	181 (11.6)	402 (12.1)	0.81 (0.62-1.05)
Current drinker	1,052 (67.3)	2,315 (69.9)	0.85 (0.69-1.04)
Missing status	144 (9.2)	273 (8.2)	1.02 (0.76-1.37)
IMD (Social Class)			
1 (least deprived)	295 (18.9)	653 (19.7)	1.00
2	324 (20.8)	688 (20.8)	1.12 (0.91-1.40)
3	318 (20.3)	710 (21.4)	1.13 (0.90-1.41)
4	319 (20.4)	665 (20.1)	1.21 (0.96-1.53)
5 (most deprived)	306 (19.6)	597 (18.0)	1.36 (1.06-1.74)
Charlson comorbidity index			
1	717 (45.8)	1,847 (55.8)	1.00
2	258 (16.5)	523 (15.8)	1.27 (1.06-1.52)
3	274 (17.5)	447 (13.5)	1.51 (1.25-1.81)
4	151 (9.7)	250 (7.6)	1.54 (1.21-1.94)
≥5	164 (10.5)	246 (7.4)	1.62 (1.27-2.06)
Drug use in the year prior the index date			
Bisphosphonates	851 (54.5)	162 (4.9)	25.11 (19.38-32.53)
Vitamin D and/or Calcium	418 (26.8)	243 (7.3)	4.47 (3.69-5.40)
History of a diagnosis ever prior the index date			
Fall	450 (28.8)	575 (17.4)	1.95 (1.65-2.27)
Any fracture	478 (31.0)	533 (16.1)	2.38 (1.98-2.68)

Abbreviations: BMI, body mass index; IMD, Index of Multiple Deprivation.
Percentages have been rounded and might not total 100. [a]Age at the index date.

Table 6-3. Characteristics of patients with fragility fractures and control subjects.

Characteristic	Cases (N=2131)	Controls (N=4421)	Unadjusted OR (95%CI)
	n (%)	n (%)	
Age[a] (mean±SD), y	65.1±14.9	64.0±14.1	-
Sex			
Male	633 (29.8)	1,215 (27.5)	-
Female	1,497 (70.2)	3,206 (72.5)	-
Smoking status			
Never	813 (38.2)	1,870 (42.3)	1.00
Former	767 (36.0)	1,693 (38.3)	1.04 (0.92-1.18)
Current	513 (24.0)	806 (18.2)	1.53 (1.32-1.77)
Missing status	38 (01.8)	52 (01.2)	1.81 (0.94-3.49)
BMI status			
Underweight (<18.5)	79 (3.7)	62 (1.4)	2.28 (1.57-3.29)
Normal (18.5 - 24.9)	507 (23.8)	905 (20.5)	1.00
Overweight (25 - 29.9)	588 (27.6)	1,291 (29.2)	0.80 (0.68-0.93)
Obese (≥30)	538 (25.2)	1,389 (31.3)	0.72 (0.61-0.84)
Missing status	419 (19.6)	774 (17.5)	0.95 (0.80-1.13)
Alcohol status			
Non-drinker	203 (09.5)	396 (09.0)	1.00
Ex-drinker	211 (09.9)	467 (10.6)	0.91 (0.72-1.17)
Current drinker	1,506 (70.7)	3,156 (71.4)	0.99 (0.82-1.20)
Missing status	211 (9.9)	402 (9.1)	1.07 (0.82-1.38)
IMD (Social Class)			
1 (least deprived)	382 (18.0)	893 (20.2)	1.00
2	468 (22.0)	916 (20.8)	1.25 (1.04-1.50)
3	442 (20.8)	952 (21.5)	1.16 (0.95-1.40)
4	418 (19.7)	819 (18.5)	1.26 (1.04-1.55)
5 (most deprived)	420 (19.7)	840 (19.0)	1.23 (1.04-1.52)
Charlson comorbidity index			
1	1,195 (56.1)	2,786 (63.0)	1.00
2	319 (15.0)	643 (14.5)	1.17 (0.99-1.38)
3	256 (12.0)	460 (10.4)	1.33 (1.11-1.59)
4	157 (7.4)	268 (6.1)	1.39 (1.11-1.75)
≥5	204 (9.6)	264 (6.0)	1.71 (1.37-2.13)
Drug use in the year prior the index date			
Bisphosphonates	255 (12.0)	217 (4.9)	2.57 (2.10-3.15)
Vitamin D and/or Calcium	194 (9.1)	260 (5.9)	1.54 (1.25-1.91)
History of a diagnosis ever prior the index date			
Fall	577 (27.1)	607 (13.7)	2.44 (2.11-2.81)
Osteoporosis	261 (12.3)	202 (4.6)	2.82 (2.29-3.46)
Any fracture	707 (33.2)	662 (15.0)	2.94 (2.57-3.36)

Abbreviations: BMI, body mass index; IMD, Index of Multiple Deprivation.
Percentages have been rounded and might not total 100. [a] Age at the index date.

6.3.2 Corticosteroids and risk of osteoporosis

A dose-response relationship was observed between the number of prescriptions and cumulative dose the year prior and risk of osteoporosis. Two to three OCS prescriptions were linked with larger odds of osteoporosis, with those receiving more OCS prescriptions (≥9 vs 0 prescriptions; aOR = 4.50; 95%CI 3.21 to 6.11) and cumulative doses (≥2,500 vs 0 mg; aOR = 4.79; 95%CI 3.38 to 6.79) being at greater risk (Table 6-4). ICS exposure was associated with osteoporosis, but the effect was less strong than with OCS. Patients prescribed eleven or more prescriptions were 1.6 times more likely to be diagnosed with osteoporosis than controls (aOR = 1.60; 95%CI: 1.22 to 2.10), after adjusting for confounders. However, the risk was slightly increased with cumulative doses more than 120mg the year prior the index date (≥120 vs 0 mg; aOR = 1.63; 95%CI 1.33 to 1.99). The risk was similar across ICS type, but budesonide had the strongest effect (aOR = 1.56; 95%CI 1.23 to 1.98). When a 10-year period prior to index date was used to identify the exposure status the results were identical (Tables 6-5 & 6-6).

Table 6-4. Association between oral and inhaled corticosteroids exposure in the year prior to the index date and risk of osteoporosis.

	Cases		Controls		Unadjusted	Adjusted[a] OR	
Type of exposure	**n**	**%**	**n**	**%**	**OR (95%CI)**	**(95%CI)**	***p*-value[*]**
No OCS use (reference)	992	63.4	2,607	78.8	1.00	1.00	
OCS prescriptions							<.0001
1	188	12.0	371	11.1	1.44 (1.19-1.77)	1.12 (0.90-1.40)	
2-3	123	7.9	189	5.7	1.88 (1.45-2.42)	1.34 (1.12-1.66)	
4-8	161	10.3	98	3.0	4.74 (3.58-6.28)	3.80 (2.81-5.13)	
≥9	100	6.4	48	1.5	5.37 (3.69-7.82)	4.50 (3.21-6.11)	
OCS cumulative dose (mg)							<.0001
≤500	244	15.6	475	14.4	1.47 (1.23-1.77)	1.21 (1.03-1.43)	
501-1000	83	5.3	99	3.0	2.44 (1.75-3.41)	2.05 (1.57-2.68)	
1001-2500	148	9.5	86	2.6	4.77 (3.59-6.40)	4.04 (3.12-5.12)	
>2500	95	6.1	44	1.3	6.10 (4.15-8.98)	4.79 (3.38-6.79)	
No ICS use (reference)	569	36.4	1,742	52.6	1.00	1.00	
ICS prescriptions							<.0001
1-6	605	38.7	1,053	31.2	1.87 (1.61-2.17)	1.35 (1.14-1.59)	
7-10	220	14.1	294	8.9	2.49 (2.01-3.07)	1.51 (1.20-1.92)	
≥11	170	10.9	224	6.8	2.66 (2.08-3.39)	1.60 (1.22-2.10)	
ICS type							
Beclomethasone	423	27.1	783	23.6	1.75 (1.49-2.06)	1.29 (1.08-1.54)	.007**
Budesonide	207	13.2	300	09.1	2.27 (1.82-2.83)	1.56 (1.23-1.98)	<.0001**
Fluticasone	352	22.5	475	14.3	2.44 (2.04-2.96)	1.44 (1.18-1.77)	<.0001**
Ciclesonide	12	0.9	12	0.5	2.55 (1.13-5.75)	1.80 (0.76-4.27)	.179**
ICS cumulative dose (mg)[b]							<.0001
≤40	209	13.4	433	13.1	1.60 (1.37-2.01)	1.18 (0.95-1.47)	
41-80	232	14.8	363	10.1	2.07 (1.62-2.40)	1.26 (0.98-1.60)	
81-120	180	11.5	282	08.5	2.02 (1.74-2.72)	1.50 (1.21-1.87)	
>120	370	23.7	488	14.7	2.55 (2.01-2.97)	1.63 (1.33-1.99)	

[a] Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonate, and number of OCS or ICS prescriptions accordingly.

[*]P-values for trend. The p-values are referred to the adjusted model.

Table 6-5. Association between oral and inhaled exposure as rate per year up to 10 years prior to the index date and risk of osteoporosis.

	Cases		Controls		Unadjusted	Adjusted[a] OR	
Type of exposure	**n**	**%**	**n**	**%**	**OR (95%CI)**	**(95%CI)**	***p*-value***
No OCS use (reference)	578	36.9	1,751	52.8	1.00	1.00	
OCS prescriptions per year							<.0001
1	265	16.9	560	16.9	1.52 (1.26-1.82)	1.21 (0.99-1.48)	
2-3	212	13.6	468	14.1	1.59 (1.30-1.94)	1.18 (0.95-1.47)	
4-8	241	15.4	335	10.1	2.58 (2.08-3.19)	1.81 (1.44-5.13)	
≥9	268	17.2	199	6.1	4.68 (3.71-5.89)	3.13 (2.44-6.11)	
OCS cumulative dose (mg) per year							<.0001
≤500	332	21.2	746	22.5	1.49 (1.25-1.76)	1.15 (0.96-1.39)	
501-1000	155	9.9	308	9.3	1.69 (1.35-2.12)	1.28 (1.01-1.63)	
1001-2500	180	11.5	274	8.3	2.35 (1.86-2.97)	1.70 (1.31-2.18)	
>2500	319	20.4	234	7.1	4.78 (3.84-5.95)	3.26 (2.57-4.14)	
No ICS use (reference)	335	22.7	1,247	37.7	1.00	1.00	
ICS prescriptions per year							<.0001
1-6	557	35.6	1,014	30.6	2.13 (1.79-2.53)	1.43 (1.19-1.74)	
7-10	350	22.4	492	14.9	2.70 (2.22-3.30)	1.42 (1.15-1.76)	
≥11	302	19.3	560	16.9	1.99 (1.64-2.43)	1.64 (1.32-2.04)	
ICS cumulative dose (mg) per year							<.0001
≤40	201	13.4	432	13.6	1.90 (1.52-2.38)	1.27 (0.98-1.62)	
41-80	430	28.0	703	21.8	2.40 (1.99-2.90)	1.52 (1.23-1.87)	
81-120	277	18.3	427	13.5	2.63 (2.13-3.25)	1.50 (1.20-1.88)	
>120	301	19.8	504	15.8	2.27 (1.85-2.77)	1.63 (1.29-2.05)	

[a] Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonate, and number of OCS or ICS prescriptions accordingly.

**P-values for trend. The p-values are referred to the adjusted model.*

Table 6-6. Association between oral inhaled exposure as rate per year from the asthma to the index date and risk of osteoporosis.

	Cases		Controls		Unadjusted	Adjusted[a] OR	
Type of exposure	**n**	**%**	**n**	**%**	**OR (95%CI)**	**(95%CI)**	***p*-value***
No OCS use (reference)	548	35.0	1,652	49.9	1.00	1.00	
OCS prescriptions per year							<.0001
1	254	14.2	586	17.7	1.39 (1.16-1.68)	1.10 (0.90-1.35)	
2-3	226	14.5	478	14.4	1.68 (1.38-2.06)	1.27 (1.02-1.58)	
4-8	233	14.9	363	11.0	2.36 (1.90-2.91)	1.66 (1.32-2.09)	
≥9	303	19.4	234	7.1	4.65 (3.71-5.82)	3.14 (2.46-4.00)	
OCS cumulative dose (mg) per year							<.0001
≤500	326	20.8	779	23.5	1.39 (1.17-1.65)	1.07 (0.89-1.30)	
501-1000	160	10.2	324	9.8	1.71 (1.36-2.15)	1.31 (1.03-1.67)	
1001-2500	179	11.4	292	8.8	2.25 (1.78-2.84)	1.58 (1.23-2.02)	
>2500	351	22.4	266	8.0	4.64 (3.75-5.74)	3.20 (2.54-4.03)	
No ICS use (reference)	456	29.2	1,543	46.6	1.00	1.00	
ICS prescriptions per year							<.0001
1-6	427	27.3	774	23.4	2.22 (1.86-2.66)	1.52 (1.25-1.85)	
7-10	346	22.1	454	13.7	2.95 (2.42-3.59)	1.61 (1.31-1.98)	
≥11	335	21.4	542	16.4	2.35 (1.95-2.84)	1.77 (1.43-2.19)	
ICS cumulative dose (mg) per year							<.0001
≤40	215	13.8	416	12.6	2.13 (1.71-2.64)	1.48 (1.17-1.87)	
41-80	305	19.5	475	14.3	2.60 (2.12-3.18)	1.54 (1.25-1.90)	
81-120	277	17.7	398	12.0	2.71 (2.21-3.33)	1.68 (1.35-2.09)	
>120	319	20.4	509	15.4	2.41 (1.98-2.93)	1.74 (1.40-2.18)	

[a] *Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonate, and number of OCS or ICS prescriptions accordingly.*

**P-values for trend. The p-values are referred to the adjusted model.*

6.3.3 Corticosteroids and risk of fragility fracture

There was an effect of OCS on risk of fragility fractures, however the effect size was smaller than on osteoporosis. More than nine OCS prescriptions in the previous year had a significant impact on risk (≥9 vs 0 prescriptions; aOR = 2.16; 95%CI 1.56 to 3.38), whereas OCS cumulative doses at more than 1000 mg led to an increased risk in the previous year, with the risk to be greater at higher doses in comparison to controls (≥2,500 vs 0 mg; aOR = 1.99; 95%CI 1.30 to 3.04) (Table 6-7). Eleven or more ICS prescriptions were associated with an increased risk of fracture (≥11 vs 0 prescriptions; aOR = 1.31; 95%CI 1.02 to 1.68). Patients exposed to cumulative doses at more than 120 mg in the year prior to the fragility fracture were 1.2 times more likely to sustain fragility fractures (aOR = 1.20; 95%CI 1.08 to 1.42). No significant association between any ICS type and fragility fracture was found. When a 10-year period prior to index

date was used to identify the exposure status the results were identical (Tables 6-8 & 6-9).

Table 6-7. Association between oral and inhaled exposure in the year prior to the index date and risk of fragility fracture.

	Cases		Controls		Unadjusted	Adjusted[a] OR	
Type of exposure	**n**	**%**	**n**	**%**	**OR (95%CI)**	**(95%CI)**	***p*-value***
No OCS use (reference)	1,663	78.0	3,676	83.1	1.00	1.00	
OCS prescriptions							.0002
1	219	10.3	410	9.3	1.23 (1.03-1.48)	1.11 (0.91-1.34)	
2-3	112	5.3	171	3.9	1.43 (1.10-1.85)	1.24 (0.95-1.62)	
4-8	85	4.0	123	2.8	1.56 (1.16-2.10)	1.31 (1.12-1.77)	
≥9	52	2.4	41	1.0	2.70 (1.75-4.17)	2.16 (1.56-3.38)	
OCS cumulative dose (mg)							.0001
≤500	279	13.1	507	11.5	1.25 (1.06-1.48)	1.11 (0.92-1.32)	
501-1000	60	2.8	98	2.2	1.39 (0.98-1.96)	1.20 (0.84-1.70)	
1001-2500	79	3.7	93	2.1	1.84 (1.33-2.55)	1.54 (1.10-2.14)	
>2500	50	2.4	47	1.1	2.36 (1.56-3.59)	1.99 (1.30-3.04)	
No ICS use (reference)	1,081	50.7	2,527	57.1	1.00	1.00	
ICS prescriptions							.010
1-6	678	31.8	1,330	30.1	1.19 (1.05-1.35)	1.02 (0.89-1.17)	
7-10	219	10.3	340	7.7	1.51 (1.24-1.84)	1.24 (1.01-1.53)	
≥11	153	7.2	224	5.1	1.66 (1.30-2.11)	1.31 (1.02-1.68)	
ICS type							
Beclomethasone	510	23.9	984	22.3	1.21 (1.06-1.40)	1.10 (0.94-1.28)	.213**
Budesonide	176	08.3	333	7.5	1.29 (1.04-1.59)	1.14 (0.90-1.44)	.269**
Fluticasone	341	16.0	548	12.4	1.38 (1.16-1.63)	1.04 (0.85-1.26)	.679**
Ciclesonide	16	0.8	24	0.5	2.21 (1.09-4.48)	1.75 (0.82-3.75)	.145**
ICS cumulative dose (mg)[b]							.021
≤40	257	12.1	560	12.7	1.06 (0.89-1.26)	0.94 (0.78-1.31)	
41-80	248	11.6	433	9.8	1.35 (1.12-1.62)	1.13 (0.93-1.63)	
81-120	194	9.1	332	7.5	1.35 (1.10-1.65)	1.14 (0.90-1.78)	
>120	348	16.3	564	12.8	1.47 (1.25-1.74)	1.20 (1.08-1.42)	

[a] Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonates, and number of ICS or OCS prescriptions accordingly.

**P-values for trend. The p-values are referred to the adjusted model.*

Table 6-8. Association between oral and inhaled exposure as rate per year up to 10 years prior to the index date and risk of fragility fractures.

	Cases		Controls		Unadjusted	Adjusted[a] OR	
Type of exposure	**n**	**%**	**n**	**%**	**OR (95%CI)**	**(95%CI)**	***p*-value***
No OCS use (reference)	1.153	54.1	2,639	59.6	1.00	1.00	
OCS prescriptions per year							.0005
1	336	15.8	750	17.0	1.02 (0.88-1.20)	0.94 (0.80-1.09)	
2-3	257	12.1	472	10.7	1.32 (1.11-1.58)	1.15 (0.95-1.38)	
4-8	211	9.9	358	8.1	1.43 (1.17-1.74)	1.25 (1.02-1.53)	
≥9	174	8.2	202	4.6	1.96 (1.56-2.48)	1.58 (1.25-2.00)	
OCS cumulative dose (mg) per year							<.0001
≤500	419	19.7	953	21.6	1.03 (0.89-1.19)	0.92 (0.80-1.07)	
501-1000	187	8.8	307	6.9	1.46 (1.18-1.80)	1.26 (0.98-1.55)	
1001-2500	186	8.7	290	6.6	1.56 (1.26-1.93)	1.37 (1.10-1.70)	
>2500	186	8.7	232	5.3	1.82 (1.46-2.27)	1.48 (1.18-1.86)	
No ICS use (reference)	781	36.7	1,998	45.2	1.00	1.00	
ICS prescriptions per year							.002
1-6	630	29.6	1,191	26.9	1.41 (1.23-1.63)	1.20 (1.03-1.40)	
7-10	353	16.6	556	12.6	1.68 (1.41-2.00)	1.27 (1.07-1.53)	
≥11	367	17.2	676	15.3	1.47 (1.24-1.73)	1.38 (1.14-1.65)	
ICS cumulative dose (mg) per year							.0006
≤40	283	13.3	535	12.3	1.38 (1.15-1.65)	1.17 (0.96-1.42)	
41-80	412	19.4	782	17.8	1.42 (1.21-1.68)	1.19 (1.01-1.41)	
81-120	293	14.0	472	11.0	1.70 (1.41-2.05)	1.31 (1.10-1.57)	
>120	361	17.1	636	14.5	1.54 (1.30-1.82)	1.38 (1.13-1.69)	

[a] Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonates, and number of ICS or OCS prescriptions accordingly.

**P-values for trend. The p-values are referred to the adjusted model.*

Table 6-9. Association between oral and inhaled exposure as rate per year from the asthma to the index date and risk of fragility fractures.

	Cases		Controls		Unadjusted	Adjusted[a] OR	
Type of exposure	**n**	**%**	**n**	**%**	**OR (95%CI)**	**(95%CI)**	***p*-value***
No OCS use (reference)	1,111	52.1	2,541	57.5	1.00	1.00	
OCS prescriptions per year							.0003
1	346	16.2	765	17.3	1.03 (0.89-1.21)	0.94 (0.80-1.10)	
2-3	260	12.2	498	11.3	1.25 (1.05-1.50)	1.10 (0.91-1.32)	
4-8	225	10.6	386	8.7	1.42 (1.17-1.72)	1.23 (1.02-1.50)	
≥9	189	8.9	231	5.2	1.89 (1.51-2.36)	1.53 (1.21-1.92)	
OCS cumulative dose (mg) per year							<.0001
≤500	433	20.3	979	22.1	1.02 (0.89-1.18)	0.92 (0.81-1.07)	
501-1000	187	8.8	327	7.4	1.35 (1.10-1.66)	1.17 (0.95-1.45)	
1001-2500	193	9.1	310	7.0	1.54 (1.25-1.90)	1.35 (1.08-1.67)	
>2500	207	9.7	264	6.0	1.80 (1.45-2.22)	1.46 (1.18-1.82)	
No ICS use (reference)	958	45.0	2,415	54.6	1.00	1.00	
ICS prescriptions per year							<.0001
1-6	481	22.6	902	20.4	1.46 (1.25-1.71)	1.23 (1.04-1.46)	
7-10	321	15.1	495	11.2	1.76 (1.47-2.10)	1.42 (1.19-1.70)	
≥11	371	17.4	609	13.8	1.67 (1.41-1.98)	1.44 (1.20-1.75)	
ICS cumulative dose (mg) per year							.0014
≤40	237	11.4	452	10.4	1.46 (1.20-1.77)	1.22 (0.99-1.50)	
41-80	313	14.9	518	11.9	1.69 (1.41-2.02)	1.40 (1.15-1.69)	
81-120	297	14.2	507	11.6	1.65 (1.38-2.96)	1.39 (1.14-1.66)	
>120	327	15.6	536	12.3	1.66 (1.39-1.96)	1.40 (1.15-1.68)	

[a] Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, bisphosphonates, and number of ICS or OCS prescriptions accordingly.

**P-values for trend. The p-values are referred to the adjusted model.*

6.3.4Sensitivity analysis

When only patients with at least one ICS prescription before the index dates were included, the risk of both osteoporosis and fragility fractures were similar compared to the main analysis (Tables 6-10 & 6-12). After including the patients who never had OCS exposure within the database records, the relationship between ICS, osteoporosis, and fragility fractures still held (Tables 6-11 & 6-13).

Table 6-10. Association between oral and inhaled corticosteroids exposure in the year prior to the index date and risk of osteoporosis including only patients with at least one ICS prescription.

	Cases		Controls		Unadjusted	Adjusted[a] OR	
Type of exposure	**n**	**%**	**n**	**%**	**OR (95%CI)**	**(95%CI)**	***p*-value***
No OCS use (reference)	378	55.3	682	64.8	1.00	1.00	
OCS prescriptions per year							<.0001
1	86	12.3	187	17.8	0.82 (0.61-1.12)	0.79 (0.58-1.10)	
2-3	75	11.0	108	10.3	1.33 (0.95-1.88)	1.15 (0.80-1.63)	
4-8	95	13.9	58	5.5	3.34 (2.29-4.87)	3.38 (2.27-5.03)	
≥9	50	7.3	17	1.6	5.57 (3.07-10.1)	4.52 (2.39-8.60)	
OCS cumulative dose (mg) per year							<.0001
≤500	119	17.3	244	23.1	0.88 (0.67-1.16)	0.81 (0.61-1.07)	
501-1000	55	8.0	60	5.7	1.79 (1.17-2.77)	1.73 (1.10-2.71)	
1001-2500	81	11.8	49	4.6	3.61 (2.41-5.42)	3.36 (2.19-5.18)	
>2500	51	7.4	19	1.8	5.70 (3.19-10.2)	5.50 (2.93-10.3)	
ICS prescriptions per year							.0099
1	73	10.6	152	14.4	1.00	1.00	
2-6	331	48.2	555	52.6	1.25 (0.91-1.72)	1.21 (0.86-1.69)	
7-10	157	22.8	193	18.3	1.77 (1.23-2.55)	1.55 (1.04-2.28)	
≥11	126	18.3	155	14.7	1.87 (1.26-2.80)	1.58 (1.06-2.41)	
ICS cumulative dose (mg) per year							.0025
≤40	146	21.4	279	26.5	1.00	1.00	
41-80	146	21.4	250	23.8	1.13 (0.83-1.52)	1.13 (0.83-1.56)	
81-120	119	17.4	193	18.4	1.17 (0.85-1.60)	1.01 (0.72-1.41)	
>120	273	39.6	330	31.4	1.63 (1.24-2.13)	1.57 (1.18-2.10)	

For footnotes look the Table 6-11.

Table 6-11. Association between oral and inhaled corticosteroids exposure in the year prior to the index date and risk of osteoporosis after restricting the individuals not in receipt of OCS within the database records.

	Cases		Controls		Unadjusted	Adjusted[a] OR	
Type of exposure	**n**	**%**	**n**	**%**	**OR (95%CI)**	**(95%CI)**	***p*-value***
No ICS use (reference)	286	28.2	579	34.9	1.00	1.00	
ICS prescriptions							.0252
1-6	413	40.7	683	41.1	1.10 (0.87-1.40)	0.94 (0.73-1.21)	
7-10	170	16.8	220	13.3	1.59 (1.19-2.13)	1.25 (1.02-1.56)	
≥11	146	14.4	179	10.7	2.04 (1.47-2.84)	1.54 (1.06-2.17)	
ICS type							
Beclomethasone	271	26.7	497	29.9	1.08 (0.85-1.40)	1.00 (0.75-1.31)	.703**
Budesonide	151	14.9	204	12.3	1.44 (1.05-1.98)	1.23 (1.06-1.72)	.034**
Fluticasone	295	29.0	372	22.4	1.58 (1.22-2.04)	1.26 (1.04-1.66)	.007**
Ciclesonide	9	0.9	8	0.5	1.72 (0.53-5.61)	2.07 (0.72-6.94)	.234**
ICS cumulative dose (mg)							.0201
≤40	128	12.6	257	15.5	0.97 (0.69-1.29)	0.82 (0.60-1.14)	
41-80	163	16.0	245	14.8	1.24 (0.93-1.82)	0.94 (0.67-1.33)	
81-120	138	13.6	212	12.8	1.23 (1.01-1.86)	1.07 (0.77-1.48)	
>120	299	29.4	365	22.0	1.85 (1.06-1.84)	1.41 (1.07-1.88)	

[a] *Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, and bisphosphonates. Percentages have been rounded and might not total 100.*

* *P-values for trend unless otherwise stated. The p-values are referred to the adjusted model.*

** *P-values from the Wald's test*

Table 6-12. Association between oral and inhaled corticosteroids exposure in the year prior to the index date and risk of fragility fractures including only patients with at least one ICS prescription.

	Cases		Controls		Unadjusted	Adjusted[a] OR	
Type of exposure	**n**	**%**	**n**	**%**	**OR (95%CI)**	**(95%CI)**	***p*-value***
No OCS use (reference)	466	64.7	728	68.7	1.00	1.00	
OCS prescriptions per year							.0181
1	114	15.8	175	16.5	1.08 (0.82-1.42)	1.05 (0.80-1.38)	
2-3	62	8.6	75	7.1	1.37 (0.94-1.99)	1.29 (0.88-1.83)	
4-8	53	7.4	65	5.8	1.47 (1.03-2.13)	1.37 (1.02-2.01)	
≥9	25	3.5	21	2.0	1.93 (1.05-3.53)	1.72 (1.08-3.21)	
OCS cumulative dose (mg) per year							.0323
≤500	151	21.0	212	20.0	1.18 (0.92-1.51)	1.14 (0.89-1.48)	
501-1000	34	4.7	48	4.5	1.12 (0.69-1.80)	1.04 (0.64-1.72)	
1001-2500	44	6.1	49	4.6	1.55 (1.21-2.41)	1.37 (1.06-2.16)	
>2500	25	3.5	23	2.2	1.84 (1.29-3.34)	1.76 (1.18-3.06)	
ICS prescriptions per year							.0404
1	94	13.1	153	14.4	1.00		
2-6	358	49.7	564	53.2	1.06 (0.95-1.16)	0.98 (0.89-1.09)	
7-10	159	22.1	205	19.3	1.30 (1.05-1.54)	1.16 (1.02-1.31)	
≥11	109	15.1	138	13.0	1.47 (1.14-1.73)	1.20 (1.04-1.37)	
ICS cumulative dose (mg) per year							.0422
≤40	170	23.4	298	28.2	1.00	1.00	
41-80	166	23.1	230	21.7	1.28 (0.96-1.70)	1.21 (0.90-1.63)	
81-120	136	18.9	195	18.4	1.26 (1.02-1.69)	1.15 (0.85-1.56)	
>120	247	34.5	335	31.7	1.34 (1.13-1.74)	1.24 (1.04-1.63)	

For footnotes look the Table 6-13.

Table 6-13. Association between oral and inhaled corticosteroids exposure in the year prior to the index date and risk of fragility fracture after restricting the individuals not in receipt of OCS within the database records.

	Cases		Controls		Unadjusted	Adjusted[a] OR	
Type of exposure	**n**	**%**	**n**	**%**	**OR (95%CI)**	**(95%CI)**	***p*-value***
No ICS use (reference)	319	31.3	651	34.6	1.00	1.00	
ICS prescriptions							.032
1-6	424	41.6	813	43.2	1.14 (0.99-1.45)	1.10 (0.86-1.41)	
7-10	154	15.1	245	13.0	1.37 (1.01-1.88)	1.29 (0.93-1.78)	
≥11	123	12.1	171	9.2	1.64 (1.14-2.36)	1.51 (1.11-2.20)	
ICS type							
Beclomethasone	302	29.6	557	29.6	1.10 (0.85-1.44)	1.05 (0.80-1.38)	.703**
Budesonide	130	12.8	224	11.9	1.34 (0.96-1.88)	1.21 (0.85-1.72)	.284**
Fluticasone	257	25.2	429	22.8	1.43 (1.09-1.89)	1.27 (0.94-1.70)	.117**
Ciclesonide	12	1.2	19	1.0	0.85 (0.25-2.89)	0.91 (0.26-3.23)	.895**
ICS cumulative dose (mg)							.0194
≤40	145	14.2	319	16.9	0.94 (0.69-1.29)	0.89 (0.96-1.42)	
41-80	170	16.7	286	15.2	1.30 (0.93-1.82)	1.19 (0.84-1.67)	
81-120	127	12.5	226	12.0	1.37 (1.01-1.86)	1.36 (0.98-1.87)	
>120	256	25.1	396	21.1	1.40 (1.06-1.84)	1.34 (1.04-1.79)	

[a] *Adjusted for smoking, BMI, social class, Charlson Comorbidity Index score, any previous fracture, any previous fall, and bisphosphonates. Percentages have been rounded and might not total 100.*

* *P-values for trend unless otherwise stated. The p-values are referred to the adjusted model.*

** *P-values from the Wald's test*

6.3.5 Bisphosphonate use

The prevalence of OCS users receiving at least one bisphosphonate prescription was 31.4% and 21.4% for osteoporosis and fragility fractures, respectively (Table 6-14). When ICS users without an OCS prescription in the year prior to the index date were included, the percentage of patients receiving at least one bisphosphonate prescription decreased further by around 2%. Only around 50% of patients receiving nine or more OCS prescriptions had at least one bisphosphonate prescription.

Table 6-14. Prevalence of patients using at least one bisphosphonate prescription after the OCS and ICS initiation in the year prior to the osteoporosis and fragility fractures diagnosis.

	Osteoporosis			Fragility Fractures		
	Patients with at least a BP prescription	Patients per corticosteroid category	Prevalence	Patients with at least a BP prescription	Patients per corticosteroid category	Prevalence
	n	n	%	n	n	%
OCS prescriptions						
Overall	401	1,275	31.4	259	1,208	21.4
1	108	559	19.3	92	629	14.6
2-3	99	309	31.7	50	283	17.6
4-8	119	259	45.9	72	208	35.5
≥9	75	148	50.6	45	93	48.4
ICS prescription						
Overall	868	2,566	33.8	573	2,944	19.4
1-6	532	1,658	32.0	348	2,008	17.3
7-10	191	514	37.1	120	559	21.4
≥11	145	394	36.8	105	377	27.8
ICS prescription*						
Overall	467	1,579	29.5	314	1,685	18.6
1-6	314	1,100	28.5	203	1,434	14.2
7-10	90	280	32.1	63	348	18.1
≥11	63	199	31.6	48	217	22.1

Abbreviations: BP, Bisphosphonate; ICS, Inhaled Corticosteroids; OCS, Oral Corticosteroid.

** ICS users without an OCS prescription the year prior the index date.*

6.4 Discussion

The findings provide evidence that both OCS and ICS exposure have deleterious effects on bone health. A clear dose-response relationship was found, with higher cumulative doses and number of OCS and ICS prescriptions being associated with increased odds of osteoporosis and fragility fracture. The percentage of patients receiving bisphosphonates after OCS initiation was low.

The present findings are similar to the limited literature. Bloechliger et al. reported a significant dose-response association between first episode of a bone-related condition and cumulative OCS dose in patients with asthma using a nested case-control design, but they did not report the odds for osteoporosis and fractures separately (198). Similarly, a cross-sectional study found that OCS were associated with an increased OR for osteoporosis (OR = 6.55; 95%CI 4.64 to 9.21) and fractures (OR = 1.65; 95%CI 1.14 to 2.39) when comparing patients with severe asthma requiring regular OCS treatment with non-asthma controls (153). This study adds more details by defining the exposure based on the number of prescriptions and cumulative dose, capturing both the short- and long-term users. Cumulative doses more than 1,000mg within a year had a significant effect. Price et al. examined the risk of osteoporosis and osteoporotic fractures in patients with asthma exposed to OCS and found similar estimates for cumulative doses (199). These data are also in line with a study reporting that the odds of developing bone and muscle-related complications increased significantly in a dose-dependent manner with OCS use (44). This study additionally found that the number of prescriptions within a year (i.e. intermittent use rather than regular) was associated with adverse bone effects, supporting the view that even short courses of OCS are harmful to bone health (66).

Although the benefits of ICS in asthma are well-documented (13), the detrimental effects of ICS on bones have been less clearly quantified with the majority of the

limited literature to be relevant to the general population and not to asthma. A Canadian study of elderly women failed to detect a high risk of hip fracture (rate ratio = 0.92; 95% CI 0.75 to 1.12) (200). Suissa et al. found no increased risk of fracture at recommended doses of ICS, but they reported a rate ratio of fracture equal to 1.61 (95% CI 1.04 to 2.50) for ≥ 2,000μg of ICS per day (201), although this study included only older people (≥65 yrs) who were already at a higher risk of fractures. Hubbard et al. used CPRD data to reveal a dose-response relationship and increased odds of hip fracture of 1.19 (95% CI 1.10 to 1.28) when adjusting for annual prescriptions of OCS which is similar to the odds ratios found in our study (202). Another study, comparing ICS users with non-users, found increased hazard ratios for fracture ranging from 1.13 to 1.51 depending on the fracture site (112). This study adds to the literature by providing estimates not only about the risk of osteoporosis, which are lacking, but also of fragility fractures, capturing a wide range of severity of asthma, whilst adjusting for important confounders.

The low percentage of bisphosphonate use after the first OCS prescription in the year prior the osteoporosis or fragility fracture diagnoses is disappointing as this class of drugs is considered the most effective bone protective agent. There is guidance on the prevention of bone loss due to OCS in the general population, suggesting bisphosphonate treatment for adults taking, for more than 3 months, any dose (121,123) or ≥2.5mg of prednisone daily (120). There is no current recommendation for bisphosphonate therapy among ICS users. It was found that only a minor percentage of ICS users at high risk had at least one bisphosphonate prescription after the first ICS prescription in the year prior to the osteoporosis or fragility fracture date.

Current guidelines on asthma do not cover the management of bone comorbidities in detail. Although the British Thoracic Society / Scottish Intercollegiate Guidelines Network and the Global Initiative for Asthma guidelines on asthma management cover specific co-morbidities including osteoporosis, no specific bone protection

guidance is given (13,16) and the asthma guideline from the National Institute for Health Care and Excellence does not mention osteoporosis at all (17). The results suggest that risk and prevention of osteoporosis and fragility fracture should be addressed in future guideline updates.

The main strengths of the study are the large study size and use of linked data. By using linked data, I have been able to provide more complete estimates of osteoporosis and fracture incidence, capturing not only those recorded in primary care as vertebral fractures or osteoporosis often do not come to clinical attention in primary care, and people might not be aware of these conditions (184) before a hospitalisation. This study reports separately the risk stratifying data by dose, number of prescriptions, and type of OCS and ICS providing pragmatic guidance to clinicians. The dose-response relationship between ICS, osteoporosis, and fractures held, even after excluding everyone with a previous OCS exposure within the database records. The population-based setting means the findings are generalizable to the wider population.

This study has some limitations. Diagnostic misclassification may occur, as we were reliant on general practitioners recording these conditions. However, these diagnoses have been previously validated in the database demonstrating a positive predictive value around 90% (163,183). Because of the nature of our data, I may have included some non-fragility fractures, however actions were taken to minimize as much as possible this bias. The dose response relationship may need to include number of years on OCS or ICS; however, the patients' medical records do not go back indefinitely. Patients may have been using a drug prescribed before the examined index periods; however, this would bias the results towards the null hypothesis. Inhalers can be difficult to use correctly, and adherence is unlikely to be perfect, leading to lesser intake of actual dose underestimating the relationship between a prescribed ICS dose and bone health. The exposure was defined based on

corticosteroid prescriptions and not on actual compliance. The study population may include some with COPD and misdiagnosis in it, but even so the increase steroid use and risk of fracture is there.

6.5 Conclusion

In summary, both OCS and ICS are associated with an increased risk of osteoporosis and fragility fracture in people with asthma. The use of OCS and ICS should be kept to the minimum necessary to treat symptoms and should be stepped down if symptoms and exacerbations are well-managed. Bisphosphonate co-medication should be considered according to guidelines for bone protection.

7 CORTICOSTEROIDS AND BONE HEALTH IN PEOPLE WITH ASTHMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

7.1 Introduction

Glucocorticoid-induced osteoporosis is considered the most common adverse effect of corticosteroids (174). Osteoporosis is characterized by structural deterioration of bone tissue and low bone mass, leading to bone fragility and increased risk of fracture. Decreased bone mineral density (BMD) is strongly related with a higher fracture risk (91), however fractures can occur at higher BMD levels in patients receiving OCS (203). Fractures are associated with morbidity, mortality, and increased health care costs (175,176).

Two reviews have evaluated the impact of ICS on BMD and fractures in asthma (189,204) with the most recent conducted six years ago (189). They reported that ICS were not associated with bone loss or increased risk of fracture. However, these reviews did not examine the risk of osteoporosis and did not include OCS as exposure. Additionally, they compared people with asthma receiving ICS with nonexposed to ICS people with asthma and healthy controls as a united group, which may have influenced the results.

A review considering as the target population all adult patients with asthma exposed to ICS or OCS (as two separate exposures) comparing them with nonexposed people with asthma and healthy controls separately was conducted. The primary objective was to examine the effect of ICS and OCS on the mean difference in BMD in absolute measure, risk of osteoporosis, and risk of fractures in asthma. The secondary outcome was to examine the effect of ICS and OCS on mean change over time in BMD in asthma.

7.2 Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (205) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (206) were used. The protocol was registered with PROSPERO database (CRD42020198236).

7.2.1 Eligibility criteria and outcomes

The Population-Exposure/Intervention-Outcome-Study Design criteria was used throughout the review process, based on type of participants, type of exposure, type of outcome, and study design.

Type of Participants: All studies of adult people with asthma aged 18 years and over were eligible for inclusion in this review.

Type of Exposure/Intervention: All studies that had assessed either OCS or ICS.

Type of Outcome: The primary outcomes of interest were the mean difference in BMD in absolute measure (g/cm^2) , the risk of osteoporosis, and risk of fracture due to ICS and OCS as separate exposures. The secondary outcome was to examine separately the effect of ICS and OCS on mean change over time in BMD (g/cm^2) in asthma.

Study Design: All RCT and observational studies (cross-sectional, case control, and cohort) were eligible.

Prespecified exclusion criteria were non-human studies; non original research (reviews, editorials, protocols); case-series, case reports studies, letters to editors; and studies of mixed groups of participants (e.g. asthma and COPD) where not solely reported for the asthma group.

7.2.2 Search strategy

The bibliographic databases MEDLINE and EMBASE (via Ovid) from their inception to 3 July 2020 were searched by using different combinations of free text and database specific index terms (Table 7-1). The reference list of included studies and existing

systematic reviews was also used to identify additional potentially relevant articles. Unpublished sources of data were not included, as the evaluation of their quality in absence of a peer-review process could not be ensured. Searches were designed with assistance from a professional research librarian.

Table 7-1. Medline (via Ovid) and EMBASE (via Ovid) search terms for primary studies.

	Search terms
1.	Exp Asthma/
2.	Asthma$.mp
3.	(((inhaled or oral) and (corticosteroid$1 or steroid$1 or glucocorticoid$1)) or steroid$1 or glucocorticoid$1 or corticosteroid$1 or beclometasone or beclomethasone or fluticasone or budesonide or mometasone or triamcinolone or ciclesonide or prednisolone).mp
4.	(osteoporosis or fracture$1 or (fracture$1 adj2 risk) or (osteoporosis adj2 risk) or (bone adj2 density) or (bone$1 or bone-resorption) or (bone$1 adj2 fracture$1) or (bone adj2 loss) or (osteoporotic adj1 fracture$1) or (fracture$1 adj1 bone$1)).mp
5.	1 or 2
6.	3 and 4 and 5

7.2.3 Selection of studies and data extraction

The results of the searches were imported to Rayyan QCRI (207) and duplicates removed. Two reviewers (CC, TM) independently screened the titles and abstracts and any conflicts resolved by discussion. Duplicates and records that did not meet eligibility criteria were excluded at this stage. All relevant studies were obtained, and the full text was screened independently by two reviewers (CC, TM). Any disagreements were resolved through discussion or with the help of the third reviewer (DS). Two review authors (CC, TM) independently extracted data and cross checked the extracted information on study characteristics, participants, interventions, and reported outcomes using a devised data extraction form. Variables of interest included: author, year of study, study design, country, data source,

reference population, type/dose/years of steroid exposure, outcome, demographic of study population, number of people recruited, and adjustment for confounders. Where the adjusted measure was not available the crude was used. Any differences related to the data extraction were resolved by rechecking the full text of the study or by discussion. When study data were ambiguous or data were not reported in a form that could be used for formal comparison, we contacted the corresponding author of the original publication via email.

7.2.4 Assessment of risk of bias

Two review authors (CC, TM) independently assessed the risk of bias for each study. Any disagreements were resolved through discussion. The Cochrane risk of bias RoB 2 (208) tool was used to evaluate the risk of bias of randomised controlled trials, whereas the risk of bias in observational studies was evaluated incorporating the Newcastle-Ottawa Scale (209). High quality was defined as a grade of ≥ 6. Both case-control and cohort studies had a maximum score of 9; whereas cross-sectional studies had a score of 7.

7.2.5 Statistical analysis

Narrative synthesis of evidence was conducted for all included studies. Meta-analysis using random effects models was performed to allow for apparent heterogeneity among studies given the different study designs and population characteristics. The studies were grouped into people with asthma on steroids versus not on steroids, or on low steroid dose, and people with asthma on steroids vs healthy controls. Separate meta-analyses were performed for RCTs and observational studies. The generic inverse variance method was used for pooling. Pooled relative estimates were calculated using either odds ratio or hazard ratio with 95% CI for osteoporosis and fractures and mean difference with 95% CI for BMD. Measures of effect adjusted for confounders were used in preference to crude. Effect estimates were manually

calculated when needed. The Dersimonian-Laird method was used to estimate the between-study variance T^2. The percentage of variability in the effect sizes not caused by sampling error was tested by using the Higgins' I^2 test, with estimates of 25%, 50% and 75% indicating low, moderate, and high heterogeneity respectively. We used the overall effect Z-test to determine the significance level for treatment effects. If a study had several arms involving different ICS or OCS doses, the highest dose was used. If a meta-analysis had high heterogeneity (I^2 ≥75%) a sensitivity analysis was also conducted excluding those studies with a substantial lower or higher estimate than the majority of the included studies in order to examine possible reasons of high heterogeneity. The symmetry of a funnel plot was inspected if a meta-analysis included five or more studies and used Egger's test was used to assess for publication bias, when data of 10 or more studies were available according to Cochrane's recommendation. All meta-analyses were conducted in R v4.0.3 using the "meta" and "metafor" packages and all statistical tests were two sided and used a significance level of $p < 0.05$.

7.3 Results

The searches yielded 3470 citations, with 2868 after removing duplicates. 2764 articles were excluded after reviewing the titles and abstracts (Figure 7-1). Of the remaining 104 studies, 76 were removed after reviewing the full article. A total of 28 studies were included in this review and 26 in the meta-analyses. Six studies were RCT and 22 were observational with 20 being included in the review on BMD, nine having data on osteoporosis, and nine having information on fractures.

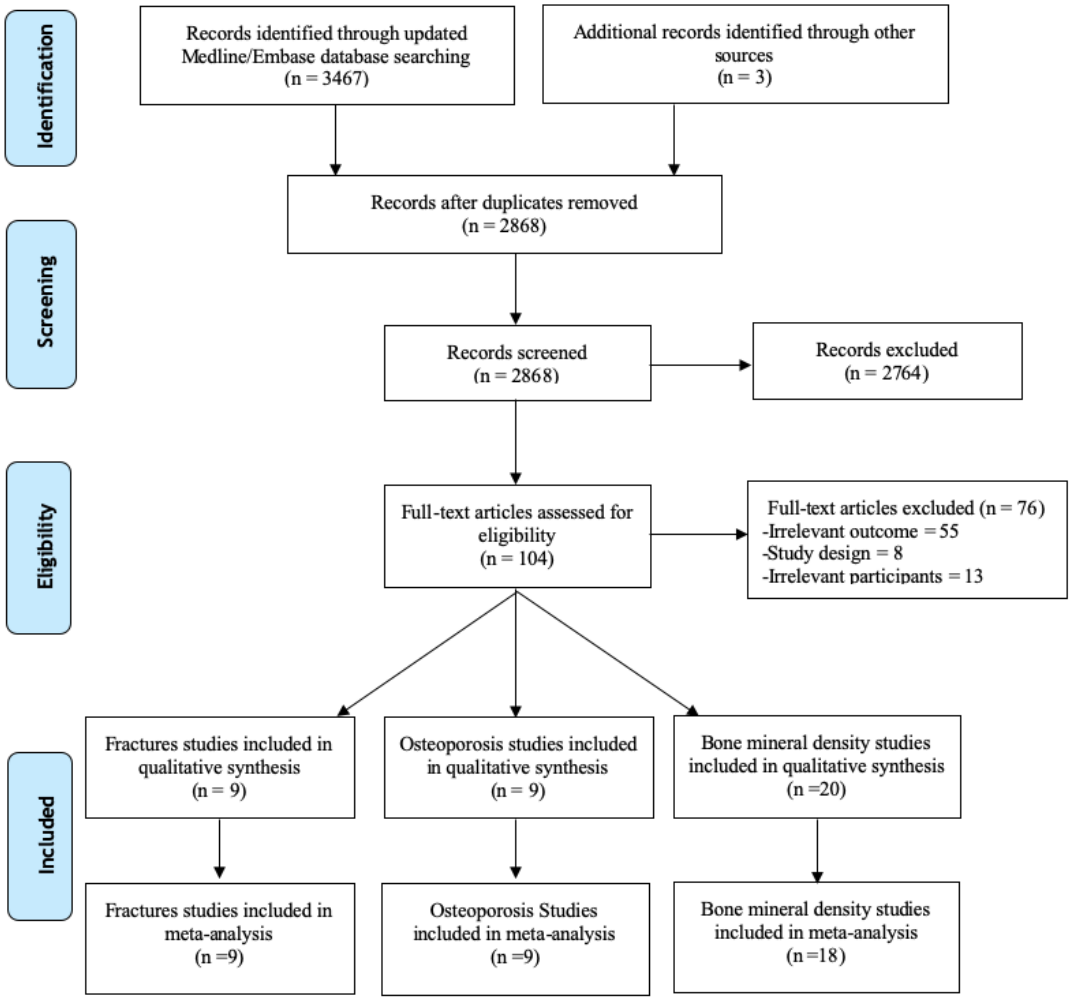

Figure 7-1. *Flow chart of studies.*

7.3.1 Bone mineral density

Twenty studies were identified reporting BMD measurement (149,150,215–224,154,177,195,210–214) of which six studies were randomized controlled trials (177,210–213,224), nine were case-controls (154,195,216–222), four were cross-sectional studies (149,150,214,215), and one cohort study (223) (Table 7-2). The search did not identify studies looking at OCS and BMD in asthma. It was not possible to calculate the 95%CI around the mean difference of two RCTs (177,212), so they were included in Table 7-2, but not in the meta-analysis. In all studies, BMD was measured using the DEXA. The sample size of the studies was relatively small ranging from 23 to 238 participants. Beclomethasone dipropionate was the most evaluated ICS and the average daily ICS dose was between 500 and 2000μg. There was a predominance of

women in studies. The mean patient age ranged from 28 to 63 years, with many of the studies consisting of people aged under 50 years.

Table 7-2. Details of the included studies having the BMD mean difference between the comparison groups as outcome.

Study, Year	Study Design, Country	Comparison Groups	Sampling (Cases/Controls)	Mean Age (yrs.) (Cases/Controls)	Female (%)	Type of corticosteroid	Corticosteroid exposure	Mean BMD# difference (95% CI) between comparison groups
People with asthma exposed to OCS/ICS vs people with asthma nonexposed or exposed to low dose								
Boulet (222), **1994**	Case-control, Canada	High ICS **VS** no or low ICS	37/37	46.8/45.4	62	BDP	1140μg/d **VS** 89μg/d (mean) For at least 18 months	L2-L4 spine: -0.01 (-0.076 to 0.056) Femoral neck: 0.025 (-0.031 to 0.081) Ward's tringle: 0.014 (-0.033 to 0.061)
Gagnon (214), **1997**	Cross-sectional, Canada	High ICS **VS** low ICS	31/27	49/45	41.3	BDP, BUD	≥800μg/d **VS** ≤500μg/d	L2-L4 spine: -0.02 (-0.101 to 0.061)
Wisniewski (215),**1997**	Cross-sectional, UK	ICS **VS** no ICS	47/34	32/28.2	53.1	BDP, BUD	≥ 5 yrs. Mean ICS: 7.8yrs. MEN: median cumulative dose: 1.37g. Median daily dose the last year: 500μg. WOMEN: median cumulative dose: 0.94g. Median daily dose the last year: 450μg.	Male L2-L4 spine: 0.07 (-0.026 to 0.166) Femoral neck: 0.08 (-0.023 to 0.183) Female L2-L4 spine: -0.045 (-0.123 to 0.033) Femoral neck: -0.06 (-0.148 to 0.028)
Egan (210), **1999**	RCT, UK	High ICS **VS** low ICS	16/16	33/30	46.9	BDP	2000μg/d **VS** ≤400μg/d	Total body: -0.061 (-0.133 to 0.011) L2-L4 spine: 0.007 (-0.132 to 0.146) Femoral neck: -0.071 (-0.203 to 0.061)
Laatikainen (149), **1999**	Cross-sectional, Finland	ICS **VS** no ICS	12/13	53.7	100	BDP, BUD	Mean daily dose: 1mg. Mean duration: 5.2 yrs.	L2-L4 spine: -0.084 (-0.209 to 0.041) Femoral neck: -0.021 (-0.114 to 0.072)

Li (211), **1999**	RCT, USA	ICS **VS** placebo	32/32	28/31.1	14	FP	1000µg/d for 104 weeks	L2-L4 spine: 0.001 (-0.095 to 0.097)
***Kaye** (212), **2000**	RCT, USA	ICS **VS** no steroids	11/18	39/39	55.2	FLUNI	500µg/d	L2-L4 spine: 0.059 Femoral neck: -0.072 Ward's tringle: -0.055 Trochanter: 0.01
Matsumoto (150), **2001**	Cross-sectional, Japan	Low ICS **VS** high ICS	9/26	60.6	57.1	BDP	1,268µg/d **VS** 615µg/d (mean) during the study.	L2-L4 spine: -0.079 (-0.171 to 0.013)
***Tattersfield** (177), **2001**	RCT, France, New Zealand, Spain, UK	ICS **VS** no steroids	74/78	36/36	53	BDP	499µg/d	Total body: -0.006 L2-L4 spine: -0.069 Femoral neck: -0.035
People with asthma exposed to OCS/ICS vs healthy controls								
Herrala (223), **1994**	Cohort, Finland	ICS **VS** healthy controls	19/19	52.6/52.6	100	BDP	1000µg/d for one year	L2-L4 spine: 0.034 (-0.078 to 0.146) Femoral neck: 0.006 (-0.067 to 0.079) Ward's tringle: 0.003 (-0.443 to 0.449) Trochanter: 0.019 (-0.07 to 0.108)
Ip (216), **1994**	Case-Control, Hong Kong	ICS **VS** healthy controls	30/30	32.5/32.5	60	BDP, BUD	≥3 months. Mean daily dose: 1,100µg. Cumulative dose: 932mg Mean duration: 40 months	L2-L4 spine: -0.067(-0.12 to -0.014) Femoral neck: -0.039 (-0.098 to 0.02) Ward's tringle: -0.11 (-0.189 to -0.031) Trochanter: -0.048 (-0.107 to 0.011)
Luengo (217), **1997**	Case-control, Spain	ICS **VS** healthy controls	48/48	56/55	68.8	BDP, BUD	≥1 yr. Mean daily dose: 662µg Mean duration: 10.6 yrs	L2-L4 spine: 0.04 (-0.034 to 0.114)
Egan (210), **1999**	RCT, UK	ICS **VS** healthy controls	16/7	33/32	43.5	BDP	2000µg/d	Total body: -0.068 (-0.154 to 0.018) L2-L4 spine: -0.07 (-0.226 to 0.086) Femoral neck: -0.072 (-0.199 to 0.055)

Fujita (218), **2001**	Case-Control, Japan	ICS **VS** healthy controls	Premenopausal: 17/24 Postmenopausal: 19/21	Premenopausal: 46.8/46.6 Postmenopausal: 53.7/52.4	100	BDP	Mean dose during the study: Premenopausal: Daily 551μg, Cumulative: 345mg. Postmenopausal: Daily: 534μg, Cumulative: 350mg.	Premenopausal: L2-L4 spine: -0.039 (-0.118 to 0.040) Postmenopausal: L2-L4 spine: -0.118 (-0.183 to -0.053)
Sivri (195), **2001**	Case-Control, Turkey	ICS **VS** healthy controls	32/26	54.2/53.7	100	BDP	Mean daily dose: 987μg. Cumulative dose: 932mg Mean duration: 5.7 yrs	L2-L4 spine: -0,11 (-0.190 to -0.03) Femoral neck: -0,12 (-0.188 to -0.052)
El (219), **2005**	Case control, Turkey	ICS **VS** healthy controls	45/46	44/44.3	100	NR	Mean: annual dose: 120.1 mg, cumulative dose: 345.7mg, daily dose: 326.4 μg ≥6 months. Mean duration: 2.8 yrs	L2-L4 spine: -0,002 (-0.092 to 0.088) Femoral neck: -0,046 (-0.093 to 0.001) Ward's tringle: -0.085 (-0.145 to -0,025) Trochanter: -0.014 (-0.06 to 0.032)
Sosa (154), **2006**	Case-control, Spain	ICS **VS** healthy controls	105/133	53/49.7	100	NR	≥ 1 yr. Median ICS:10 yrs.	L2-L4 spine: -0.031 (-0.078 to 0.016) Femoral neck: -0.004 (-0.038 to 0.03)
Yanik (220), **2009**	Case-control, Turkey	ICS **VS** healthy controls	46/60	62.5/63	100	BUD, FP, BDP	Cumulative dose: 798.3μg, mean daily dose:324.9μg Median ICS: 4.3 yrs.	Total spine: 0.07 (-0.021 to 0.161) Femoral neck: 0.09 (0.022 to 0.158)
Monadi (221), **2015**	Case-control, Iran	ICS **VS** healthy controls	44/50	49.2/47.4	70	FP, BUD, BDP	Mean daily dose: FP: 650mcg, BDP:	Aged ≥ 50 yrs L2-L4 spine: 0.02 (-0.039 to 0.079) Femoral neck: 0 (-0.059 to 0.059)

		600mcg, BUD: 640mcg. Median ICS: 6.5 yrs.	Aged ≥ 50 yrs L2-L4 spine: -0.06 (-0.123 to 0.003) Femoral neck: -0.08 (-0.131 to -0.029)

Abbreviations: BDP, Beclomethasone dipropionate; BUD, Budesonide; TA, Triamcinolone acetonide; FL, Flunisolide; FP, Fluticasone propionate; NA, Not applicable; NR, Not reported.

**Not able to calculate the 95%CI due to lack of data.*

[#]The BMD was measured using Dual energy x-ray absorptiometry (DEXA).

7.3.2 BMD at lumbar spine

People with asthma exposed to ICS had not a statistically significant reduced BMD at spine compared to healthy controls according to observational studies (pooled mean difference = -0.032 g/cm^2 ; 95%CI -0.064 to 0.0; p = 0.05; I^2 = 62%) and RCT (mean difference = -0.07g/cm^2 ; 95%CI -0.227 to 0.87) (Figure 7-2). The mean daily ICS dose lay between 325 and 1100 μg/d in the majority of the studies. However, meta-analysis of both RCTs and observational studies comparing exposed and nonexposed people with asthma did not find evidence of decreased BMD between people with asthma receiving and not receiving ICS (Figure 7-3). Similarly, meta-analysis of RCTs was not able to detect spinal bone loss over two years for people with asthma on ICS compared to those not receiving an ICS (pooled mean difference = -0.003 g/cm^2 ; 95%CI -0.009 to 0.002; I^2 = 0%) (Table 7-3; Figure 7-5).

7.3.3 BMD at femoral neck

ICS use was not associated with decreased BMD at the femoral neck when comparing exposed people with asthma and healthy controls (Figure 7-2). Similar findings were seen in the observational studies and in one RCT (Figure 7-4) between people with asthma either receiving ICS, or not. Additionally, a meta-analysis of RCT was not able to detect femoral neck bone loss over time between people with asthma taking ICS, or not, (pooled mean difference = 0 g/cm^2 ; 95%CI -0.013 to 0.014; I^2 = 29%) (Table 7-3; Figure 7-5).

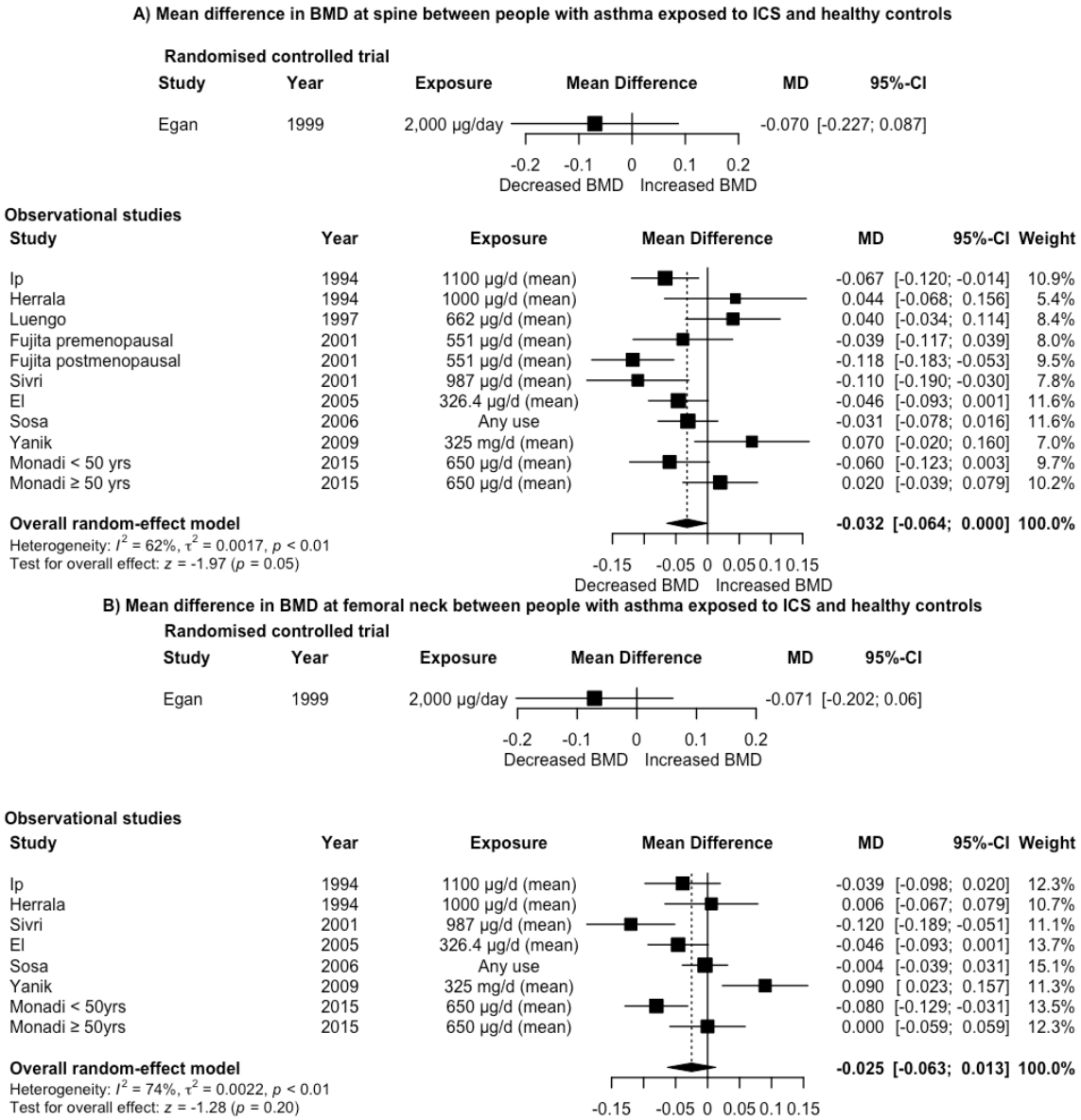

***Figure 7-2**. Meta-analysis of mean difference in BMD at (A) spine and (B) femoral neck. Black box, effect estimates from single studies; Diamond, pooled result with confidence interval; Vertical line at '0' on the x-axis is the line of no effect; Weight (in %), influence an individual study had on the pooled result.*

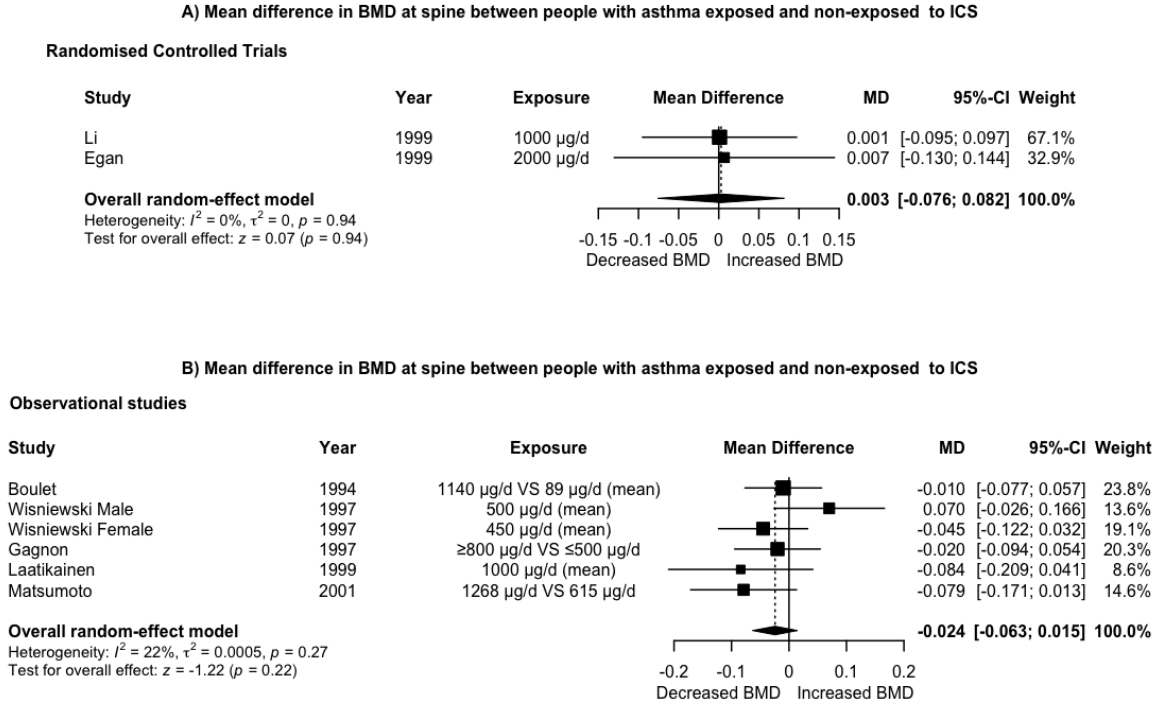

***Figure 7-3**. Meta-analysis of (A) randomized clinical trials and (B) observational studies on mean difference in BMD at spine. Black box, effect estimates from single studies; Diamond, pooled result with confidence interval; Vertical line at '0' on the x-axis is the line of no effect; Weight (in %), influence an individual study had on the pooled result.*

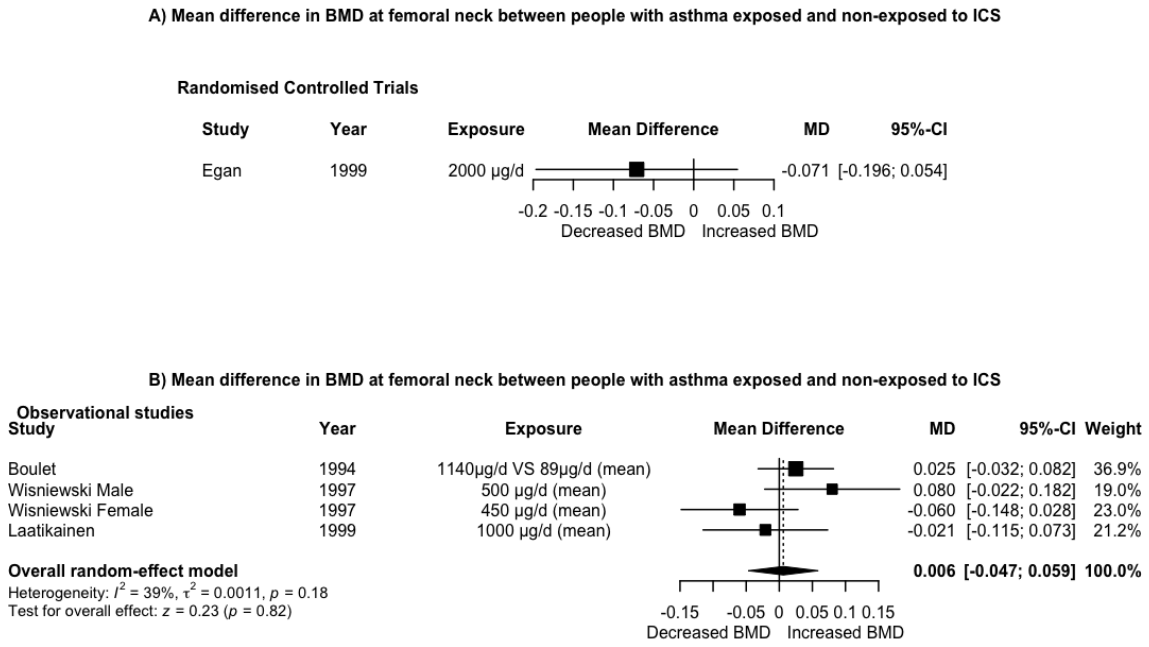

Figure 7-4*. Meta-analysis of (A) randomized clinical trials and (B) observational studies on mean difference in BMD at femoral neck. Black box, effect estimates from single studies; Diamond, pooled result with confidence interval; Vertical line at '0' on the x-axis is the line of no effect; Weight (in %), influence an individual study had on the pooled result.*

Table 7-3. Details of the included studies having the BMD mean change over time between the comparison groups as outcome.

Study, Year	Study Design, Country	Comparison Groups	Sampling (Cases/Controls)	Mean Age (yrs.) (Cases/Controls)	Female (%)	Type of corticosteroid	Corticosteroid exposure	Mean BMD change over time (95% CI) between comparison groups
People with asthma exposed to OCS/ICS vs people with asthma nonexposed or exposed to low dose								
Egan, 1999	RCT, UK	High ICS **VS** low ICS	16/16	33/30	46.9	BDP	High ICS: 1000-2000μg/d Low ICS: ≤400μg	Total body: 0.009 (-0.069 to 0.087) L2-L4 spine: 0.047 (-0.092 to 0.186) Femoral neck: -0.024 (-0.144 to 0.096)
Li, 1999	RCT, USA	ICS **VS** placebo	32/32	28/31.1	14	FP	500μg twice/d for 104 weeks	L2-L4 spine: 0.001 (-0.024 to 0.026)
***Kaye, 2000**	RCT, USA	ICS **VS** no steroids	11/18	39/39	55.2	FLUNI	500μg/d	L2-L4 spine: 0.059 Femoral neck: -0.072 Ward's tringle: -0.055 Trochanter: 0.01
Matsumoto, 2001	Cross-sectional, Japan	Low ICS **VS** high ICS	9/26	60.6	57.1	BDP	High ICS: Mean ICS daily dose: 1,268μg during the study. Low ICS: Mean ICS daily dose: 615μg during the study.	L2-L4 spine: -0.015 (-0.047 to 0.017)
***Tattersfield, 2001**	RCT, France, New Zealand, Spain, UK	ICS **VS** no steroids	74/78	36/36	53	BDP	BDP: 499μg/d	Total body: -0.006 L2-L4 spine: -0.008 Femoral neck: -0.005
Kemp, 2004	RCT, USA	ICS **VS** placebo		30.3/28.4	14	FP	88μg or 440 μg twice daily for 104 weeks	L2-L4 spine: -0.004 (-0.022 to 0.014) Femoral neck: -0.013 (-0.035 to 0.009) Total body: -0.003 (-0.015 to 0.009)
Maspero, 2013	RCT, Europe, America,	ICS **VS** placebo	424/142	29.2/28.2	63.4	MF, ML	MF 400μg/d, for 52 weeks	L2-L4 spine: -0.003 (-0.009 to 0.003) Femoral neck: 0.006 (-0.002 to 0.014)

	Africa, Caribbean							
People with asthma exposed to OCS/ICS vs healthy controls								
Luengo, 1997	Case-control, Spain	ICS **VS** healthy subjects	48/48	56/55	68.8	BDP, BUD	Cases: ≥1 yr. Mean daily dose: 662µg Mean duration: 10.6 yrs	L2-L4 spine: 0 (-0.073 to 0.073)
Egan, 1999	RCT, UK	ICS **VS** healthy subjects	32/7	34.5/32	43.5	BDP	1000-2000µg/d	Total body: 0.09 (-0.038 to 0.218) L2-L4 spine: 0.058 (-0.091 to 0.207) Femoral neck: 0.027 (-0.106 to 0.160)

**Not able to calculate the 95%CI due to lack of data.*

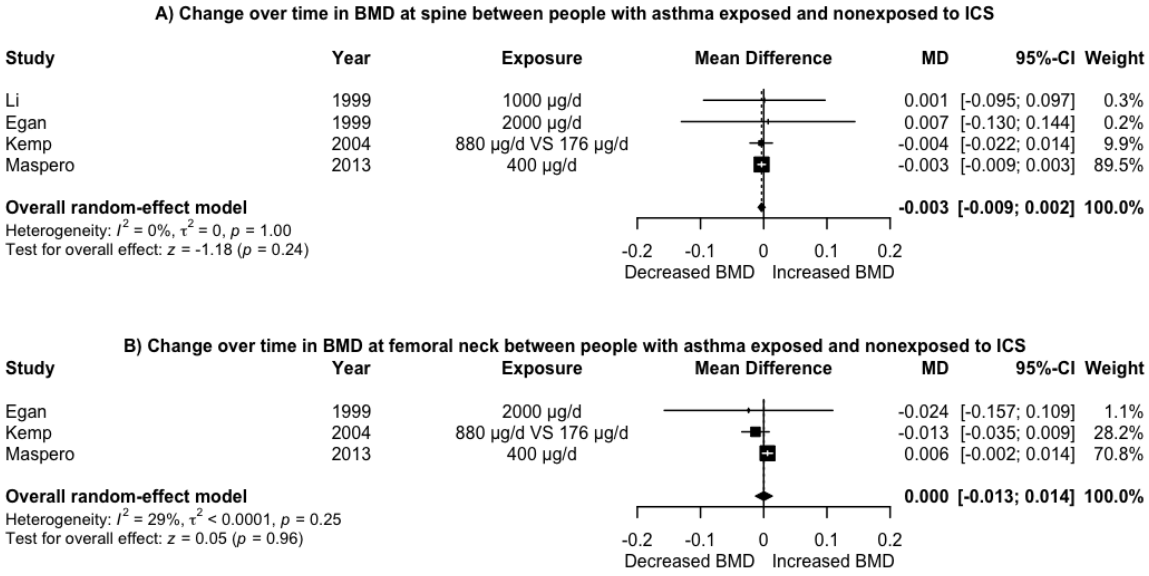

Figure 7-5. *Meta-analysis of RCTs of change over time in BMD at (A) spine and (B) femoral neck between people with asthma exposed to ICS and nonexposed. Black box, effect estimates from single studies; Diamond, pooled result with confidence interval; Vertical line at '0' on the x-axis is the line of no effect; Weight (in %), influence an individual study had on the pooled result.*

7.3.4 Risk of osteoporosis

Details of the included studies are shown in Tables 7-4 & 7-5. Nine studies (43,198,199,220,221,225–228) were identified reporting the risk of osteoporosis. There were two cross-sectional studies (43,220), four case-controls studies (198,199,221,228), and three cohort studies (225–227). In all of the studies, the percentage of females was much higher than males and the mean age of the study populations ranged from 38 to 69.4 yrs. Six studies reported the risk of osteoporosis comparing people with asthma exposed and nonexposed to OCS (43,198,199,225–228), two studies estimated the risk between people with asthma exposed to ICS and healthy controls (220,221), and just one the risk of osteoporosis between people with asthma taking ICS compared to non-users (228). Prednisolone was the predominant OCS, and the evaluated ICS were fluticasone proprionate, budesonide and beclomethasone.

The pooled OR of the five studies between people with asthma exposed and nonexposed to OCS was 2.38 (95%CI 1.51 to 3.75; $I^2 = 97\%$) and other two studies reported a pooled HR of 1.76 (95%CI 1.48 to 2.09; $I^2 = 68\%$) (Figure 7-6). The high degree of heterogeneity of the pooled OR is to some extent attributable to the two large studies that found participants taking OCS had around a fivefold greater risk of being diagnosed with osteoporosis than nonexposed people with asthma. In a sensitivity analysis removing these studies, OCS were still significantly associated with osteoporosis, with less heterogeneity (pooled OR = 1.41; 95%CI 1.21 to 1.63; $I^2 = 69\%$) (Figure 7-7). Just one study reported the odds of osteoporosis due to ICS between people with asthma receiving high doses (>120 mg/y) and nonexposed people with asthma (OR = 1.63; 95%CI 1.33 to 1.99). A non-statistically significant increased odds of osteoporosis with ICS exposure between people with asthma and healthy controls was seen (OR = 1.03; 95%CI 0.54 to 1.98; $I^2 = 0\%$).

7.3.5 Risk of fractures

Tables 7-4 & 7-5 summarise the details of the nine studies (43,154,198,220,225,227–230) reporting on the risk of fracture. Two were cross-sectional studies (43,220), four case-controls (154,198,228,230), and three cohort studies (225,227,229). There is a predominance of females in all of the studies and the mean age was between 28.2 and 63 yrs. Six studies compared people with asthma exposed and nonexposed to OCS (43,198,225,227–229), two included people with asthma exposed and nonexposed to ICS (228,230), and in two studies the comparison groups were people with asthma on ICS and healthy controls (154,220). Prednisolone was the most frequent used OCS type, whereas budesonide and beclomethasone were the common ICS in the studies, when reported.

People with asthma exposed to OCS were at greater risk of fracture than nonexposed people with asthma (pooled OR = 1.45; 95%CI 1.24 to 1.70; $I^2 = 77\%$) (Figure 7-8). Larger doses (>120 mg/y) of ICS elevated the risk (pooled OR = 1.19; 95%CI 1.05 to 1.35; $I^2 = 0\%$). Exposed people with asthma had a greater risk than healthy controls, but it was not statistically significant (pooled OR = 1.73; 95%CI 0.56 to 5.38; $I^2 = 53\%$).

Table 7-4. Details of the included studies having a diagnosis of osteoporosis or fractures as outcomes.

Study, Year	Study Design, Country	Comparison Groups	Outcome	Ascertainment of Osteoporosis/Fracture	Sampling (Cases/Controls)	Mean Age (yrs) (Cases/Controls)	Female (%)
People with asthma exposed to ICS/OCS vs people with asthma nonexposed or exposed to low dose							
Adinoff (229), **1983**	Prospective/Retrospective cohort, USA	Long-term OCS **VS** intermittent or no OCS exposure	Fracture	NA / X-ray	Prospective:19/11 Retrospective: 128/54	Prospective: 44.4/47.7 Retrospective: NR	Prospective: 70 Retrospective: 67
Johannes (230), **2005**	Case-control, USA	With fractures on ICS **VS** without fractures on ICS	Fracture	NA / ICD-9 codes	1033/10244	52.9/52.2	70.6
Zazzali (225), **2015**	Cohort, USA	OCS **VS** no OCS	Osteoporosis, Fracture	ICD-9 codes/ICD-9 codes	1980/1964	54.4/54.4	68.1
Sweeney (43), **2016**	Cross-sectional, UK	OCS **VS** no OCS	Osteoporosis, Fracture	Read codes / Read codes	808/3975	59/58	63
Daugherty (226), **2017**	Cohort, UK	OCS **VS** no OCS	Osteoporosis	Read codes / NA	35424/24994	54.8/51.5	61.8
Bloechliger (198), **2018**	Nested case control, UK	Fracture or osteoporosis on OCS **VS** without fracture or osteoporosis on OCS	Osteoporosis and fracture (combined)	Read codes / Read codes	8907/35445	54.3/NR	69.1
Price (199), **2018**	Case-control, UK	OCS **VS** no OCS	Osteoporosis	Read codes / NA	23422/23422	49/44	65
Sullivan (227), **2018**	Cohort, USA	OCS **VS** no OCS	Osteoporosis, Fracture	ICD-9 codes / ICD-9 codes	72063/72063	38/38	66
Chalitsios (228), **2020**	2 Case-controls, UK	ICS **VS** no ICS OCS **VS** no OCS	Osteoporosis, Fracture	Read codes / Read codes	Osteoporosis: 1564/3313 Fractures: 2131/4421	Osteoporosis: 69.4/68.1 Fractures: 65.1/64	Osteoporosis: 81 Fractures: 71
People with asthma exposed to ICS/OCS vs healthy controls							
Sosa (154), **2006**	Case-control, Spain	ICS **VS** healthy controls	Fracture	NA / Radiologists' and emergency reports, and X-rays.	105/133	53/49.7	100
Yanik (220), **2009**	Cross-sectional, Turkey	ICS **VS** healthy controls	Osteoporosis, Fracture	BMD / History of doctor-diagnosed bone fractures.	46/60	62.5/63	100

Monadi (221), **2015**	Case-control, Iran	ICS **VS** healthy controls	Osteoporosis	BMD classification / NA	44/50	49.2/47.4	70

Abbreviations: ICS, Inhaled corticosteroids; OCS, Oral corticosteroids; BMD, Bone mineral density; NA, Not available; NR, Not reported.

Table 7-5. Outcomes and results of the included studies having a diagnosis of osteoporosis or fractures as outcomes.

Study/Year	Type of corticosteroid	Corticosteroid exposure	Adjustments	OR/HR (95% CI) Fractures	OR/HR (95% CI) Osteoporosis
People with asthma exposed to ICS/OCS vs people with asthma nonexposed or exposed to low dose					
Adinoff (229), **1983**	Prospective: NR Retrospective: Prednisone	Prospective: NR Retrospective: Mean daily dose: 30mg Mean duration: 8 yrs.	No adjustment	Prospective: OR: 17 (0.87 to 330) Retrospective: OR: 13.8 (0.81 to 235.69)	NA
Johannes (230), **2005**	FP, BDP, BUD, FLUNI, TA	Mean daily dose μg: 1-167 168-504 > 505 (or 184 mg mean cumulative dose/y)	Demographics, comorbidities, medications, OCS use	OR: 1.00 (0.84 to 1.18) 1.02 (0.83 to 1.26) 1.14 (0.80 to 1.62)	NA
Zazzali (225), **2015**	Prednisolone	Mean dose: 4519mg	No adjustment. Matching on age, gender, region.	OR: 2.23 (1.30 to 3.83)	OR: 1.83 (1.31 to 2.56)
Sweeney (43), **2016**	Prednisolone	Median cumulative dose/y: 1960mg	Hospital, age and gender	OR: 1.54 (1.06 to 2.22)	OR: 5.23 (3.97 to 6.89)
Daugherty (226), **2017**	NR	Mean daily dose mg: ≤2.5	Age>60 yrs.	NA	HR: 1.64 (1.51 to 1.78)
Bloechliger (198), **2018**	Prednisolone	Current use (<180 days) Recent use (180-365 days) Past use (>365 days)	Alcohol, smoking, BMI, medication, ICS, Charlson score. Matching on index date, age, gender, follow-up.	OR: 1.27 (1.17 to 1.37) 1.18 (1.08 to 1.29) 1.05 (1.00 to 1.10)	OR: 1.27 (1.17 to 1.37) 1.18 (1.08 to 1.29) 1.05 (1.00 to 1.10)
Price (199), **2018**	Prednisolone, methylprednisolone,	Any use cumulative dose g 0.5-1	Age, gender, BMI, smoking.	NA	HR: 1.96 (1.63 to 2.34) 1.20 (0.94 to 1.53)

	prednisone, betamethasone, dexamethasone, hydrocortisone, or cortisone acetate	1-2.5 2.5-5 5-10 ≥10			1.87 (1.48 to 2.36) 3.65 (2.84 to 4.70) 4.65 (3.52 to 6.14) 8.23 (6.20 to 10.91)
Sullivan (227)**, 2018**	NR	1-3 OCS prescriptions ≥ 4 OCS prescriptions	Age, sex, region, years since the index date, insurance type, immunosuppressive medication (not OCS), comorbidity.	OR: 1.08 (1.02 to 1.14) 1.21 (1.04 to 1.40)	OR: 1.05 (0.99 to 1.11) 1.44 (1.28 to 1.63)
Chalitsios (228)**, 2020**	Prednisolone, FP, BDP, BUD	OCS cumulative dose mg ≤500 501-100 1001-2500 >2500 ICS cumulative dose mg ≤40 41-80 81-120 >120	smoking, BMI, social class, Charlson Comorbidity Index, any previous fracture, any previous fall, bisphosphonates, and number of ICS or OCS prescriptions. Matching on age, gender	OCS OR: 1.11 (0.92 to 1.32) 1.20 (0.84 to 1.70) 1.54 (1.10 to 2.14) 1.99 (1.30 to 3.04) ICS OR: 0.94 (0.78 to 1.31) 1.13 (0.93 to 1.63) 1.14 (0.90 to 1.78) 1.20 (1.08 to 1.42)	OCS OR: 1.21 (1.03 to 1.43) 2.05 (1.57 to 2.68) 4.04 (3.12 to 5.12) 4.79 (3.38 to 6.79) ICS OR: 1.18 (0.95 to 1.47) 1.26 (0.98 to 1.60) 1.50 (1.21 to 1.87) 1.63 (1.33 to 1.99)
People with asthma exposed to ICS/OCS vs healthy controls					
Sosa (154)**, 2006**	NR	≥ 1 yr. Median duration: 10 yrs.	Age	OR: 2.79 (1.19 to 6.54)	NA
Yanik (220)**, 2009**	BUD, FP, BDP	Cumulative dose: 798.3mg, Mean daily dose: 324.9µg Median duration: 4.3 yrs.	No adjustment	OR: 0.85 (0.22 to 3.23)	OR: 0.84 (0.38 to 1.84)
Monadi (221)**, 2015**	FP, BUD, BDP	Mean daily dose: FP: 650mcg, BDP: 600mcg, BUD: 640mcg. Median duration: 6.5 yrs.	No adjustment. Matching on age, gender.	NA	OR: 1.60 (0.51 to 5.10)

Abbreviations: BDP, Beclomethasone dipropionate; BUD, Budesonide; TA, Triamcinolone acetonide; FL, Flunisolide; FP, Fluticasone propionate. NA, Not applicable; NR, Not reported.

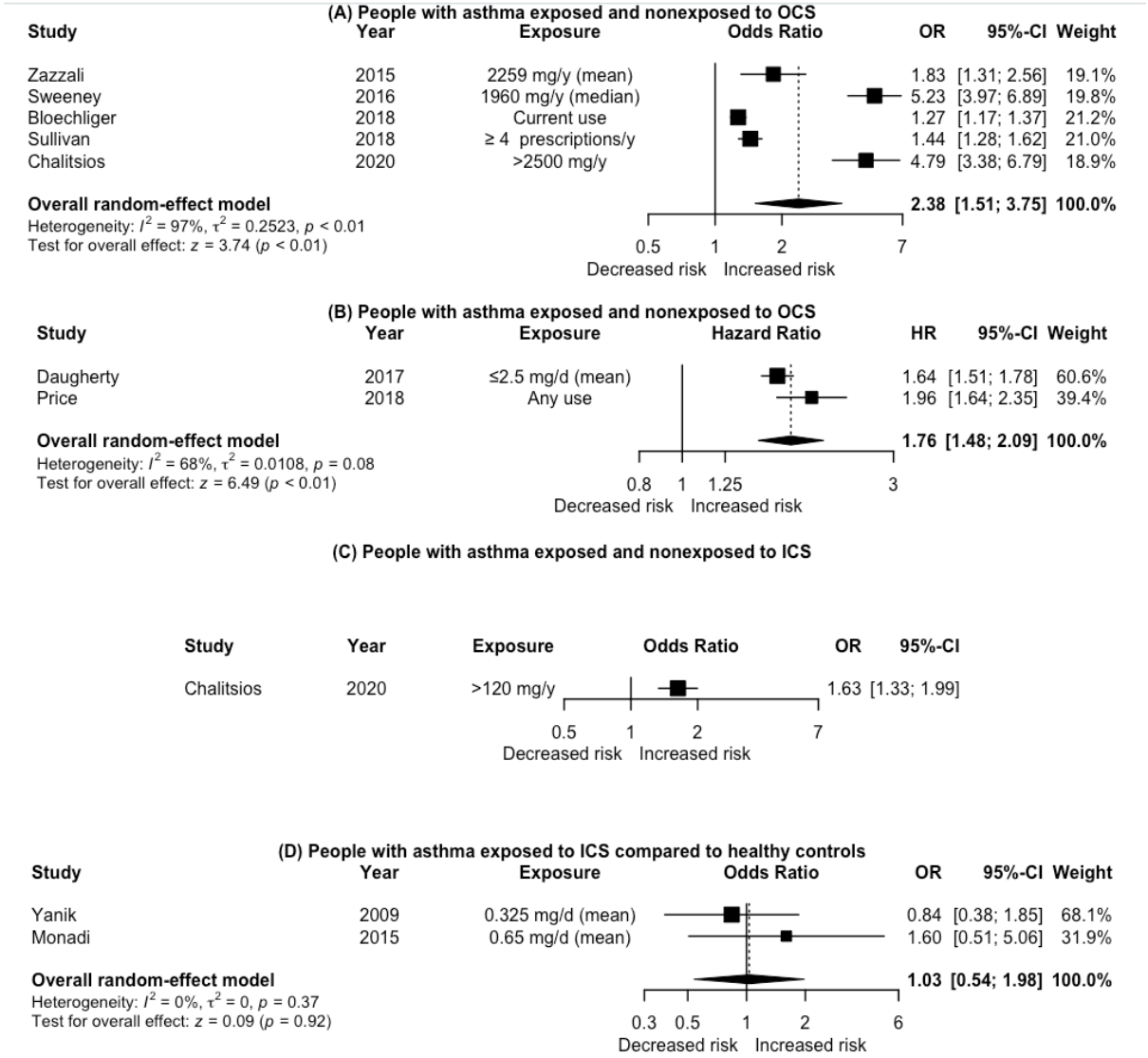

Figure 7-6. *Meta-analysis of observational studies on odds ratio and hazard ratio of osteoporosis in asthma. Black box, effect estimates from single studies; Diamond, pooled result with confidence interval; Vertical line at '1' on the x-axis is the line of no effect; Weight (in %), influence an individual study had on the pooled result.*

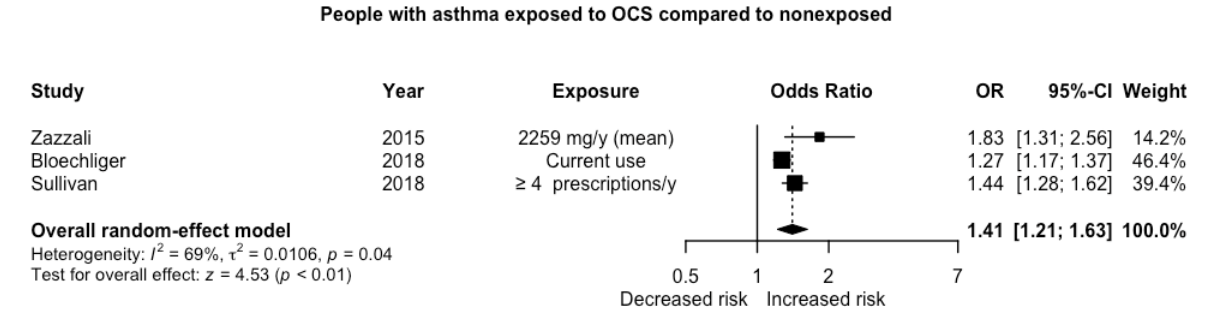

Figure 7-7*. Meta-analysis of observational studies on odds ratio of osteoporosis in asthma. Black box, effect estimates from single studies; Diamond, pooled result with confidence interval; Vertical line at '1' on the x-axis is the line of no effect; Weight (in %), influence an individual study had on the pooled result.*

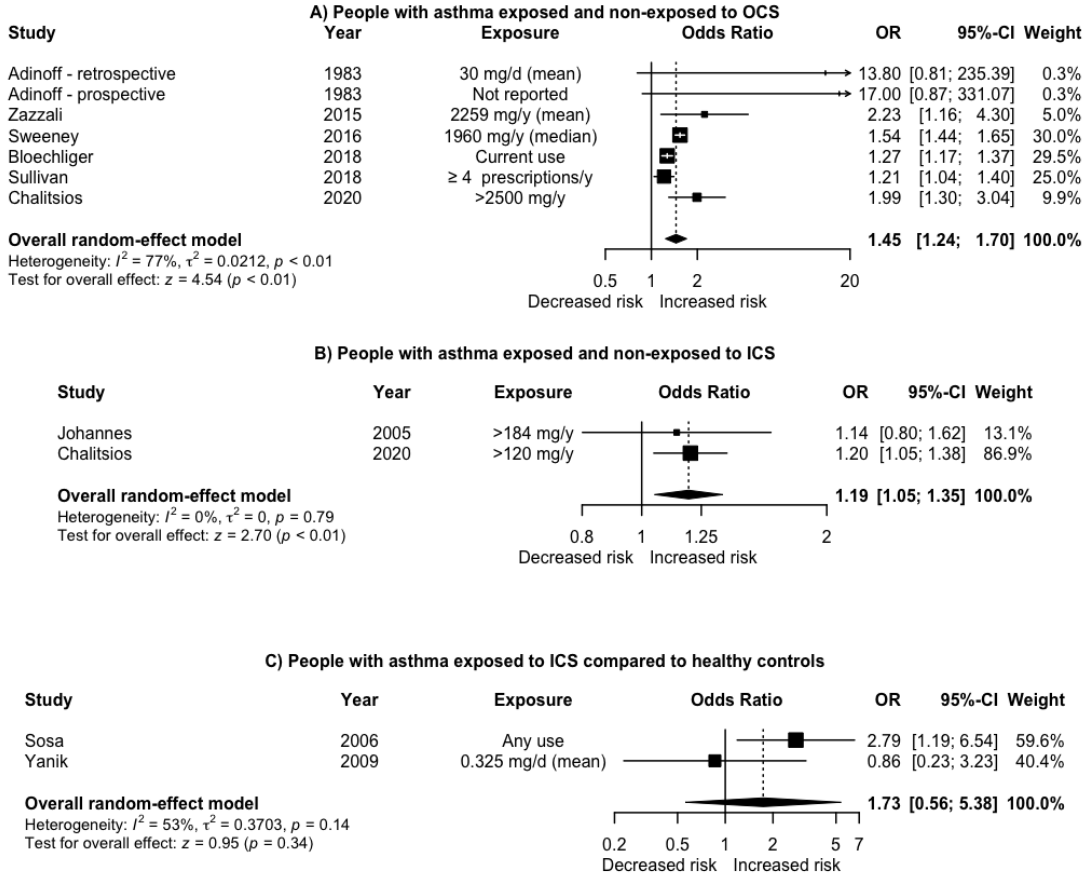

Figure 7-8*. Meta-analysis of observational studies on odds ratio of fractures in asthma. Black box, effect estimates from single studies; Diamond, pooled result with confidence interval; Vertical line at '1' on the x-axis is the line of no effect; Weight (in %), influence an individual study had on the pooled result.*

7.3.6 Quality assessment

Overall, the risk of the included studies ranged from moderate to high/serious risk. Two RCTs did not provide details about the allocation concealment process (210,211) and one RCT did not perform allocation concealment (212) (Tables 7-6 & Figure 7-9). The BMD was ascertained via DEXA scanning. All the RCTs had some loss to follow-up for the BMD measurements. Many observational studies did not achieve an adequate adjustment for confounders (Tables 7-7). No publication bias was detected where funnel plot or Egger's test were available (Figures 7-10 to 7-14). Osteoporosis and fracture were evaluated using diagnostic codes which carry the possibility of misclassification bias apart from two studies used x-rays (154,229).

Table 7-6. Quality assessment of the included RCTs according to Cochrane risk of bias RoB 2 tool.

Study	Risk of bias arising from the randomization process	Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Egan, 1999	High risk	Low risk	Some concerns	Low risk	Low risk	**High risk**
Li, 1999	High risk	Low risk	Some concerns	Low risk	Low risk	**High risk**
Kaye, 2000	High risk	Low risk	Some concerns	Low risk	Low risk	**High risk**
Tattersfield, 2001	Some concerns	Low risk	Some concerns	Low risk	Low risk	**Some concerns**
Kemp, 2004	Low risk	Low risk	Some concerns	Low risk	Low risk	**Low risk**
Maspero, 2013	Low risk	Some concerns	Some concerns	Low risk	Low risk	**Some concerns**

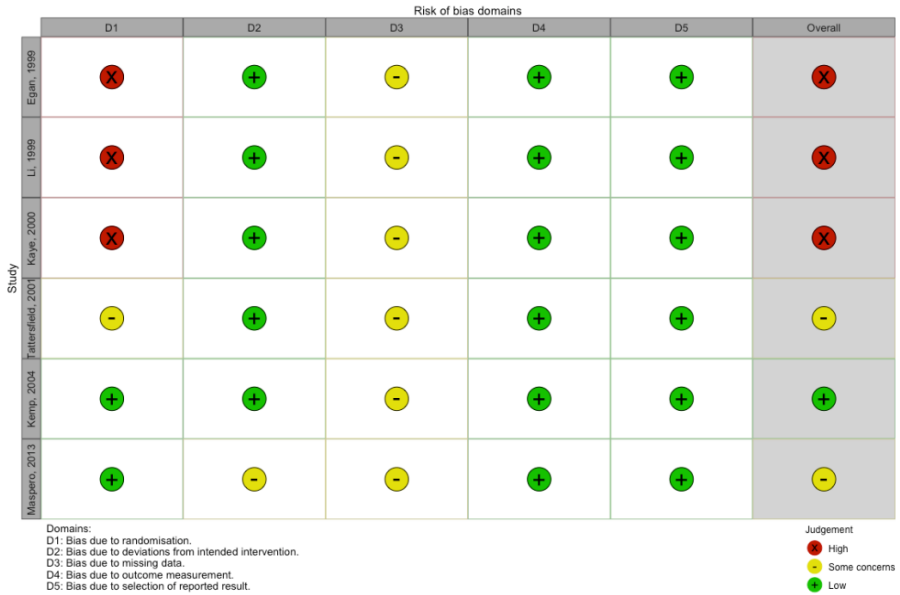

Figure 7-9. Traffic light plot depicting the risk of bias of RCT according to Cochrane risk of bias RoB 2 tool

Table 7-7. Quality assessment of the included observational studies according to Newcastle-Ottawa scale.

Study[a]	Selection	Comparability	Outcome	Overall risk
Adinoff, 1983	3	0	3	**6**
Ip, 1994	3	2	3	**8**
Boulet, 1994	2	1	2	**5**
Herrala,1994	3	1	3	**7**
Gagnon, 1997*	1	0	2	**3**
Luengo, 1997	3	2	2	**7**
Wisniewski, 1997*	1	0	2	**3**
Laatikainen, 1999*	1	1	2	**4**
Fujita, 2001	2	2	2	**6**
Matsumoto, 2001*	1	1	2	**4**
Sivri, 2001	2	2	2	**6**
El, 2005	2	1	2	**5**
Johannes, 2005	1	2	3	**6**
Monadi, 2005	1	2	2	**5**
Sosa, 2006	1	1	2	**4**
Yanik, 2009	1	0	2	**3**
Zazzali, 2015	3	2	1	**6**
Sweeney, 2016*	2	2	3	**7**
Daugherty, 2017	3	2	2	**8**
Bloechlinger, 2018	2	2	3	**7**
Price, 2018	2	2	3	**7**
Sullivan, 2018	3	2	2	**8**
Chalitsios, 2020	2	2	3	**7**

[a]*If a study name includes an (*) then is it is a cross-sectional study with a maximum overall score equal to 7. Otherwise, it is a cohort/case-control study with a maximum overall score equal to 9.*
Selection: maximum four stars; Comparability: maximum two starts; Outcome: maximum three starts.
Selection: maximum three stars; Comparability: maximum two starts; Outcome: maximum two starts.*

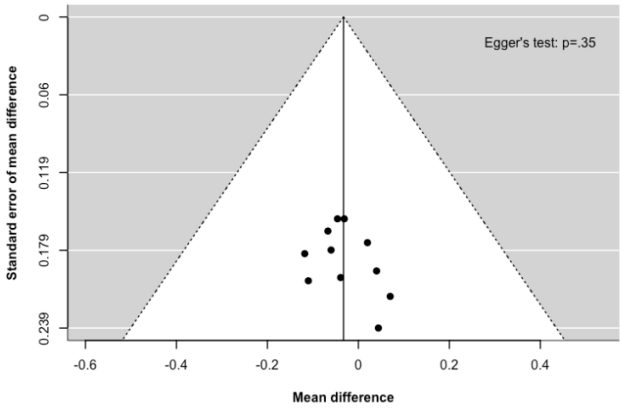

Figure 7-10. Funnel plot with Egger's test for meta-analysis of mean difference in BMD at spine comparing people with asthma exposed to ICS and healthy controls.

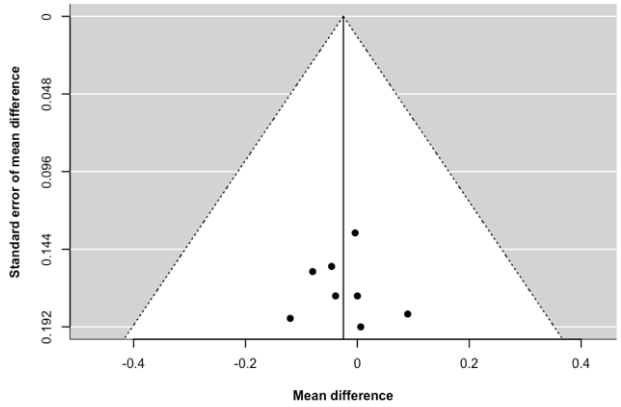

Figure 7-11. Funnel plot for meta-analysis of mean difference in BMD at femoral neck comparing people with asthma exposed to ICS and healthy controls.

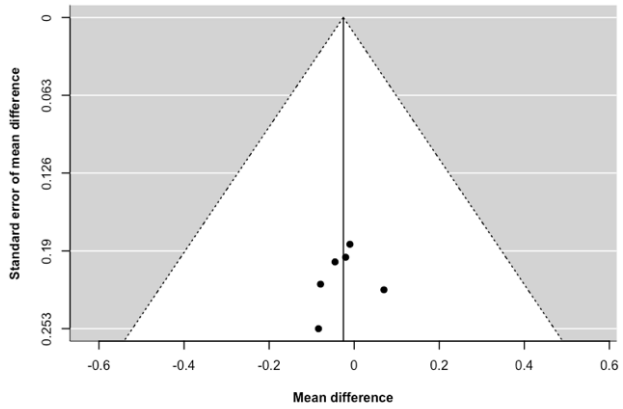

Figure 7-12. Funnel plot for meta-analysis of mean difference in BMD at spine comparing people with asthma exposed to ICS and not exposed to ICS people with asthma.

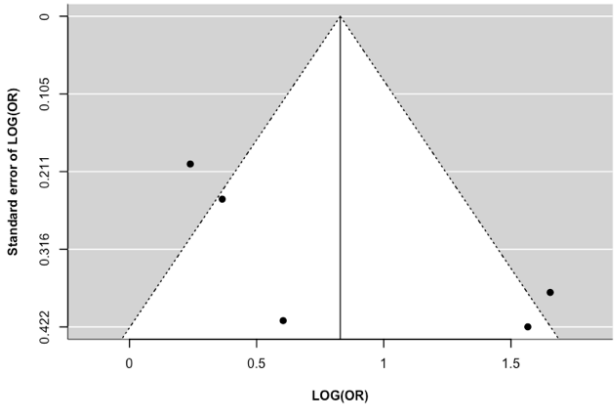

Figure 7-13. Funnel plot for meta-analysis of risk of osteoporosis comparing people with asthma exposed to OCS and not exposed to OCS people with asthma.

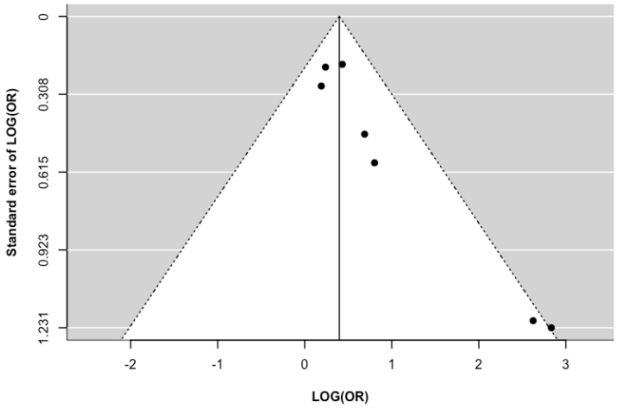

Figure 7-14. Funnel plot for meta-analysis of risk of osteoporosis comparing people with asthma exposed to OCS and not exposed to OCS people with asthma.

7.4 Discussion

This systematic review examined the impact of corticosteroids on bone health in asthma. It did not find any association between ICS and reduced BMD at the spine and femoral neck in people with asthma. However, there was evidence of increased risk of osteoporosis and fracture in people with asthma exposed to OCS or high doses of ICS compared to people with asthma not receiving corticosteroids.

Previous reviews followed a different methodology comparing people with asthma exposed to ICS not only with nonexposed people with asthma but also with healthy controls as a united group (189,204). They did not demonstrate a significant effect of ICS on BMD in people with asthma. In our specific analysis, we also did not find evidence of decreased BMD in people with asthma using ICS when compared to healthy controls. We were unable to show a statistically significant bone loss in people with asthma receiving ICS compared to nonexposed to ICS people with asthma. The small sample size of the studies and potential previous use of ICS during the study period may explain this result. Oddly, there appears to be a gap in the literature with respect to the effect of OCS on bone loss in asthma. The clinical significance of BMD measurement is important as this is the test used to detect osteoporosis and start protective treatment. Retrospective studies have shown that a reduction of $0.1 g/cm^2$ in spine BMD is linked with a doubling of spine fracture rate (231,232).

The adverse effect of OCS on bone health has been reported in a general population of OCS users (109) is confirmed in that study comparing exposed and nonexposed people with asthma. Compliance with current bone protection guidelines is important, and physicians should offer bone protection when prescribing OCS at high dose or for prolonged periods. Comparing people with asthma exposed and nonexposed to ICS, this review found that ICS had a negative impact on the risk of osteoporosis and fractures, but this occurred at higher doses (more than 80 and 120 mg/y, respectively).

The findings might suggest that ICS users may experience fractures at higher BMD levels, as happens with OCS users (91). The absence of a statistically significant association between ICS, osteoporosis, and fractures between exposed people with asthma and healthy controls, despite the increased odds, is likely the result of insufficient power, as only two small studies (osteoporosis: n = 94, n = 106; fractures: n = 106, n = 238) reported results for these comparison groups. Surprisingly, the literature is limited regarding the effects of ICS on bone health in people with asthma and this is probably the reason why there is no clear asthma specific bone protection guideline.

Both ICS and OCS are used to treat asthma or prevent exacerbations. Patients should be advised to use the lowest effective dose that adequately controls their asthma symptoms and future risk to reduce the chance of bone related, side effects. Bone density screening and management of osteoporosis should be considered using available guidelines; however, physicians should be aware that, according to our findings, fractures can also occur even at normal BMD levels. Consequently, the overall risk of osteoporosis and need for prophylaxis should be assessed using parameters including long-term use of corticosteroids, age, and previous fracture. The FRAX risk tool (115) can also be used to distinguish patients at high-risk. Patients at high-risk should receive pharmacologic preventative treatment. Lifestyle changes (e.g. weight-bearing activities, smoking cessation etc.) are recommenced for patients with asthma receiving long-term corticosteroids. Given the prevalence of asthma, need for long term steroid therapy and consequent risk of osteoporosis/fracture, an asthma specific bone protection guideline is needed to educate clinicians and patients, and reduce the risk of preventable osteoporotic fractures.

Some limitations of this study should be mentioned. There is a potential bias due to uncontrolled confounders and heterogeneity in observational studies. The included studies did not provide sufficient data to conduct meaningful analyses according to steroid type and dosage. Searching was limited to published literature, as the evaluation

of their quality in absence of a peer-review process could not be ensured. Additionally, data provided in this review were derived from studies that varied in study design and sources of data. Selective reporting cannot be excluded because tests and graphical assessment for publication bias are not sensitive enough owing to the small number of studies included in our meta-analysis (233).

7.5 Conclusion

The crucial role of corticosteroids in the treatment of asthma is well-recognised. However, physicians should be aware of the potential adverse effects on bone health and consider avoiding the inappropriate use of these treatments.

8 A RETROSPECTIVE DATABASE STUDY OF ORAL CORTICOSTEROID AND BISPHOSPHONATE PRESCRIBING PATTERNS IN ENGLAND

8.1 Introduction

Oral corticosteroids are used to treat chronic conditions including autoimmune (234), and respiratory diseases (19,235). Asthma is among the most common indication for prolonged OCS use (more than 90 days) (170). Both short-term (5 to 90 days) and prolonged exposure to OCS can lead to deleterious effects (66,236) including bone loss resulting in osteoporosis and fragility fractures (174). Bone loss is substantial and rapid during the first months of the treatment (83). Patients with severe asthma exposed to prednisolone 5mg per day are more likely to be diagnosed with osteoporosis (OR = 6.53) and have a fracture (OR = 1.65) compared to those without asthma (43). After OCS initiation, spine fracture risk increases by 55% with exposure at doses as low as prednisone 2.5 mg per day, whereas hip fracture risk goes up by 77% among patients exposed between 2.5 and 7.5 mg per day (67,190).

Due to the substantial burden of fragility (89,176) guidelines suggest all patients exposed to any dose of OCS for more than three months should be considered for bisphosphonate therapy to prevent glucocorticoid-induced osteoporosis (121,124). The bisphosphonate class is effective in reducing bone loss and risk of fragility fractures (237,238). Despite this, only a minority of patients with increased fragility fracture risk receive appropriate therapy (239,240). There is no specific guidance for glucocorticoid-induced osteoporosis in asthma and the size of the potential problem is not well established.

The aim was to comprehensively assess OCS and bisphosphonate prescribing patterns, using data from England and investigate factors associated with their prescribing, in order to gain a better understanding of prescribing enabling us to reduce any variation and optimise glucocorticoid-induced osteoporosis prevention.

8.2 Methods

8.2.1 Data sources

Monthly practice-level data on all items prescribed in NHS primary care in England and dispensed in the community is published by the NHS Business Services Authority. Data from OpenPrescribing.net (https://openprescribing.net/) were used, which imports this data, alongside various other datasets giving practice characteristics. National prescribing data record the number of items of each individual drug presentation prescribed by every practice in England, for every month. Prescribing activity for each drug presentation is measured as the number of items. A prescribed item refers to a single supply of a medicine prescribed on a prescription form. If a prescription form includes three medicines, it is counted as three prescription items.

8.2.2 Study design

A retrospective study was conducted on all English practices and CCG, measuring patterns in OCS and bisphosphonate prescribing items over time. The ratio in prescribing rate between OCS and bisphosphonates was estimated and any geographical variation among CCG was described. Monthly practice-level and open access data from Public Health England were linked to investigate reasons for any variation in prescribing at practice and CCG level.

8.2.3 Drugs extraction

Prescribing data were extracted for the following oral corticosteroids: Beclometasone Dipropionate (Systemic) (Brand name: Clipper), Budesonide (Brand names: Entocort, Budenofalk) derived from the section "1.2.5: Corticosteroids" of the British National Formulary (BNF) book. Betamethasone Sodium Phosphate (brand names: Betnesol, Betameth sod phos, all systemic), Cortisone Acetate (brand name: Cortisone acet), Deflazacort (brand name: Calcort), Dexamethasone (brand name: Dexameth (systemic)), Hydrocortisone (brand name: Hydrocortone, Hydrocort (systemic)),

Methylprednisolone (brand name: Medrone (systemic)), Prednisolone (brand name: Prednisolone (systemic)), and Prednisone (brand name: Lodotra) were derived from the section "6.3.2: Glucocorticoid therapy" of the BNF (Appendix 2).

Prescribing data were extracted for bisphosphonates following guidance from the National Osteoporosis Guideline Group (124). These were: Alendronic acid (brand names: Alendronic acid, Fosamax), risedronate sodium (brand names: Actonel, Risedronate sod), and Zoledronic acid (brand name: Zometa). All bisphosphonates were checked against section "6.6.2: Bisphosphonates and other drugs" of the BNF (Appendix 2).

8.2.4 Long-term patterns

Data from OpenPrescribing.net were obtained describing the annual patterns in OCS and bisphosphonate prescribing items per 1,000 population from 1998 to 2018. The total annual items per 1,000 population of each OCS or bisphosphonates type were aggregated. Stacked graphs were created to depict the annual volume of each chemical of each drug.

8.2.5 Ratio between OCS and bisphosphonate prescriptions

Monthly data of OCS and bisphosphonates prescribed items per CCG from January 2015 to December 2018 were extracted. Monthly items of each CCG per year of both OCS and bisphosphonate items were aggregated obtaining the total annual number. The ratio between the above classes of drugs was calculated using:

$$Ratio = \left(\frac{Total\ OCS\ items\ the\ year\ of\ interest}{Total\ bisphosphonate\ items\ the\ year\ of\ interest}\right)$$

8.2.6 Variations among CCG for OCS and bisphosphonate items

In 2012, each practice was grouped into Clinical Commissioning Groups. The CCG are responsible for the planning and commissioning of health care in a local community. To examine geographical variations in OCS and bisphosphonate prescribing in 2018, practices were grouped by CCG. The prescribing rate per 1,000 patients of dispensed OCS and bisphosphonates for each CCG was derived by dividing the total number of prescribing items by the mean patient list size over the year in each CCG, multiplied by 1,000. Then, they were categorised into quantiles.

8.2.7 Associations between OCS and bisphosphonate prescribing

After calculating the rate of OCS and bisphosphonate items per 1,000 patients per practice, other independent variables were determined to examine which indicators were associated with OCS and bisphosphonate prescriptions in 2018. The analysis was also repeated for 2015, 2016 and 2017. Data were extracted on the following factors from the Public Health England (https://fingertips.phe.org.uk/profile/general-practice/data): the percentage of a) asthma diagnosis, b) COPD diagnosis, c) patients over 65 years old, d) patients with a long-term health condition defined as the percentage of people who answered "*Yes*" in the practices' patient survey (http://www.gp-patient.co.uk/practices-search) question: *"Do you have any long-term physical or mental health conditions, disabilities or illnesses?"*, e) the IMD score, and f) the mean practice list size. All the above figures were derived from the correspondence year of interest apart from the IMD score which was available only for 2015; this score was used for the analysis in each year of interest. All of the above indicators were obtainable based on the CCG which were active in 2017/2018. Furthermore, data about the QOF score were additionally extracted by practice (https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data). The 2017/2018 QOF score was used not only in the analysis for the year 2017 but also in 2018 as the 2018/2019 QOF score had not been released yet.

8.2.8 Practice exclusion

In 2018, there were 7,093 practices from 195 CCG. Initially, all practices (n=255) without having achieved a QOF score have been excluded and then, all practices (n=331) with a patient list size less than 1,000 patients. Firstly, practices without a having achieved a QOF score may have simply opted out and could be normal active practices, but there is likely to be a high proportion of unusual practices amongst those without scores. For example, practices may opt out because they are in the process of opening, closing, or merging, be under special measures or other temporary closure, have very few patients in the relevant clinical areas, or perhaps are very small and don't have the resource or incentive to complete the necessary paperwork. Secondly, practices with a small patient list size were serving a population which is sufficiently different "atypical" (e.g. serving elderly or homeless populations) (241). A limit of 1,000 patients throughout our analysis was used because this has been used elsewhere (242,243). Furthermore, it was not possible to compare the practices without a QOF score with the included ones, as most of them had missing values in all variables. However, this can confirm the fact that the excluded practices were inactive through the whole year or for a long period during this.

8.2.9 Statistical Methods

Practices characteristics were analysed using descriptive analysis reporting them as median along with IQR. A paired t-test was performed examining the significance of variation between OCS and bisphosphonate prescriptions among CCG. To examine the association between OCS or bisphosphonates per 1,000 patients and the potential associated factors a negative binomial regression analysis was performed. The rate of OCS and bisphosphonates prescribing was stratified for each one of the investigating factors. I put these factors in the model. I also split the OCS per 1,000 patients into quintiles and put them in the bisphosphonate analysis. Afterwards, as healthcare policies and commissioning differ among CCG, a mixed-effect negative binomial model was used, defining the rate of OCS and bisphosphonate prescriptions per 1,000 patients

as the dependent variable. The factors defined above as fixed-effects explanatory variables and the CCG of each practice as a random-effect variable were used. The variables were grouped into quintiles to allow for non-linearity of effects. IRRs with a 95% CI were used to determine the strength of associations and R^2 to show the value and significance of variance associated with CCG grouping. *P*-values < 0.05 were considered statistically significant. Practices with missing values were less than 0.25%. Python was used for data management and graphs construction. Statistical analysis was conducted by using Stata v16.

8.3 Results

8.3.1 Practice characteristics

195 CCG containing 6,586 practices after the exclusion of 507 were included. In 2018, the median (IQR) OCS and bisphosphonate prescriptions per 1,000 patients was 120.8 (84.8 to 160.4) and 107.7 (73.8 to 147.4), respectively. The characteristics of practices are summarised in the Table 8-1. Identical results were also found in the previous years (Tables 8-2 to 8-4).

Table 8-1. Characteristics of practices included in the analysis from January to December 2018.

	Median	IQR
Asthma prevalence (%)	6.0	5.1 - 6.8
COPD prevalence (%)	1.8	1.3 - 2.5
Practice list size	7,478	4,664 - 11,270
Patients with long-term health conditions (%)	51.7	45.5 - 59.1
Patients over 65 years old (%)	17.4	12.2 - 21.8
Quality Outcomes Framework score	549.0	534.7 - 556.8
OCS prescribed items per 1,000 patients	120.8	84.8 - 160.4
BP prescribed items per 1,000 patients	107.7	73.8 - 147.4

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; OCS, Oral Corticosteroids; BP, Bisphosphonates.

Table 8-2. Characteristics of practices included in the analysis from January to December 2017.

	Median	IQR
Asthma prevalence (%)	6.0	5.1 - 6.8
COPD[1] prevalence (%)	1.8	1.3 - 2.4
Practice list size	7,273	4,462 - 10,885
Patients with long-term health conditions (%)	53.8	48 - 59
Patients over 65 years old (%)	17.2	12 - 22
Quality Outcomes Framework score	549	535 - 557
OCS prescribed items per 1,000 patients	128.5	86.9 - 163.4
BP prescribed items per 1,000 patients	118.3	76.9 - 154.6

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; OCS, Oral Corticosteroids; BP, Bisphosphonates.

Table 8-3. Characteristics of practices included in the analysis from January to December 2016.

	Median	IQR
Asthma prevalence (%)	5.9	5.1 - 6.7
COPD[1] prevalence (%)	1.8	1.2 - 2.4
Practice list size	6,949	4,230 - 10,565
Patients with long-term health conditions (%)	53.3	48.2 - 58.4
Patients over 65 years old (%)	17.3	12.3 - 21.4
Quality Outcomes Framework score	545.9	528.9 - 555.2
OCS prescribed items per 1,000 patients	130.5	88.2 - 1167.2
BP prescribed items per 1,000 patients	126.5	82.2 - 165.9

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; OCS, Oral Corticosteroids; BP, Bisphosphonates.

Table 8-4. Characteristics of practices included in the analysis from January to December 2015.

	Median	IQR
Asthma prevalence (%)	6.0	5.1 - 6.8
COPD[1] prevalence (%)	1.7	1.2 - 2.4
Practice list size	7,044	4,380 - 10,538
Patients with long-term health conditions (%)	54.2	49.8 - 59.3
Patients over 65 years old (%)	17.2	12.3 - 21.23
Quality Outcomes Framework score	543.3	524.3 - 553.6
OCS prescribed items per 1,000 patients	128.8	92.5 - 167.6
BP prescribed items per 1,000 patients	134.8	91.9 - 186.5

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; OCS, Oral Corticosteroids; BP, Bisphosphonates.

8.3.2 Long-term patterns and ratio between OCS and bisphosphonate prescriptions

Prednisolone was the most frequently prescribed OCS. There was a steady increase in OCS prescriptions over time (Figure 8-1a). In 1998, there were 95 OCS prescriptions per 1,000 population increasing to 140 in 2018 (55% rise). Similarly, an increase in bisphosphonate prescribing rates over the time was observed (Figure 8-1b). In 1998, there were 10 bisphosphonate prescriptions, while the total prescriptions reached 120 per 1,000 population in 2018 (1,200% increase). The most prescribed bisphosphonate was alendronic acid. There were 0.99 OCS prescriptions per 1 bisphosphonate item in 2015, however this relationship changed slightly to 1.16 by 2018 (Table 8-5).

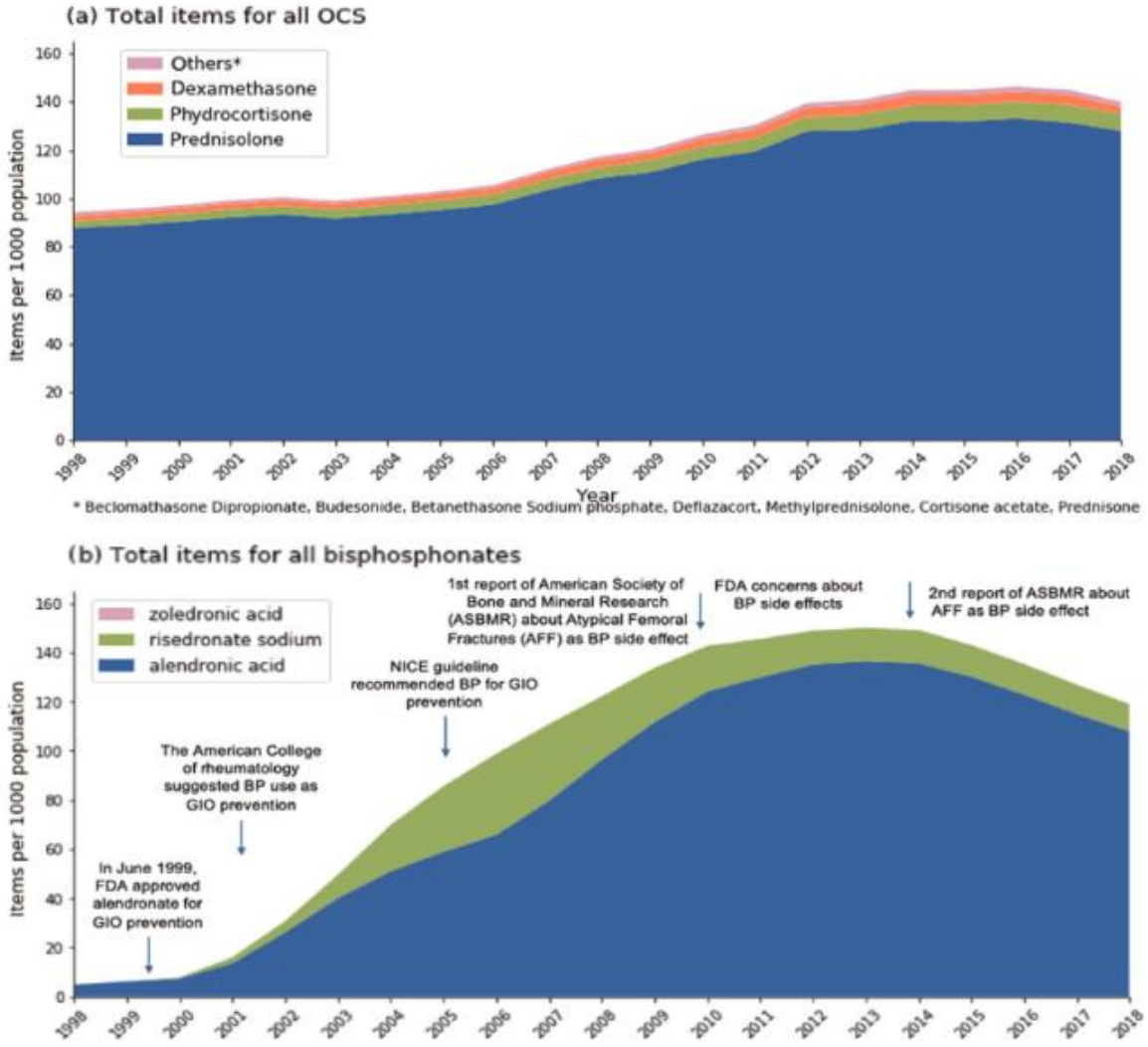

Figure 8-1. *Long-term prescribing patterns. Total (a) oral corticosteroids (OCS) and (b) bisphosphonates (BP) prescribed items per 1000 population over the period from 1998 to 2018. The arrows provide factors that may have affected their prescribing.*

Table 8-5. Trends in ratio between oral corticosteroids and bisphosphonates over the period of 2015 to 2018.

Year	OCS items	BP items	Ratio scale (OCS/BP)
2015	7,781,584	7,836,568	0.99
2016	7,958,014	7,479,733	1.06
2017	7,911,005	7,062,931	1.12
2018	7,799,798	6,728,997	1.16

Abbreviations: OCS, Oral Corticosteroids; BP, Bisphosphonates.

8.3.3 Variations among practices and CCGs for OCS and bisphosphonate items

In 2018, there was a significant variation between OCS (mean = 129.6; SD = 38.9) and bisphosphonate (m = 118.5; SD = 34.2) prescriptions per 1,000 patients; t = 6.27; p <.0001. OCS prescriptions varied between 48 and 239 and bisphosphonates ranged from 38 to 207 prescriptions per 1,000 patients across CCG. 60 out of 195 CCG prescribed less OCS than bisphosphonate items, and 135 more OCS than bisphosphonate items per 1,000 patients (Figure 8-2).

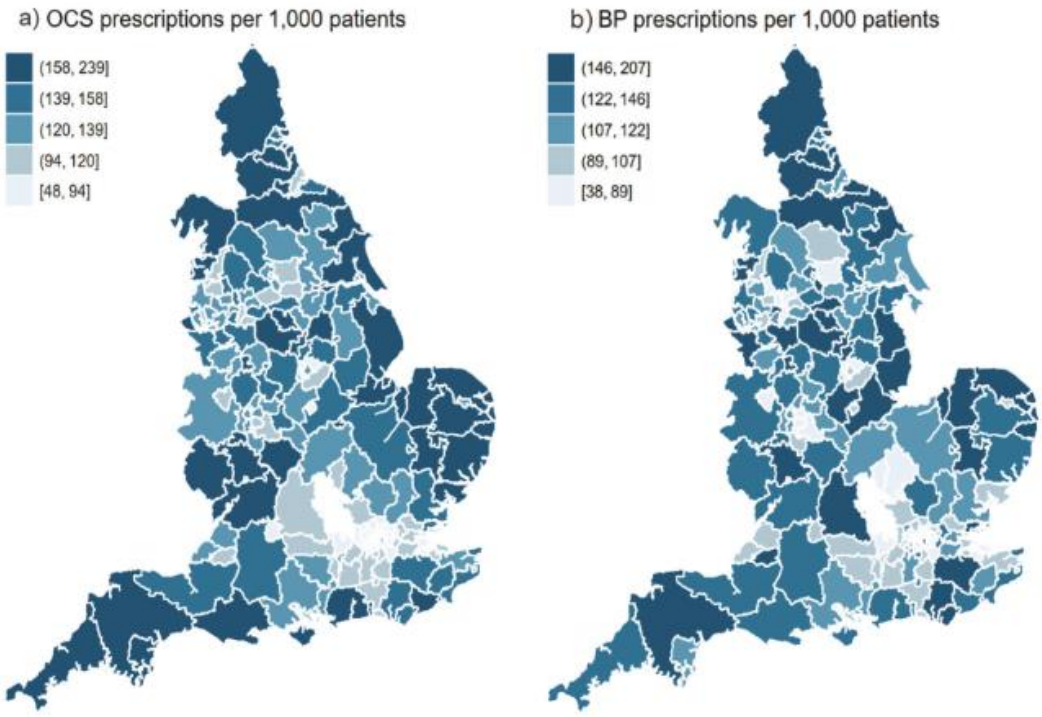

Figure 8-2. *Geographical variation in prescribing. Geographical variations in (a) oral corticosteroids (OCS) and (b) bisphosphonates (BP) prescribed items categorised into quantiles among Clinical Commissioning Groups from January to December 2018.*

8.3.4 Factors associated with OCS and bisphosphonates prescribing

OCS prescriptions were associated with the factors listed in Table 8-6 apart from the QOF score and percentage of patients with a long-term health disease. Asthma was significantly associated with the OCS use ($p < .0001$). The percentage of patients aged 65 years old, or more was the strongest predictor of OCS prescriptions ($p < .0001$). Practices in the highest quintile prescribed 1.74 times more OCS (IRR = 1.74; 95%CI 1.64 to 1.84) than those in the lowest one. Practise list size was also a positive predictor of OCS prescribing ($p < .0001$) and the most deprived areas were less likely to prescribe less OCS than the least deprived areas (IRR = 0.84; 95%CI 0.80 to 0.88).

OCS were associated with bisphosphonate prescriptions ($p < .0001$), with higher OCS prescribing rates to have been associated with higher bisphosphonate prescribing rates (5^{th} to 1^{st} quintile- IRR = 1.99; 95%CI 1.88 to 2.10). (Table 8-7). Asthma was not significantly associated with a bisphosphonate prescription ($p = .6848$). Practices located in more deprived areas were 28% less likely to prescribe less bisphosphonates than the least deprived practices (IRR = 0.72; 95%CI 0.68 to 0.77).

The CCG to which a practice belongs was significantly associated with prescribing rates and accounted for 11% and 5% of the variation in OCS and bisphosphonate prescribing, respectively.

Similar results in previous years were also found (Tables 8-8 to 8-13).

Table 8-6. Oral corticosteroids prescribing rates in 2018, stratified by seven practice characteristics and two respiratory diseases in a negative binomial model reporting incidence rate ratio.

	Quintile range	Median OCS prescription per 1,000 patients	Univariate model IRR (95%CI)*	Multivariate model IRR (95%CI)$	*p*-value**
Asthma	≤4.85	69.26	Reference	Reference	<.0001
Prevalence	4.86-5.67	109.48	1.46 (1.39-1.51)	1.11 (1.08-1.15)	
(%)	5.68-6.29	128.56	1.69 (1.61-1.76)	1.18 (1.13-1.23)	
	6.30-6.98	144.31	1.90 (1.82-1.98)	1.23 (1.18-1.29)	
	6.99-12.56	157.61	2.10 (2.01-2.19)	1.28 (1.22-1.34)	
COPD	≤1.17	69.68	Reference	Reference	<.0001
Prevalence	1.18-1.65	107.95	1.48 (1.42-1.55)	1.13 (1.09-1.17)	
(%)	1.66-2.10	128.56	1.77 (1.70-1.85)	1.20 (1.15-1.25)	
	2.11-2.69	144.67	1.95 (1.87-2.04)	1.26 (1.21-1.33)	
	2.70-10.45	155.17	2.10 (2.01-2.20)	1.34 (1.27-1.41)	
Practice list size	≤4,127	112.14	Reference	Reference	<.0001
	4,128-6,287	120.98	1.03 (0.98-1.08)	1.01 (0.97-1.05)	
	6,290-8,809	127.64	1.04 (0.99-1.09)	1.00 (0.97-1.05)	
	8,810-12,335	129.77	1.05 (1.01-1.10)	0.98 (0.95-1.02)	
	≥12,336	118.48	0.91 (0.86-0.95)	0.88 (0.85-0.91)	
QOF score	≤529.81	111.24	Reference	Reference	.2579
	529.82-545.04	115.02	1.05 (1.01-1.11)	1.03 (0.99-1.07)	
	545.05-552.16	118.01	1.08 (1.03-1.13)	1.02 (0.99-1.06)	
	552.17-557.84	128.73	1.15 (1.10-1.21)	1.01 (0.98-1.06)	
	557.85-559	137.49	1.24 (1.18-1.30)	1.02 (0.98-1.07)	
% over 65 years old	≤11.00	68.16	Reference	Reference	<.0001
	11.01-15.63	106.01	1.50 (1.44-1.56)	1.24 (1.20-1.28)	
	15.64-18.86	126.68	1.78 (1.70-1.85)	1.39 (1.34-1.46)	
	18.87-22.77	139.56	1.95 (1.87-2.04)	1.49 (1.42-1.57)	
	≥22.78	172.23	2.40 (2.30-2.50)	1.74 (1.64-1.84)	
% patients with a long-term health disease	≤43.95	73.53	Reference	Reference	.1923
	43.97-49.65	109.62	1.40 (1.34-1.47)	1.03 (0.99-1.06)	
	49.66-53.85	128.86	1.64 (1.56-1.71)	1.04 (1.01-1.08)	
	53.86-58.44	140.36	1.77 (1.69-1.85)	1.03 (0.99-1.07)	
	≥58.45	151.76	1.91 (1.83-2.00)	1.04 (0.99-1.08)	
IMD score	Least deprived	126.98	Reference	Reference	<.0001
	-	134.29	1.03 (0.98-1.08)	0.92 (0.88-0.95)	
	-	122.00	0.96 (0.91-1.01)	0.87 (0.83-0.90)	
	-	115.85	0.89 (0.85-0.94)	0.85 (0.81-0.88)	
	Most deprived	110.01	0.88 (0.84-0.92)	0.84 (0.80-0.88)	

Abbreviations: *OCS, Oral Corticosteroids; COPD, Chronic Obstructive Pulmonary Disease; QOF, Quality and Outcomes Framework; IMD, Index of Multiple Deprivation.*

**Negative Binomial model, $ Mixed-effects Negative Binomial Model, **From multivariate analysis using the likelihood ratio test.*

Table 8-7. Bisphosphonates prescribing rates in 2018, stratified by seven practice factors and OCS per 1,000 patients in a negative binomial model reporting incidence rate ratio.

	Quintile range	Median BP prescription per 1,000 patients	Univariate model IRR (95%CI)*	Multivariate model IRR (95%CI)$	*p*-value**
Asthma	≤4.85	72.87	Reference	Reference	.6848
Prevalence	4.86-5.67	100.36	1.23 (1.21-1.33)	1.01 (0.96-1.04)	
(%)	5.68-6.29	115.37	1.44 (1.38-1.52)	1.04 (0.99-1.08)	
	6.30-6.98	121.57	1.55 (1.47-1.63)	1.01 (0.96-1.05)	
	6.99-12.56	128.56	1.67 (1.59-1.76)	1.01 (0.97-1.07)	
COPD	≤1.17	67.37	Reference	Reference	<.0001
Prevalence	1.18-1.65	98.71	1.40 (1.37-1.47)	1.08 (1.04-1.12)	
(%)	1.66-2.10	115.18	1.63 (1.56-1.72)	1.13 (1.08-1.19)	
	2.11-2.69	123.80	1.72 (1.64-1.80)	1.15 (1.09-1.21)	
	2.70-10.45	131.90	1.85 (1.76-1.94)	1.19 (1.12-1.26)	
OCS per	≤75.37	52.66	Reference	Reference	<.0001
1000 patients	75.40-108.44	89.60	1.63 (1.56-1.70)	1.39 (1.34-1.46)	
	108.56-136.24	110.94	2.00 (1.91-2.09)	1.58 (1.51-1.66)	
	136.27-169.84	128.78	2.32 (2.22-2.43)	1.74 (1.66-1.83)	
	≥169.85	161.98	2.94 (2.82-3.07)	1.99 (1.88-2.10)	
Practice list	≤4,127	102.46	Reference	Reference	<.0001
size	4,128-6,287	110.85	1.03 (0.98-1.09)	0.99 (0.96-1.03)	
	6,290-8,809	113.50	1.04 (0.98-1.08)	0.97 (0.93-1.01)	
	8,810-12,335	112.61	1.04 (0.98-1.09)	0.97 (0.90-0.97)	
	≥12,336	104.82	0.90 (0.85-0.95)	0.96 (0.90-0.91)	
QOF score	≤529.81	97.30	Reference	Reference	<.0001
	529.82-545.04	102.15	1.04 (0.99-1.10)	1.05 (1.01-1.09)	
	545.05-552.16	106.40	1.08 (1.03-1.14)	1.07 (1.03-1.11)	
	552.17-557.84	115.61	1.16 (1.10-1.23)	1.07 (1.03-1.11)	
	557.85-559	123.05	1.25 (1.19-1.32)	1.09 (1.04-1.13)	
% over 65	≤11	54.77	Reference	Reference	<.0001
years old	11.01-15.63	95.43	1.63 (1.56-1.71)	1.35 (1.29-1.40)	
	15.64-18.86	112.63	1.98 (1.89-2.07)	1.50 (1.42-1.58)	
	18.87-22.77	127.56	2.20 (2.10-2.30)	1.59 (1.50-1.68)	
	≥22.78	154.39	2.66 (2.54-2.78)	1.82 (1.71-1.94)	
% patients	≤43.95	70.30	Reference	Reference	.3457
with a long-	43.97-49.65	98.73	1.36 (1.30-1.43)	1.03 (0.99-1.08)	
term health	49.66-53.85	116.34	1.56 (1.49-1.64)	1.03 (0.98-1.08)	
disease	53.86-58.44	123.56	1.66 (1.59-1.75)	1.01 (0.96-1.05)	
	≥58.45	131.17	1.82 (1.73-1.91)	1.04 (0.99-1.09)	
IMD score	Least deprived	117.83	Reference	Reference	<.0001
	-	122.89	1.03 (0.97-1.18)	0.93 (0.90-0.97)	
	-	111.17	0.92 (0.87-0.96)	0.85 (0.82-0.90)	
	-	102.84	0.84 (0.81-0.88)	0.80 (0.76-0.84)	
	Most deprived	85.29	0.74 (0.70-0.78)	0.72 (0.68-0.77)	

Abbreviations: *BP, Bisphosphonates; COPD, Chronic Obstructive Pulmonary Disease; OCS, Oral Corticosteroids; QOF, Quality and Outcomes Framework; IMD, Index of Multiple Deprivation.*

**Negative Binomial model, $ Mixed-effects Negative Binomial Model, ** From multivariate analysis using the likelihood ratio test.*

Table 8-8. Oral corticosteroids prescribing rates in 2017, stratified by seven practice characteristics and two respiratory diseases in a negative binomial model reporting incidence rate ratio.

	Quintile range	Median OCS prescription per 1,000 patients	Univariate model IRR (95%CI)*	Multivariate model IRR (95%CI)$	*p*-value**
Asthma	≤4.84	73.83	Reference	Reference	<.0001
Prevalence	4.85-5.65	112.40	1.45 (1.39-1.52)	1.13 (1.08-1.16)	
(%)	5.66-6.29	128.20	1.64 (1.57-1.71)	1.18 (1.13-1.23)	
	6.30-6.96	147.06	1.86 (1.78-1.94)	1.21 (1.16-1.26)	
	6.97-14.37	160.38	2.03 (1.95-2.12)	1.28 (1.22-1.32)	
COPD	≤1.14	72.06	Reference	Reference	<.0001
Prevalence	1.15- 1.60	110.58	1.45 (1.39-1.52)	1.11 (1.07-1.15)	
(%)	1.61-2.04	132.96	1.73 (1.65-1.80)	1.19 (1.14-1.24)	
	2.05-2.64	148.27	1.92 (1.84-2.01)	1.27 (1.21-1.33)	
	2.65-11.25	158.29	2.04 (1.96-2.13)	1.34 (1.27-1.41)	
GP list size	≤3,947	112.46	Reference	Reference	<.0001
	3,949-6,050	122.46	1.03 (0.98-1.08)	1.01 (0.97-1.02)	
	6,051-8,508	129.68	1.06 (1.01-1.11)	1.01 (0.98-1.02)	
	8,509-11,920	134.14	1.07 (1.02-1.13)	0.99 (0.95-1.06)	
	≥11,922	124.35	0.95 (0.90-0.99)	0.90 (0.86-1.16)	
QOF score	≤530.81	108.84	Reference	Reference	.0589
	530.82-545.04	115.04	1.08 (1.03-1.13)	1.06 (1.01-1.10)	
	545.05-553.16	123.93	1.14 (1.09-1.19)	1.04 (1.01-1.08)	
	553.17-557.84	133.85	1.20 (1.14-1.26)	1.04 (1.01-1.05)	
	557.85-559	141.05	1.29 (1.23-1.35)	1.05 (1.01-1.09)	
% over 65	≤11	70.17	Reference	Reference	<.0001
years old	530.82-545.04	115.04	1.08 (1.03-1.13)	1.06 (1.01-1.10)	
	545.05-553.16	123.93	1.14 (1.09-1.19)	1.04 (1.01-1.08)	
	553.17-557.84	133.85	1.20 (1.14-1.26)	1.04 (1.01-1.05)	
	557.85-559	141.05	1.29 (1.23-1.35)	1.05 (1.01-1.09)	
% patients	≤47.28	88.92	Reference	Reference	.0388
with a long-	47.29-52.13	114.96	1.28 (1.23-1.33)	1.05 (1.01-1.09)	
term health	52.14-55.50	129.53	1.47 (1.40-1.54)	1.04 (1.01-1.08)	
disease	55.51-60.03	143.10	1.56 (1.50-1.64)	1.04 (1.01-1.19)	
	≥60.04	152.62	1.71 (1.63-1.79)	1.06 (1.01-1.10)	
IMD score	Least deprived	129.11	Reference	Reference	<.0001
	-	138.69	1.04 (1.00-1.09)	0.94 (0.90-0.97)	
	-	125.62	0.96 (0.92-1.01)	0.87 (0.83-0.90)	
	-	117.41	0.89 (0.86-0.94)	0.85 (0.80-0.88)	
	Most deprived	113.43	0.89 (0.86-0.94)	0.85 (0.80-0.89)	

Abbreviations: *OCS, Oral Corticosteroids; COPD, Chronic Obstructive Pulmonary Disease; GP, General Practice QOF, Quality and Outcomes Framework; IMD, Index of Multiple Deprivation.*

**Negative Binomial model, $Mixed-effects Negative Binomial Model, **From multivariate analysis using the likelihood ratio test.*

Table 8-9. Bisphosphonates prescribing rates in 2017, stratified by seven practice characteristics and two respiratory diseases in a negative binomial model reporting incidence rate ratio.

	Quintile range	Median BP prescription per 1,000 patients	Univariate model IRR (95%CI)*	Multivariate model IRR (95%CI)$	*p*-value**
Asthma	≤4.84	77.60	Reference	Reference	.5972
Prevalence	4.85-5.65	108.18	1.29 (1.23-1.36)	1.03 (0.99-1.08)	
(%)	5.66-6.29	122.14	1.44 (1.37-1.52)	1.04 (0.99-1.09)	
	6.30-6.96	131.04	1.55 (1.47-1.63)	1.01 (0.95-1.05)	
	6.97-14.37	134.32	1.63 (1.55-1.71)	1.01 (0.96-1.06)	
COPD	≤1.14	72.16	Reference	Reference	<.0001
Prevalence	1.15- 1.60	103.62	1.39 (1.33-1.47)	1.07 (1.02-1.11)	
(%)	1.61-2.04	122.34	1.61 (1.53-1.70)	1.11 (1.05-1.16)	
	2.05-2.64	129.33	1.73 (1.64-1.81)	1.13 (1.07-1.19)	
	2.65-11.25	141.67	1.86 (1.77-1.95)	1.16 (1.09-1.24)	
OCS per	≤76.80	53.86	Reference	Reference	<.0001
1000 patients	76.81-110.54	94.02	1.69 (1.62-1.77)	1.52 (1.45-1.59)	
	110.58-139.54	117.53	2.05 (1.97-2.15)	1.73 (1.65-1.82)	
	139.56-173.95	138.07	2.40 (2.30-2.51)	1.91 (1.81-2.01)	
	≥173.96	168.04	2.99 (2.86-3.13)	2.20 (2.07-2.33)	
GP list size	≤4,127	106.78	Reference	Reference	<.0001
	4,128-6,287	113.85	1.03 (0.98-1.09)	0.99 (0.96-1.03)	
	6,290-8,809	118.50	1.04 (0.99-1.10)	0.97 (0.93-1.01)	
	8,810-12,335	119.72	1.05 (1.01-1.11)	0.94 (0.90-0.97)	
	≥12,336	110.68	0.90 (0.85-0.94)	0.87 (0.84-0.91)	
QOF score	≤529.81	97.81	Reference	Reference	.0005
	529.82-545.04	108.15	1.08 (1.03-1.14)	1.07 (1.01-1.10)	
	545.05-552.16	112.34	1.12 (1.07-1.19)	1.06 (1.02-1.10)	
	552.17-557.84	121.22	1.21 (1.15-1.27)	1.06 (1.03-1.11)	
	557.85-559	128.71	1.30 (1.23-1.37)	1.09 (1.04-1.13)	
% over 65	≤11	58.16	Reference	Reference	<.0001
years old	11.01-15.63	99.98	1.59 (1.51-1.66)	1.29 (1.24-1.35)	
	15.64-18.86	120.38	1.91 (1.88-2.00)	1.44 (1.37-1.51)	
	18.87-22.77	135.05	2.13 (2.04-2.24)	1.55 (1.47-1.65)	
	≥22.78	159.22	2.55 (2.43-2.67)	1.77 (1.66-1.89)	
% patients	≤43.95	88.92	Reference	Reference	.0356
with a long-	43.97-49.65	107.05	1.28 (1.22-1.35)	1.02 (0.99-1.06)	
term health	49.66-53.85	122.56	1.45 (1.38-1.52)	1.03 (0.99-1.08)	
disease	53.86-58.44	126.80	1.51 (1.43-1.59)	1.03 (0.98-1.08)	
	≥58.45	137.20	1.63 (1.55-1.72)	1.05 (1.01-1.10)	
IMD score	Least deprived	124.81	Reference	Reference	<.0001
	-	130.09	1.04 (0.99-1.10)	0.96 (0.92-1.01)	
	-	117.35	0.93 (0.88-0.98)	0.87 (0.84-0.91)	
	-	109.58	0.86 (0.81-0.90)	0.82 (0.78-0.87)	
	Most deprived	91.49	0.77 (0.73-0.81)	0.74 (0.70-0.78)	

Abbreviations: *BP, Bisphosphonates; OCS, Oral Corticosteroids; COPD, Chronic Obstructive Pulmonary Disease; GP, General Practice QOF, Quality and Outcomes Framework; IMD, Index of Multiple Deprivation.*

**Negative Binomial model, $Mixed-effects Negative Binomial Model, **From multivariate analysis using the likelihood ratio test*

Table 8-10. Oral corticosteroids prescribing rates in 2016, stratified by seven practice characteristics and two respiratory diseases in a negative binomial model reporting incidence rate ratio.

	Quintile range	Median OCS prescription per 1,000 patients	Univariate model IRR (95%CI)*	Multivariate model IRR (95%CI)$	*p*-value**
Asthma	≤4.83	75.42	Reference	Reference	<.0001
Prevalence	4.84-5.59	114.96	1.42 (1.36-1.48)	1.11 (1.08-1.16)	
(%)	5.60-6.21	132.31	1.61 (1.55-1.68)	1.17 (1.13-1.21)	
	6.22-6.90	151.23	1.81 (1.73-1.89)	1.22 (1.17-1.27)	
	6.91-12.59	163.24	1.97 (1.89-2.06)	1.26 (1.21-1.31)	
COPD	≤1.13	74.20	Reference	Reference	<.0001
Prevalence	1.14- 1.58	113.41	1.44 (1.37-1.50)	1.11 (1.08-1.15)	
(%)	1.58-2.01	137.49	1.72 (1.63-1.79)	1.20 (1.15-1.24)	
	2.02-2.60	148.40	1.88 (1.82-1.97)	1.25 (1.20-1.31)	
	2.60-10.78	162.15	2.02 (1.94-2.11)	1.32 (1.25-1.39)	
GP list size	≤3,747	110.76	Reference	Reference	<.0001
	3,748-5,808	125.04	1.04 (0.99-1.09)	1.02 (0.98-1.05)	
	5,809-8,172	134.21	1.08 (1.03-1.13)	1.02 (0.99-1.06)	
	8,173-11,514	135.97	1.09 (1.04-1.14)	0.99 (0.96-1.02)	
	≥11,518	128.42	0.97 (0.92-1.01)	0.90 (0.87-0.93)	
QOF score	≤522.37	110.48	Reference	Reference	.0140
	522.39-540.63	116.58	1.04 (0.99-1.08)	1.03 (1.01-1.07)	
	540.67-550.00	127.72	1.10 (1.05-1.15)	1.02 (0.99-1.06)	
	550.01-556.39	133.80	1.16 (1.09-1.21)	1.03 (1.01-1.07)	
	556.40-559.00	143.48	1.26 (1.21-1.32)	1.05 (1.01-1.09)	
% over 65	≤11	71.67	Reference	Reference	<.0001
years old	11.01-15.50	111.07	1.45 (1.39-1.52)	1.19 (1.15-1.24)	
	15.51-18.89	134.21	1.70 (1.63-1.77)	1.33 (1.27-1.38)	
	18.90-22.47	144.76	1.84 (1.77-1.92)	1.39 (1.32-1.47)	
	≥22.48	177.19	2.25 (2.16-2.35)	1.62 (1.54-1.71)	
% patients	≤47.00	85.27	Reference	Reference	.0015
with a long-	47.01-51.42	114.96	1.28 (1.23-1.34)	1.05 (1.02-1.09)	
term health	51.43-55.28	134.93	1.46 (1.40-1.53)	1.06 (1.02-1.10)	
disease	55.28-59.61	143.71	1.59 (1.53-1.66)	1.07 (1.03-1.11)	
	≥59.62	158.45	1.73 (1.65-1.80)	1.07 (1.03-1.11)	
IMD score	Least deprived	131.08	Reference	Reference	.0001
	-	140.25	1.06 (0.99-1.08)	0.93 (0.89-0.96)	
	-	128.13	0.96 (0.92-1.01)	0.87 (0.84-0.91)	
	-	120.57	0.90 (0.86-0.95)	0.85 (0.81-0.89)	
	Most deprived	120.61	0.92 (0.88-0.97)	0.86 (0.82-0.90)	

Abbreviations: *OCS, Oral Corticosteroids; COPD, Chronic Obstructive Pulmonary Disease; GP, General Practice QOF, Quality and Outcomes Framework; IMD, Index of Multiple Deprivation.*

**Negative Binomial model, $Mixed-effects Negative Binomial Model, **From multivariate analysis using the likelihood ratio test*

Table 8-11. Bisphosphonates prescribing rates in 2016, stratified by seven practice characteristics and two respiratory diseases in a negative binomial model reporting incidence rate ratio.

	Quintile range	Median BP prescription per 1,000 patients	Univariate model IRR (95%CI)*	Multivariate model IRR (95%CI)$	*p*-value**
Asthma	≤4.83	84.23	Reference	Reference	.5919
Prevalence	4.84-5.59	114.71	1.28 (1.22-1.35)	1.02 (0.98-1.06)	
(%)	5.60-6.21	129.58	1.42 (1.35-1.50)	1.03 (0.98-1.08)	
	6.22-6.90	138.70	1.54 (1.47-1.62)	0.99 (0.94-1.04)	
	6.91-12.59	145.62	1.61 (1.54-1.70)	1.01 (0.96-1.06)	
COPD	≤1.13	76.45	Reference	Reference	<.0001
Prevalence	1.14- 1.58	111.89	1.39 (1.33-1.47)	1.05 (1.01-1.10)	
(%)	1.58-2.01	132.02	1.60 (1.52-1.68)	1.08 (1.04-1.14)	
	2.02-2.60	138.61	1.72 (1.63-1.80)	1.10 (1.05-1.16)	
	2.60-10.78	151.72	1.84 (1.75-1.93)	1.13 (1.06-1.20)	
OCS per	≤78.23	59.84	Reference	Reference	<.0001
1000 patients	78.26-112.50	99.81	1.62 (1.55-1.69)	1.46 (1.40-1.52)	
	112.51-141.98	124.55	1.99 (1.91-2.08)	1.65 (1.57-1.74)	
	141.98-176.62	147.60	2.31 (2.21-2.42)	1.81 (1.72-1.90)	
	≥176.63	182.25	2.90 (2.77-3.03)	2.10 (1.98-2.23)	
GP list size	≤3,747	113.97	Reference	Reference	<.0001
	3,748-5,808	119.23	1.01 (0.96-1.07)	0.97 (0.93-1.01)	
	5,809-8,172	126.60	1.06 (1.01-1.11)	0.97 (0.93-1.01)	
	8,173-11,514	129.41	1.07 (1.02-1.13)	0.94 (0.90-0.98)	
	≥11,518	120.37	0.94 (0.89-0.99)	0.88 (0.84-0.92)	
QOF score	≤522.37	107.32	Reference	Reference	.0011
	522.39-540.63	110.28	1.02 (0.96-1.07)	1.01 (0.96-1.04)	
	540.67-550.00	124.38	1.13 (1.07-1.19)	1.04 (1.01-1.08)	
	550.01-556.39	128.91	1.17 (1.11-1.22)	1.04 (1.01-1.08)	
	556.40-559.00	137.60	1.26 (1.20-1.32)	1.07 (1.02-1.11)	
% over 65	≤11	62.86	Reference	Reference	<.0001
years old	11.01-15.50	107.04	1.61 (1.54-1.69)	1.32 (1.26-1.38)	
	15.51-18.89	126.89	1.92 (1.83-2.01)	1.46 (1.38-1.53)	
	18.90-22.47	143.74	2.14 (2.04-2.24)	1.56 (1.48-1.65	
	≥22.48	170.81	2.54 (2.43-2.67)	1.75 (1.64-1.87)	
% patients	≤47.00	84.69	Reference	Reference	.008
with a long-	47.01-51.42	115.65	1.29 (1.22-1.35)	1.05 (1.02-1.09)	
term health	51.43-55.28	126.42	1.40 (1.33-1.47)	1.04 (0.99-1.08)	
disease	55.28-59.61	136.97	1.54 (1.46-1.62)	1.05 (1.02-1.09)	
	≥59.62	152.16	1.69 (1.60-1.77)	1.07 (1.02-1.12)	
IMD score	Least deprived	132.87	Reference	Reference	<.0001
	-	138.44	1.03 (0.98-1.07)	0.95 (0.92-0.99)	
	-	125.58	0.93 (0.88-0.98)	0.87 (0.84-0.92)	
	-	117.26	0.86 (0.82-0.91)	0.82 (0.78-0.86)	
	Most deprived	100.18	0.77 (0.74-0.81)	0.73 (0.69-0.77)	

Abbreviations: *BP, Bisphosphonates; OCS, Oral Corticosteroids; COPD, Chronic Obstructive Pulmonary Disease; GP, General Practice QOF, Quality and Outcomes Framework; IMD, Index of Multiple Deprivation.*
**Negative Binomial model, $Mixed-effects Negative Binomial Model, **From multivariate analysis using the likelihood ratio test*

Table 8-12. Oral corticosteroids prescribing rates in 2015, stratified by seven practice characteristics and two respiratory diseases in a negative binomial model reporting incidence rate ratio.

	Quintile range	Median OCS prescription per 1,000 patients	Univariate model IRR (95%CI)*	Multivariate model IRR (95%CI)$	*p*-value**
Asthma	≤4.90	75.58	Reference	Reference	<.0001
Prevalence	4.91-5.66	113.06	1.39 (1.33-1.46)	1.12 (1.08-1.16)	
(%)	5.67-6.29	129.62	1.59 (1.52-1.66)	1.20 (1.12-1.21)	
	6.30-7.00	145.39	1.74 (1.67-1.83)	1.24 (1.15-1.25)	
	7.01-12.45	158.53	1.92 (1.83-2.00)	1.33 (1.21-1.32)	
COPD	≤1.10	73.57	Reference	Reference	<.0001
Prevalence	1.11-1.55	111.50	1.44 (1.37-1.50)	1.13 (1.09-1.17)	
(%)	1.56-1.97	135.04	1.72 (1.64-1.80)	1.20 (1.14-1.25)	
	1.98-2.55	145.39	1.85 (1.77-1.93)	1.24 (1.19-1.30)	
	2.56-9.01	158.80	2.01 (1.92-2.10)	1.33 (1.26-1.40)	
GP list size	≤3,540	109.05	Reference	Reference	<.0001
	3,543-5,587	121.06	1.04 (0.99-1.09)	1.01 (0.97-1.05)	
	5,589-7,942	131.96	1.10 (1.05-1.15)	1.02 (0.98-1.06)	
	7,943-11,221	131.74	1.09 (1.04-1.15)	0.99 (0.95-1.02)	
	≥11,230	126.17	0.98 (0.93-1.03)	0.90 (0.86-0.93)	
QOF score	≤516.27	107.36	Reference	Reference	.0061
	516.28-536.62	119.87	1.08 (1.03-1.13)	1.02 (0.98-1.06)	
	536.63-547.52	125.68	1.13 (1.07-1.18)	1.04 (1.01-1.08)	
	547.53-555.09	128.82	1.16 (1.10-1.21)	1.03 (0.99-1.07)	
	555.10-559.00	142.72	1.27 (1.21-1.33)	1.06 (1.02-1.10)	
% over 65	≤10.93	70.62	Reference	Reference	<.0001
years old	10.93-15.43	108.05	1.47 (1.41-1.54)	1.20 (1.15-1.25)	
	15.44-18.76	131.07	1.71 (1.63-1.78)	1.32 (1.25-1.38)	
	18.77-22.28	142.67	1.87 (1.79-1.95)	1.42 (1.35-1.49)	
	≥22.29	172.66	2.27 (2.18-2.37)	1.62 (1.53-1.71)	
% patients	≤47.40	83.42	Reference	Reference	.0003
with a long-	47.42-52.21	118.13	1.33 (1.27-1.39)	1.07 (1.03-1.11)	
term health	52.22-56.18	129.89	1.45 (1.39-1.52)	1.07 (1.03-1.11)	
disease	56.19-60.65	140.17	1.58 (1.51-1.65)	1.07 (1.03-1.12)	
	≥60.66	155.16	1.73 (1.65-1.81)	1.09 (1.05-1.13)	
IMD score	Least deprived	129.43	Reference	Reference	<.0001
	-	138.41	1.04 (0.99-1.10)	0.93 (0.90-0.97)	
	-	125.87	0.97 (0.93-1.02)	0.87 (0.84-0.91)	
	-	115.76	0.89 (0.85-0.94)	0.84 (0.80-0.88)	
	Most deprived	114.37	0.90 (0.86-0.95)	0.84 (0.80-0.88)	

Abbreviations: *OCS, Oral Corticosteroids; COPD, Chronic Obstructive Pulmonary Disease; GP, General Practice QOF, Quality and Outcomes Framework; IMD, Index of Multiple Deprivation.*

**Negative Binomial model, $Mixed-effects Negative Binomial Model, **From multivariate analysis using the likelihood ratio test*

Table 8-13. Bisphosphonates prescribing rates in 2015, stratified by seven practice characteristics and two respiratory diseases in a negative binomial model reporting incidence rate ratio.

	Quintile range	Median BP prescription per 1,000 patients	Univariate model IRR (95%CI)*	Multivariate model IRR (95%CI)$	*p*-value**
Asthma	≤4.90	88.65	Reference	Reference	.2614
Prevalence	4.91-5.66	124.46	1.30 (1.24-1.37)	1.03 (0.98-1.07)	
(%)	5.67-6.29	137.73	1.44 (1.37-1.52)	1.01 (0.96-1.05)	
	6.30-7.00	146.46	1.55 (1.47-1.63)	1.01 (0.95-1.05)	
	7.01-12.45	152.55	1.60 (1.52-1.68)	0.99 (0.94-1.04)	
COPD	≤1.10	81.56	Reference	Reference	<.0001
Prevalence	1.11-1.55	118.06	1.40 (1.33-1.47)	1.06 (1.02-1.12)	
(%)	1.56-1.97	141.46	1.63 (1.55-1.71)	1.10 (1.05-1.15)	
	1.98-2.55	148.03	1.72 (1.64-1.81)	1.12 (1.07-1.18)	
	2.56-9.01	158.55	1.84 (1.75-1.94)	1.15 (1.08-1.22)	
OCS per	≤77.31	61.16	Reference	Reference	<.0001
1000 patients	77.33-110.27	106.01	1.68 (1.61-1.76)	1.46 (1.40-1.53)	
	110.28-139.07	130.31	2.04 (1.95-2.14)	1.63 (1.55-1.71)	
	139.11-174.28	154.11	2.35 (2.25-2.46)	1.76 (1.66-1.85)	
	≥174.36	191.96	2.98 (2.85-3.11)	2.06 (1.94-2.18)	
GP list size	≤3,540	121.02	Reference	Reference	<.0001
	3,543-5,587	124.93	1.02 (0.97-1.07)	0.97 (0.93-1.01)	
	5,589-7,942	133.67	1.08 (1.02-1.13)	0.96 (0.92-0.99)	
	7,943-11,221	136.78	1.08 (1.03-1.14)	0.95 (0.91-0.99)	
	≥11,230	127.49	0.96 (0.91-1.01)	0.86 (0.82-0.90)	
QOF score	≤516.27	113.37	Reference	Reference	<.0001
	516.28-536.62	121.52	1.07 (1.02-1.12)	1.05 (1.01-1.08)	
	536.63-547.52	128.38	1.14 (1.08-1.20)	1.06 (1.02-1.11)	
	547.53-555.09	133.59	1.18 (1.12-1.24)	1.07 (1.03-1.11)	
	555.10-559.00	146.91	1.29 (1.23-1.36)	1.09 (1.05-1.14)	
% over 65	≤10.93	65.39	Reference	Reference	<.0001
years old	10.93-15.43	113.04	1.65 (1.57-1.72)	1.32 (1.26-1.38)	
	15.44-18.76	136.50	1.97 (1.88-2.06)	1.46 (1.37-1.54)	
	18.77-22.28	143.74	2.14 (2.04-2.24)	1.56 (1.48-1.65	
	≥22.29	170.81	2.54 (2.43-2.67)	1.75 (1.64-1.87)	
% patients	≤47.40	82.2	Reference	Reference	.001
with a long-	47.42-52.21	122.85	1.32 (1.25-1.39)	1.05 (1.01-1.09)	
term health	52.22-56.18	132.23	1.42 (1.35-1.50)	1.05 (1.01-1.10)	
disease	56.19-60.65	147.75	1.57 (1.49-1.65)	1.08 (1.04-1.13)	
	≥60.66	156.66	1.68 (1.60-1.77)	1.10 (1.05-1.15)	
IMD score	Least deprived	140.46	Reference	Reference	<.0001
	-	149.19	1.03 (0.98-1.08)	0.93 (0.90-0.97)	
	-	131.13	0.92 (0.88-0.97)	0.86 (0.82-0.90)	
	-	121.36	0.85 (0.80-0.89)	0.80 (0.75-0.84)	
	Most deprived	103.66	0.76 (0.72-0.80)	0.71 (0.67-0.75)	

Abbreviations: *BP, Bisphosphonates; OCS, Oral Corticosteroids; COPD, Chronic Obstructive Pulmonary Disease; GP, General Practice QOF, Quality and Outcomes Framework; IMD, Index of Multiple Deprivation.*
**Negative Binomial model, $Mixed-effects Negative Binomial Model, **From multivariate analysis using the likelihood ratio test*

8.4 Discussion

Overall, it was observed an increase in prescribed OCS and bisphosphonate items between 1998 and 2018. A large variation in prescribing rates across practices in England was found. Asthma was significantly related with OCS prescriptions, but not with bisphosphonates. Patient list size, deprivation and advanced age were all associated with variation in both drugs. The CCG to which each practice belongs also contributed to some extent to the prescribing variation. Finally, OCS was positively associated with bisphosphonate prescriptions.

The increase in bisphosphonates (2000-2010) could be explained by the uptake of clinical guidance. The FDA approved the alendronate use in June 1999 (244), the first guidance for the glucocorticoid-induced osteoporosis prevention from the American College of Rheumatology was published in 2001 (245) and NICE recommended bisphosphonates as first line glucocorticoid-induced osteoporosis prophylaxis in 2005 (246). The plateauing of bisphosphonate prescriptions from 2010 with a downward trend from 2015, in contrast with the steady OCS prescriptions, may reflect the FDA concerns (247,248) about side effects of bisphosphonates such as osteonecrosis of the jaw and atypical femoral fractures. In 2014, the release of the 2nd report of American Society of Bone and Mineral Research provided more robust evidence about the atypical fractures as side effects of bisphosphonates probably was the reason for a further decrease (132). An investigation in the USA found a similar 50% reduction in bisphosphonate use between 2008 and 2012 following concers about their safety (249). However, these side effects might be greater concern in younger age groups, as they will may benefit less using bisphosphonates. The findings are also consistent with two other studies which found a steady increase in bisphosphonate use from 2000 onwards (250,251).

Establishing an optimal ratio of bisphosphonates to OCS prescriptions is challenging. The management of multi-morbidities makes prescribing decisions complex and although prescriptions should be guideline informed, they should not be guideline directed (252,253). Initiation of bisphosphonate medication may also depend on how long past three months OCS exposure is expected. There is good evidence the benefits of bisphosphonates in preventing glucocorticoid-induced osteoporosis outweigh the risks (132,254) and bone mineral density testing is recommended within 6 months after OCS initiation, repeating it every 1-3 years (255). Other potential options for glucocorticoid-induced osteoporosis may be recommended (Vitamin D, HRT), but have less data.

This analysis demonstrates geographical variation across practices and CCG in prescribing rates of both classes of drugs and in between the drugs. Apart from variation associated with practice factors, the results revealed that CCG accounted for variation in each medication which may indicate differences in prescribing policy. Interestingly, prescribing differences related to deprivation, in terms of OCS, may reflect inequity of access to treatment difference, whereas in bisphosphonate rates, may reflect access to DEXA scanning. These findings are consistent with another UK study which found marked regional differences in the anti-osteoporosis prescribing rates (26). Other studies have also confirmed the impact of deprivation and the other examined factors on variation in drug prescribing (120,256)

Despite the proven benefits of bisphosphonates as an osteoporosis therapy, there is evidence that they are underutilised both in the UK and USA (240,251). Addressing this issue will hinge on education in both primary and secondary care, and provision of suitable guidelines. One practical solution in healthcare systems that use electronic records/prescribing would be to flag patients who meet bisphosphonate criteria based on age, gender, and OCS use. Alerts already occur for several conditions (including

excess salbutamol use) and this flag could be incorporated into and chronic disease review.

To my knowledge, this is the first study to examine the OCS and bisphosphonate prescribing patterns and their association with practice-level factors. This analysis uses real prospectively collected prescribing data based on NHS Digital files and included practices and CCG covering the entire country. There are some limitations; it was not possible to evaluate prescriptions in secondary care. Secondly, it was not possible to know the indication for each prescription. Thirdly, it was not possible to perform individual level analysis to identify the OCS prescriptions which need bisphosphonate therapy according to guidelines' recommendations.

8.5 Conclusion

The overall levels of OCS and bisphosphonate prescription have increased since 1998. Concerns about adverse effects of bisphosphonates may account for a latter reduction in bisphosphonate prescriptions in contrast to steady or increased OCS prescriptions. Clear variation in OCS and bisphosphonates was shown, and this unwarranted variation appears to be driven to a large extent by factors including deprivation, patient list size and CCG. The variation in prescribing suggests there is still a need to improve glucocorticoid-induced osteoporosis prevention.

9 RISK OF SUBTROCHANTERIC AND FEMORAL SHAFT FRACTURES IN ASTHMA: A POPULATION BASED NESTED CASE-CONTROL STUDY

9.1 Introduction

Studies have reported people with asthma are at greater risk of osteoporosis and fragility fractures (257) as well as deleterious effects on bone health associated with ICS and OCS (111,228). These bone conditions can affect patients' daily life (89,176), so the identification and treatment of the people being at greater risk are important to avoid their consequences.

Bisphosphonates are recommended as the first-line bone protection medication. They inhibit bone resorption by osteoclasts and indirectly reduce bone formation coupled to resorption without direct effects on bone formation by osteoblasts. They increase bone mineral density and decrease osteoporotic fracture risk between 40 and 70% (258). However, in 2006 concerns were raised when bisphosphonate use was associated with unusual fractures in the subtrochanteric and femoral shaft regions (259), now called atypical femoral fractures because of their unusual morphology. Atypical fractures have distinctive characteristics including a transverse morphology, a thickened cortex, and occurred either spontaneously or with low trauma. In order to distinguish from common osteoporotic fractures the American Society of Bone and Mineral Research (ASBMR) published a definition based on specific radiographic criteria (132). Nevertheless, significant uncertainty and controversy remain with respect to the magnitude of the association between bisphosphonates and atypical fractures (260,261). Some studies have shown minimal risk,(134) whereas others have reported a clear association, especially with prolonged use (262,263).

As osteoporosis is a common side effect of corticosteroid use, and as steroids are frequently prescribed in asthma, one of the most prevalent chronic health conditions, this study examined the risk of ST/FS fractures in asthma in order to guide the clinical

use of bisphosphonates. The aim was to improve knowledge of ST/FS risk and to inform future updates on asthma guidelines.

9.2 Methods

9.2.1 Study population

A population-based nested case-control study was conducted utilising the Clinical Practice Research Datalink GOLD, a large longitudinal primary care database (158), linked to the Hospital Episode Statistics database (196). All adult patients (≥18 years old) with a Read code for asthma between 1st April 2004 (activation of Quality and Outcomes Framework score) to 31th December 2017, with at least 1 year of data collection prior to the diagnosis of asthma date ensuring that only 'incident' cases were picked (180). Only patients classed as "acceptable" research quality data and registered to an up-to standard practice were included according to CPRD's recommendations.

9.2.2 Cases, controls, and outcomes definition

In this nested case-control study cases were defined by the first-recorded Read or ICD-10 coded subtrochanteric or femoral shaft fracture (Appendix 2). The date of the first Read or ICD-10 coded subtrochanteric or femoral shaft fracture served as the index date for the cases. Each case was matched with up to four randomly selected patients from the remaining patients with asthma by age (±1 year), gender and practice. The same index date was assigned to controls and cases.

9.2.3 Potential confounders

For each participant in this study, information on the following variables was obtained which are well-established risk for fracture or thought to have an impact on fracture risk and are also likely to be recorded within the databases: age at the index date; sex, including only those clearly classified as male or female; BMI using the nearest

measurement prior the index date and categorised according to the World Health Organization; smoking and alcohol status using the nearest measurement ever prior to the index date; socioeconomic status measured by using the patient-level IMD 2015 in quintiles, with quintile 1 being the least and quintile 5 the most deprived. Patients with at least one prescription of oral corticosteroids, vitamin D and calcium the year prior the index date were also identified. Cumulative dose of OCS and ICS was also considered. Finally, all patients with a previous diagnosis of osteoporosis or fragility fracture were extracted. The comorbidities were also summarised using the Charlson comorbidity index score (169). If there was no record for a medication or diagnosis, patients were assumed to have not had the exposure.

9.2.4 Exposure assessment

Bisphosphonate exposure was identified via the prescription records. Bisphosphonates to be included were identified in the British National Formulary section 6.6.2 as treatment for osteoporosis: alendronate, etidronate, ibandronate, and risedronate. Bisphosphonate use was categorised in several ways. All prescriptions prior to the index date were identified. Initially, all patients with at least one prescription were extracted. Bisphosphonate use was also examined as the number of prescriptions filled. Bisphosphonates were grouped according to type as listed above. Where the type of bisphosphonate was changed during the year, we considered the most frequently prescribed. The bisphosphonates cumulative duration and dose in milligrams (mg) over the previous years was additionally assessed. To calculate the cumulative bisphosphonate dose, information from tablet strength (e.g. 70mg) and prescribed quantity was used, multiplying the quantity by strength for each prescription, and then all doses per patient were summed. The time since last use of bisphosphonate prior to the fracture was calculated. There were not missing or implausible values in the specific patients records of bisphosphonate use. The reference category for all analyses was no bisphosphonate exposure.

9.2.5 Statistical analysis

Descriptive statistics were used to summarise the characteristics of the cases and controls. To account for the matched design, conditional logistic regression was used deriving unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) assessing the effect of bisphosphonate exposure on the first subtrochanteric and femoral shaft fractures after the Read coded asthma date. Firstly, a univariate analysis was performed between the exposure and outcome of interest to establish the unadjusted OR. The *a priori* confounders were BMI and smoking status. The next step was to fit the conditional logistic regression model including the exposure of interest and the *a priori* confounders. Each of the other potential confounding variables was added in the model one at a time, removing this potential confounder before adding the next. If the inclusion of the confounder changed the effect of the exposure of interest by more than 5% then it was an important confounder and was placed in the fully adjusted model. Missing data for BMI and smoking status were assumed as missing at random and imputed using chained equations. Ten imputations were generated, and the imputed model consisted of all listed confounders, bisphosphonate exposure, and the case-control indicator. Missing data for IMD were assigned a new category. All analyses were undertaken in R v4.0.3 and $P < 0.05$ was considered statistically significant.

9.3 Results

9.3.1 Characteristics of the study population

From a cohort of 69,074 people with asthma we identified 67 patients with asthma and subtrochanteric of femoral shaft fractures and 260 matched control subjects (Table 9-1). The vast majority were women (70.9 vs 29.1%), and the median age of the study population was 79.3 years (range, 68.4-86.7 years). Ex-smokers with asthma were 4.53 times more likely to sustain a ST/FS fracture than never smokers with asthma (aOR = 4.53; 95%CI 2.04 to 10.05). Similarly, underweight patients with asthma were more

susceptible to ST/FS fractures than those with a normal BMI (aOR = 7.05; 95%CI 1.42 to 34.9). Finally, both a previous diagnosis of osteoporosis (aOR = 3.31; 95%CI 1.21 to 9.05) or fragility fracture (aOR = 4.17; 95%CI 2.46 to 9.00) were linked with an event of ST/FS fracture.

Table 9-1. Characteristics of patients with subtrochanteric or femoral shaft fractures and control subjects.

Characteristic	Cases (N=67) n (%)	Controls (N=260) n (%)	Adjusted[b] OR (95%CI)
Age[a], yrs.			-
Mean ± SD	75.7 ± 14.2	75.7 ± 14.1	
Median (IQR)	79.3 (68.4-86.7)	79.3 (68.4-86.7)	
Sex			
Male	19 (28.4)	76 (29.2)	-
Female	48 (71.6)	184 (70.8)	-
Smoking status			
Never	19 (28.4)	126 (48.5)	1.00
Ex	39 (58.2)	94 (36.2)	4.53 (2.04 - 10.05)
Current	8 (11.9)	35 (13.5)	1.59 (0.53 - 4.77)
Missing status	1 (01.5)	5 (1.9)	2.58 (0.24 - 28.01)
BMI status			
Underweight (<18.5)	3 (4.5)	7 (2.7)	7.05 (1.42 - 34.9)
Normal (18.5 – 24.9)	12 (17.9)	64 (24.6)	1.00
Overweight (25 – 29.9)	13 (19.4)	70 (26.9)	1.16 (0.44 - 3.11)
Obese (≥30)	23 (34.3)	70 (26.9)	1.79 (0.66 - 4.80)
Missing status	16 (23.9)	49 (18.9)	
Alcohol status			
Non-drinker	5 (7.5)	23 (8.9)	1.00
Ex-drinker	8 (11.9)	39 (15.0)	1.06 (0.26 - 4.39)
Current drinker	46 (68.7)	170 (65.4)	1.53 (0.50 - 4.70)
Missing status	8 (11.9)	28 (10.8)	1.47 (0.33 - 6.54)
IMD (Social Class)			
1 (least deprived)	12 (17.9)	47 (18.1)	1.00
2	16 (23.9)	72 (27.7)	0.52 (0.19 - 1.41)
3	13 (19.4)	41 (15.8)	1.50 (0.56 - 4.04)
4	12 (17.9)	48 (18.5)	0.91 (0.33 - 2.56)
5 (most deprived)	14 (20.9)	52 (20.0)	0.66 (0.24 - 1.84)
Charlson comorbidity index			.
1	27 (40.3)	123 (47.3)	1.00
2	10 (14.9)	38 (14.6)	1.16 (0.45 - 2.99)
3	10 (14.9)	36 (13.8)	1.32 (0.65 - 5.07)
4	8 (11.9)	28 (10.8)	1.81 (0.46 - 3.86)
≥5	12 (17.9)	35 (13.5)	2.18 (0.77 - 6.17)
Drug use in the year prior to the index date			
Oral corticosteroids	37 (55.2)	132 (50.8)	1.17 (0.61 - 2.26)
Vitamin D and/or calcium	29 (43.3)	66 (25.4)	1.06 (0.47 - 2.40)
Previous diagnoses			
Osteoporosis	16 (23.9)	17 (6.5)	3.31 (1.21 - 9.05)

Fragility fracture	31 (46.3)	36 (13.9)	4.17 (2.46 - 9.00)

Abbreviations: BMI, body mass index; IMD, Index of Multiple Deprivation.

[a] *Age at the index date.*

[b] *Adjusted for smoking, body mass index, index of multiple deprivation, Charlson Comorbidity Index score, previous diagnosis of osteoporosis and fragility fracture, when not stratified by those.*

Percentages have been rounded and might not total 100.

9.3.2 Bisphosphonates and risk of ST/FS fractures

40.3% of the case patients had received bisphosphonates as compared with 14.2% of the controls (Table 9-2). This finding corresponds to an adjusted odds ratio of 4.42 (95%CI, 2.98 to 8.53), with a similar estimate for patients with asthma who had been exposed to alendronate and risedronate. A dose-response relationship was observed between the number of prescriptions and cumulative dose. The risk of ST/FS fractures was higher with increasing number of bisphosphonate prescriptions, with an odds ratio of 10.01 (95% CI, 2.90 to 34.8) between 61 and 130 prescriptions. Similarly, the higher the dose the greater the risk (16000mg vs no use: aOR=7.32; 95% CI, 1.73 to 30.83). Most ST/FS fractures associated with bisphosphonate use occurred within 2 years after the last prescription. For duration of bisphosphonate use, the adjusted odds ratio as compared with no use ranged from 3.85 (95% CI, 1.47 to 9.99) for 1 year or less to 7.67 (95% CI, 1.75 to 33.91) for 5 years or more. In the subgroup analyses, it was found that both males and females had around the same odds of ST/FS fractures, however people aged less than 80 yrs. had increased odds than those aged 80 or more years (Table 9-3).

Table 9-2. Association between bisphosphonate exposure ever prior the index date and risk of subtrochanteric and femoral shaft fractures.

	Cases		Controls		Age sex-adjusted	Adjusted[a]	
Type of exposure	**n**	**%**	**n**	**%**	**OR (95%CI)**	**OR (95%CI)**	**p-value**
Bisphosphonate use							
Never	40	59.7	223	85.8	1.00	1.00	
Ever	27	40.3	37	14.2	4.35 (2.23 – 8.26)	4.42 (2.98 - 8.53)	<.0001
Total prescriptions							.0015[b]
≤ 20	14	20.9	20	7.7	3.90 (1.80 - 8.45)	3.98 (1.80 - 8.77)	
21- 60	4	6.0	10	3.9	2.56 (0.74 - 8.84)	2.65 (0.73 - 9.59)	
61-130	9	13.4	7	2.7	10.13 (3.01 - 34.5)	10.01 (2.90 - 34.8)	
Cumulative alendronate dose, mg							.0244[b]
≤ 2200	6	9.8	7	2.8	4.14 (0.95 - 12.75)	4.63 (0.98 - 14.46)	
2201 – 8000	5	8.2	6	2.0	5.49 (1.41 - 21.33)	5.46 (1.36 - 21.86)	
8001 – 16000	5	6.6	9	3.2	2.55 (0.68 - 9.54)	3.48 (0.95 - 12.62)	
>16000	6	9.8	5	2.0	7.90 (1.90 - 33.13)	7.32 (1.73 - 30.83)	
Time since last use, yrs.							.001
≤ 0.5	20	29.8	21	8.1	5.80 (2.72 - 12.30)	5.76 (2.67 - 12.40)	
0.51 – 2	4	6.0	6	2.3	4.04 (1.08 - 15.10)	4.67 (1.19 - 18.40)	
>2	3	4.5	10	3.8	1.80 (0.45 - 7.06)	1.76 (0.44 - 7.00)	
Duration of use[c], yrs.							.0403[b]
≤1	9	13.8	13	5.1	3.81 (1.50 - 9.61)	2.85 (0.97 - 9.99)	
1.1-3	8	12.3	8	3.1	5.13 (1.77 - 14.83)	4.17 (1.78 - 15.24)	
3.1-5	3	4.6	7	2.8	2.08 (0.43 - 9.97)	2.28 (0.43 - 11.57)	
>5	5	7.7	4	1.6	8.03 (1.88 - 35.21)	7.67 (1.75 - 33.91)	
Type of bisphosphonate							
Alendronate	22	32.9	27	7.5	4.64(2.31- 9.31)	4.74 (2.31 - 9.72)	<.0001
Risedronate	5	7.5	1	0.4	4.08 (1.13 - 14.7)	3.98 (1.09 - 14.8)	.0370
Etidronate	0	0	2	0.8	NA	NA	
Ibandronate	0	0	7	2.6	NA	NA	

[a] *Adjusted for smoking, body mass index, index of multiple deprivation, Charlson Comorbidity Index score, previous diagnosis of osteoporosis - fragility fractures, and cumulative dose of OCS/ICS.*

[b] *P-value for trend.*

[c] *Was not able to determine duration for 7 individuals.*

Percentages have been rounded and might not total 100.

Table 9-3. Subgroup analysis by sex and age for association between bisphosphonate exposure ever prior the index date and risk of subtrochanteric and femoral shaft fractures.

Type of exposure by subgroup	Cases n	Cases %	Controls n	Controls %	Age sex-adjusted OR (95%CI)	Adjusted[a] OR (95%CI)	p-value
Men							
Bisphosphonate use							
Never	15	78.9	72	94.7	1.00	1.00	
Ever	4	21.1	4	5.3	4.00 (1.00 – 15.90)	4.85 (1.11 – 21.13)	.035
Women							
Bisphosphonate use							
Never	25	52.1	151	82.1	1.00	1.00	
Ever	23	47.9	33	17.9	4.45 (2.16 – 9.20)	4.66 (2.19 – 9.93)	<.0001
<80 yrs.							
Bisphosphonate use							
Never	22	62.9	125	91.9	1.00	1.00	
Ever	13	37.1	11	8.1	7.51 (2.62 – 21.53)	11.12 (3.35 – 36.91)	<.0001
≥80 yrs.							
Bisphosphonate use							
Never	18	56.3	98	79.1	1.00	1.00	
Ever	14	43.7	26	20.9	2.98 (1.30 – 6.82)	2.78 (1.16 – 6.67)	.021

[a] *Adjusted for smoking, body mass index, index of multiple deprivation, Charlson Comorbidity Index score, previous diagnosis of osteoporosis - fragility fractures, and cumulative dose of OCS/ICS.*
Percentages have been rounded and might not total 100.

9.4 Discussion

This nested case-control study shown that bisphosphonate exposure was associated with ST/FS fractures. A dose-response relationship was reported, with higher cumulative dose and long-term duration being associated with increased odds of ST/FS fractures.

Patients with asthma are at increased risk of osteoporosis compared to the general population (257), a common side effect of corticosteroid use in asthma (228) with 54.5% of patients with asthma and osteoporosis to have used bisphosphonates at least once (228). Although the BTS/SIGN and the GINA guidelines on asthma management cover specific comorbidities, no specific bone protection guidance is given. BTS/SIGN mentions "*Bone mineral density should be monitored in adults. When a significant reduction*

occurs, treatment with a long-acting bisphosphonate should be offered"(16) and GINA states "*They should be assessed and monitored for risk of corticosteroid-induced osteoporosis, and those expected to be treated for ≥3 months should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate)*" (19). This is not clear and pragmatic guidance; they do not also mention atypical fractures as a potential side effect of bisphosphonates as well as that in some patients a drug holiday can be more beneficial for bone health. All the above probably reflects the lack of asthma specific studies related to the bisphosphonates and atypical fractures.

The increased odds found are consistent with a meta-analysis in which the overall odds for any bisphosphonate exposure from the case-control studies was 11.12 (95%CI, 2.7 to 46.2) (260). Five case-control studies included in the above meta-analysis with the OR to range from 2.11 to 69.74. The difference in estimates is hard to be explained, but AFF assessment and study populations can have affected them. Despite the differences, the main message was that the use of bisphosphonate was associated with larger atypical ST/FS risk. The findings also revealed an increased risk with longer bisphosphonate exposure similar to other studies reporting identical trend (135,142,155,262,264). This can be a useful information to maximise the benefits of the drug since bisphosphonate discontinuation can drastically diminish the occurrence of a ST/FS fracture.

Osteoporosis is a chronic condition that is typically not cured or sufficiently improved after just 3 years of bisphosphonate medication (the usual duration of the majority of phase 3 trials) to allow for cessation of therapy. Consequently, patients may receive bisphosphonates for longer (max = 9.27 yrs. in the study). In this study bisphosphonate holiday was associated with a decrease in the risk of ST/FS fractures, a finding consistent with other reports (142,263). Two recent studies showed no or a minimal increase in the risk of hip or other fractures after bisphosphonate withdraw (265,266), suggesting that risk of atypical fracture considered together with risk of hip

and other fractures could inform more effective therapy. Thus, it is recommended that patients using bisphosphonates between 3 and 5 years and are at low risk of common fracture can safely discontinue the treatment from 2 to 3 years but not for more than 5 years (261,267). Drug holiday is based on data showing inhibition of bone resorption and residual effects after discontinuation (268).

Even though the odds of ST/FS fractures appeared increased in bisphosphonate users with asthma, the public health consequences are probably minor considering the rarity of these fractures compared to the usual fragility fractures, let alone in the first years of medication. In the examined cohort 2,131 fragility fractures were observed whereas just 67 ST/FS fractures. Consequently, our findings should not scare and discourage physicians and patients from using bisphosphonates when needed, as the risk of an osteoporotic fracture is much higher and immediate, as the risk of an osteoporotic fracture is much higher and immediate, especially in patients prescribed steroids. A recent study found that the absolute risk of fragility fractures in patients with asthma is 3.1% (257), whereas this of ST/FS fractures in asthma is just 0.1% according to our study. Studies have proven the benefits of bisphosphonate therapy for typical fragility fractures (155,258) and evidence suggests that this therapy is underutilised (269). A recent study including white women aged 65 yrs. or older shown that the number of fractures prevented for each fracture type far outweighed bisphosphonate-associated atypical fractures at all time points. For example, after 3 years, there were 2 bisphosphonate associated atypical fractures as compared with 149 hip fractures prevented and 541 clinical fractures prevented. After 5 years, the respective numbers were 8, 286, and 859. The benefits remained in Asian and Hispanic women, but to a lesser extent than the Whites (155).

This is the first study examining the association between bisphosphonates and ST/FS fractures in asthma. Another strength of the study is the use of linked data capturing those events recorded in both primary and secondary care providing more complete

estimates of ST/FS fractures. The population-based setting means the findings are generalizable to the wider population. This study has also some limitations that deserve mention. Diagnostic misclassification may occur, as data were reliant on general practitioners recording these conditions. It was not possible to ascertain the specific radiological features listed in the recent ASBMR Task Force Report on atypical femoral fractures (132). However, the ICD-10 codes for ST/FS fractures have been validated showing a positive predictive value of 90% (95% CI, 88%-92%) and a sensitivity of 81% (95% CI, 78%-84%) (133). Similarly, Van Staa et al. carried out external validation of fracture diagnosis in CPRD and found that 91% of hip fracture (where ST/FS fractures are located) diagnoses were verified by physicians (180). Read coded fractures that probably is the result of a high-energy trauma such as open fractures have been excluded. Nonetheless, the fact that these fractures were observed to occur more often among bisphosphonate users is clinically important, independent of radiographic appearance. The exposure was defined based on bisphosphonate prescriptions and not on actual compliance. As with all epidemiological studies, residual confounding is a potential limitation however, several steps were taken to minimize the potential for residual confounding including matching and adjustment.

9.5 Conclusion

The findings report that bisphosphonate exposure, especially the prolonged, is associated with an increased risk of ST/FS fracture in asthma. It is important to conduct a thoughtful evaluation of patients' risk of osteoporosis and fragility fracture and reconsider long-term exposure to bisphosphonates in patients with low risk. Considering the reduction in risk of ST/FS fractures after discontinuation of bisphosphonates it might be reasonable a drug holiday for patients at low risk of osteoporotic fractures.

10 DISCUSSION

This chapter gives a summary of the key findings, key recommendations for practice, and suggestions for further research. The strengths and limitations of the data, and of each study have been discussed in the corresponding chapters.

10.1 Summary of findings

This section discusses and summarises the findings by each of the original research objectives of this thesis (Table 10-1).

Objective 1: To describe the incidence of osteoporosis and fragility fractures in asthma compared to the general population.

Overall, patients with asthma are 18% (aHR = 1.18, 95% CI 1.13 to 1.23) and 12% (aHR = 1.12, 95% CI 1.07 to 1.16) more likely to develop osteoporosis and sustain fragility fractures than the general population, respectively. Age modified the effect of asthma on osteoporosis and fragility fractures, such that the effect was stronger in younger people, but sex modified only the effect of asthma on osteoporosis such that the effect was stronger in males. The vertebra and forearm/wrist were the sites linked with a larger incidence.

Objective 2: To estimate the risk of osteoporosis and fragility fractures due to OCS and ICS comparing exposed and non-exposed people with asthma.

The findings suggest that exposure to OCS or ICS is an independent risk factor for bone health in patients with asthma. Specifically, there was a dose–response relationship between both cumulative dose and number of OCS/ICS prescriptions, and risk of osteoporosis and fragility fracture. After adjusting for confounders, people receiving more OCS prescriptions (≥9 vs 0) had a 4.50 (95% CI 3.21 to 6.11) and 2.16 (95% CI 1.56 to 3.32) increased odds of osteoporosis and fragility fractures, respectively. For ICS (≥11 vs 0) the OR were 1.60 (95% CI 1.22 to 2.10) and 1.31 (95%

CI 1.02 to 1.68). The cumulative dose had a similar impact, with those receiving more OCS or ICS being at greater risk.

Objective 3: To perform a systematic review and meta-analysis quantifying the impact of OCS and ICS on bone mineral density, and risk of osteoporosis and fractures in asthma.

There was no statistically significant effect of ICS on bone loss at the spine or femoral neck in asthma. However, people with asthma receiving OCS were at greater risk of osteoporosis than nonexposed people with asthma (pooled HR = 1.76; 95%CI: 1.48 to 2.09; $I^2 = 68\%$). Similarly, higher ICS exposure was associated with higher risk of osteoporosis (OR = 1.20; 95%CI: 1.08 to 1.42) and fracture (pooled OR = 1.19; 95%CI: 1.05 to 1.35; $I^2 = 0\%$) when comparing people with asthma receiving ICS and not. In conclusion, patients with asthma exposed to OCS or high ICS doses are more susceptible to bone comorbidities.

Objective 4: To assess OCS and bisphosphonates prescribing patterns at practice level and investigate factors associated with their prescribing.

There was a rise in OCS and bisphosphonate prescriptions between 1998 and 2018. Asthma was significantly associated with OCS use, but not with bisphosphonates. Although OCS use is positively associated with bisphosphonate prescription, variation among practices and CCG exists. The variation in prescribing suggests there is still a need to improve glucocorticoid-induced osteoporosis prevention.

Objective 5: To estimate the risk of ST/FS fractures due to bisphosphonate therapy comparing exposed and non-exposed people with asthma.

I found that patients with asthma exposed to bisphosphonates have greater odds of atypical ST/FS fractures (aOR = 4.42; 95%CI, 2.98 to 8.53). The duration of use influenced the risk with long-term users to be at a greater risk (> 5 yrs. vs no exposure;

aOR= 7.67; 95%CI, 1.75 to 33.91). Drug withdrawal was associated with diminished odds of ST/FS fractures.

Table 10-1. Summary of studies undertaken in thesis

Objective	Participants	Main outcomes and measures	Conclusion
To describe the incidence of osteoporosis and fragility fractures in asthma compared to the general population (Chapter 5).	138,123 patients with asthma and 520,626 patients without asthma matched on age, sex, practice.	Osteoporosis and fragility fracture incidence rates were calculated, and Cox regression was performed comparing hazard rates to the general population.	Patients with asthma are more likely to develop osteoporosis or sustain fragility fractures than the general population, with a particular concern in younger people.
To estimate the risk of osteoporosis and fragility fractures due to OCS and ICS comparing exposed and non-exposed people with asthma (Chapter 6)	1,564 patients with asthma and 3,313 matched on age, sex, practice patients with asthma without osteoporosis 2,131 patients with asthma and 4,421 matched on age, sex, practice patients with asthma without fragility fractures	Conditional logistic regression was used to determine the association between ICS and OCS exposure, and the risk of osteoporosis or FF. The prevalence of patients receiving at least one bisphosphonate was also calculated.	The findings suggest that exposure to OCS or ICS is an independent risk factors for bone health in patients with asthma. Steroid administration at the lowest possible level to maintain asthma control is recommended.
To perform a systematic review and meta-analysis quantifying the impact of OCS and ICS on bone mineral density (BMD), and risk of osteoporosis and fractures in asthma (Chapter 7).	This review consists of 28 studies (six randomized control trials and 22 observational).	Data were narratively synthesized, and a series of meta-analyses were performed using the random-effects inverse variance method.	Patients with asthma exposed to OCS or high ICS doses become more susceptible to bone comorbidities. Striking the right balance between efficacy and safety of steroids in asthma is important to improve patients' quality of life.
To assess OCS and bisphosphonates prescribing patterns at practice level and investigate factors associated with their prescribing (Chapter 8).	195 Clinical Commissioning Groups containing 6,586 practices were included.	The aim was to examine the prescribing of OCS and bisphosphonate at practice level and investigate reasons for variation using a mixed-effect negative binomial regression analysis.	In conclusion, although OCS use is positively associated with BP prescription, variation among practices and CCG exists. The variation in prescribing suggests there is still a need to improve GIOP prevention.
To estimate the risk of ST/FS fractures due to bisphosphonate therapy comparing exposed and non-exposed people with asthma (Chapter 9).	Using an asthma cohort, we identified 67 patients with ST/FS fractures and 260 sex, age, and practice-matched controls	Conditional logistic regression was used to determine the association between bisphosphonate exposure and the risk of ST/FS fractures.	The risk of both osteoporotic and ST/FS fractures should be considered before bisphosphonate initiation, and clinicians should be aware of the need for a drug holiday for patients at lower risk of osteoporotic fractures in order to maximise bisphosphonate benefits and minimise risk of ST/FS fractures.

10.2 Implications

According to the findings of this thesis people with asthma are at greater risk of osteoporosis and fractures with the effect of asthma to be stronger in younger age groups, and men. Consequently, although the focus of osteoporosis prevention is generally on older females, in asthma, given its chronicity and requirements for high dose ICS/OCS, awareness of the potential effect on bone health is needed in men and younger people too. A BMD measurement and fracture risk assessment using tools such as FRAX should be performed within the 6 months of the start of oral glucocorticoids for early detection of osteoporosis in patients with asthma. Other risk factors including BMI, smoking status, and history of osteoporosis should be also considered in the evaluation of fracture risk assessment in patients. All adults starting on glucocorticoids should be given lifestyle advice to optimize bone health. Furthermore, the findings of this thesis suggest that corticosteroids, not only OCS but also high ICS doses, can promote the development of osteoporosis and fragility fractures. Consequently, they should be administrated at the lowest possible dose to maintain asthma control minimising their risks. It's crucial that anyone with poorly controlled asthma should have their diagnosis, adherence, inhaler technique and triggers checked before increasing their inhaled corticosteroids dose or starting oral corticosteroids. The current evidence also supports the need for continuing development and identification of alternative and safer medication for treating asthma exacerbations and for patients with severe asthma to reduce exposure to OCS. The variation found on bisphosphonates prescribing makes clear that clinicians should be aware of bisphosphonates as bone protection therapy and prescribe them in patients exposed to any dose of prednisone for more than 3 months and considering existing bone protection guidelines. However, a specific bisphosphonate prescribing plan such as medication break is recommended to increase the benefits and reduce the adverse effects of this class of drugs in asthma.

The increased risk of osteoporosis and fractures in patients with asthma and their consequences on morbidity and mortality highlight the need for an integrated approach to care. This includes greater coordination and communication between primary care, secondary care, and specialist services to adequately monitor patients and their other medical conditions. An integrated approach is particularly important as such an approach would move away from the established "single-disease" care and consider the interactions of multiple conditions and therapies within each patient. Treating asthma in a patient as if it exists in isolation will lead to less good outcomes and complicate and duplicate interactions with the healthcare system. Clustering of diseases, and how we might better tackle management of them, should be embedded into medical training and continuous professional development, including for specialists.

Another important implication of this PhD thesis is the need for bone specific clinical guidelines on the prevention and management of bone health in asthma. Current asthma guidelines are focussed on other comorbidities but not on osteoporosis and fractures. Findings from this thesis has shown that future guidelines should consider the risk of osteoporosis and fractures in patients with asthma and provide further guidance. Patients with asthma are at greater risk of osteoporosis and fragility fractures than the general population and this should be explored in asthma guidelines to increase awareness. One underappreciated point is that ICS are also associated with poor bone health if received in high doses. Furthermore, patients with asthma on corticosteroids can sustain a fragility fracture with normal BMD values, so it is crucial to highlight the need for a fracture risk assessment. This thesis also highlights the need for a personalised specific bone protection management plan, including bisphosphonate holiday, to minimise the harms of the osteoporosis medication. This advice could be built into individual's personalised asthma action plans.

10.3 Future research

This thesis using routinely collected primary and secondary care data has answered many research questions regarding the bone health in asthma. This hopefully demonstrates the usefulness and potential of the databases for future epidemiological research in asthma. The future direction of research mainly involves the use of the linked primary and secondary care data some of which are presented below:

- Since high ICS doses are associated with increased risk of poor bone health in asthma, further studies shedding light on other potential adverse effects (e.g. ophthalmic effects, diabetes) associated with ICS in patients with asthma can improve patients' quality of life. A nested case-control study could be performed including adult patients with asthma with the outcome of interest exposed to ICS compared to nonexposed using conditional logistic regression to determine the odds of the outcome of interest due to ICS use. If there is an association, it would be interesting to see whether high ICS doses or any dose are responsible to identify optimal use of ICS.

- New studies examining the co-prescribing rate of bisphosphonates and OCS in primary care in patients with asthma is needed to understand whether there is adequate bone protection according to the current guidelines or the necessary support should be provided in order to improve bone protection in routine practice. A cohort study could be performed including patients with asthma on OCS. In detail, co-prescription of corticosteroids and bisphosphonates can be defined as an overlapping prescription that occur within 60 days of each other. Thus, it will be able to establish the co-prescription rate in asthma by age, gender, and calendar year over the whole period for the cohort. The co-prescription rate will be calculated by dividing the number of co-prescriptions by the total time of follow-up. Multiple Poisson regression to determine

associations between risk factors (e.g. age, gender, BMI, smoking status) and overall co-prescription can be performed.

- More evidence is needed about risk factors for ST/FS atypical fractures among patients with asthma on bisphosphonates. New studies of risk factors can lead to development of ST/FS atypical fractures risk prediction tools. This could help clinicians individualise treatment so that the best possible benefit/harm ratio is achieved for each patient separately. Patients with asthma who had a femoral subtrochanteric or shaft fracture could be identified, and their radiographs can be reviewed to confirm atypical features. Age-sex-stratified incidence proportions of atypical fractures can be calculated for those received bisphosphonates and with no reported use of bisphosphonates; these calculations can be used to estimate both the age-sex-adjusted relative risk and the absolute risk of atypical fracture in the asthma population. The duration of bisphosphonate use and the time since the last use should be also considered. Associations between risk factors (e.g. BMI, smoking status, previous disease or medication) can also be determined.

10.4 Overall conclusion

Electronic health records play a significant role in asthma research. This thesis discusses the bone health among patients with asthma. There is evidence that asthma and its treatments are associated with osteoporosis and fractures, which have a substantial effect on health care costs, morbidity, and mortality. This PhD has utilised different methodologies and datasets to address several areas related to bone comorbidities in patients with asthma, which had not been adequately researched. Increasing the understanding of bone-related conditions in patients with asthma can substantially improve their quality of life. The findings outlined in this thesis advance our knowledge about osteoporosis and fragility fractures risk and provide new

evidence into the pharmaceutical management of these bone conditions. Results highlight the need to update the asthma guidelines incorporating bone specific guidance to inform patients, clinicians, and policy makers in order to provide more effective management of associated bone comorbidities.

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APPENDIX 1: ISAC 19_041RA PROTOCOL

INDEPENDENT SCIENTIFIC ADVISORY COMMITTEE (ISAC) PROTOCOL APPLICATION FORM

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*' and justification provided.

Study Title (Max. 255 characters)

An investigation into the association of asthma and fractures.

Study Title (Max. 255 characters)

An investigation into the association of asthma and fractures.

Lay Summary (Max. 250 words)

Asthma is a common disease, especially in the UK. Although asthma itself can have a major effect on a person's health and wellbeing, asthma treatments can also have important side effects that are harmful. Asthma treatments include inhaled (ICS) and oral (OCS) corticosteroids both of which can lead to thinning of the bones (also known as osteoporosis), and fracture. Despite the high proportion of people who have been diagnosed with asthma, little is known about how often these side effects occur. Information on the risk of osteoporosis is scarce and there are no asthma specific bone protection guidelines either nationally or internationally. This has become more important with the recognition that drugs used to prevent osteoporosis and fractures can themselves lead to significant side effects.

Our purpose is to a) understand how frequently people with asthma experience an osteoporotic fracture due to corticosteroids b) to establish the current use of bisphosphonate (drugs which used to prevent osteoporosis and fractures) and oral

corticosteroids and c) examine whether the exposure to bisphosphonates is associated with other side effects in people with asthma.

Our study will provide guidance for patients, clinicians, and policy makers. More precisely, our results will help the development of specific related bone protection guidelines, which will guide patients/clinician decision making on treatment.

Technical Summary (Max. 300 words)

The objective of this study is to understand the link between asthma, corticosteroids, osteoporosis and fractures, bisphosphonates, and atypical fractures. Specifically, we are interested in the following using CPRD linked HES data:

- Determine the incidence of osteoporosis and fragility fractures separately in asthma compared to the general population adjusting for the appropriate confounding factors.
  - Matched cohort study
  - Cox regression

- To establish the risk of fragility fractures in patients with asthma due to inhaled or oral corticosteroids.
  - Nested case control study
  - Conditional logistic regression

- To examine the incidence and the risk of femoral shaft and subtrochanteric fractures due to bisphosphonate use in people with asthma.
  - Nested case control study
  - Conditional logistic regression

Outcomes to be Measured

Primary outcomes

The incidence of osteoporosis and fragility fracture and in people with asthma compared to the general population.

The risk of fragility fracture in people with asthma associated with inhaled (ICS) or oral (OCS) corticosteroids.

The risk of femoral shaft and subtrochanteric fractures associated with bisphosphonate use in patients with asthma.

Objectives, Specific Aims and Rationale

The broad research objectives are to a) understand the current burden and risk of fragility fracture in asthma as related to asthma treatment; b) establish the current use of bisphosphonate prophylaxis and c) establish the femoral shaft and subtrochanteric fracture risk related to bisphosphonate exposure. All the above will be achieved by examining data from CPRD and HES with the aim of delivering guidance for patients, clinicians, and policy makers on the need for bone protection in asthma and the risks associated with its use.

The specific aims and rationale of this study are:

To calculate the incidence of osteoporosis, fragility fractures, subtrochanteric, and femoral shaft fractures within the UK by age-gender-region within people with asthma.

To establish the risk of osteoporosis and fragility fracture in asthma associated with ICS or OCS.

To examine the risk of femoral shaft and subtrochanteric (atypical) fractures associated with bisphosphonate use in people with asthma.

Given the difficulties in designing and recruiting to randomised controlled trials of osteoporosis and fractures prophylaxis in asthma, large long-term observational datasets are required to generate relevant evidence. Consequently, these studies will provide information that is currently missing about asthma, asthma treatment and fracture enabling better health service planning.

Study Background

Asthma is among the most common chronic diseases worldwide and poses a substantial public health burden (1). In the United Kingdom (UK), the lifetime-asthma prevalence rate was found to be 113 per 1000 patient-years (2) and the disease accounts for more than 1000 deaths a year (3). The main treatment for asthma is corticosteroids normally in inhaled or oral form. Inhaled corticosteroids (ICS) are used extremely widely; two of the top 10 drugs by cost prescribed in the NHS in 2012 contained ICS (Seretide and Symbicort). Although the risk of ICS treatment is thought to be low by healthcare professionals there are well-recognised side effects including osteoporosis (4), diabetes and cataracts (5). These side effects can affect compliance and deter patients from taking long-term treatment (6) even though proper ICS use is linked with symptom improvement and reduced mortality (7).

Osteoporosis is also a high burden disease, as in the UK 1 in 2 women and 1 in 5-men will suffer a fragility fracture after the age of 50 (8). The economic burden of new and prior fractures is £3.5 billion each year, which is estimated to increase in 2025 burden by 24% to £5.5 billion (9).

There is a well-recognised association between asthma, corticosteroids (especially OCS) which are widely used in asthma, and corticosteroid-induced osteoporosis (CIO) (10), leading to a higher incidence of fragility fractures. Data from the British Thoracic Society (BTS) asthma registry shows that over half the patients with difficult asthma receive the equivalent of 15mg prednisolone and over 2000 mcg of ICS per day (11). Prednisolone reduces proliferation and differentiation and increases apoptosis of osteoblasts. Synthesis of type I collagen and b1 integrin is also reduced, while

collagenase-3 is increased, thus attenuating the ability of osteoblasts to form a bone matrix.

OCS also decreases Osteocalcin gene expression in osteoclasts. Importantly patients with CIO experience fragility fractures at higher bone density than those with postmenopausal or age- related osteoporosis (12) suggesting preventative treatment should be started earlier for patients receiving regular OCS therapy.

Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in a fracture, known as low-energy trauma (13). According to The World Health Organization (WHO), this is defined as a force equivalent to a fall from a standing height or less. Fragility fracture occurs most commonly in the spine (vertebrae), hip (proximal femur) and wrist (distal radius). It may also occur in the arm (humerus), pelvis, ribs, and other bones. It is estimated that the number of hip fractures worldwide may increase from an estimated 1.7 million in 1990 to a projected 6.3 million in 2050 (14). Additionally, another significant factor is the financial cost for the UK healthcare economy. It has been calculated that the cost from fragility fractures was £1.8 billion in 2000, with the potential to increase to £2.2 billion by 2025 (15).

Despite the clear link between corticosteroids, osteoporosis and as a result fragility fractures as well as the high prevalence of both asthma and osteoporosis, there are no asthma specific osteoporosis guidelines and very little data on the risk of fracture related to treatment in asthma. For example, the recent BTS/SIGN guidelines on asthma management cover specific co-morbidities including osteoporosis and bone protection. They state *"bone mineral density should be monitored in adults. When a significant reduction occurs, treatment with a long-acting bisphosphonate should be offered (further guidance is at* www.nos.orq.uk)". The hyperlink is to the National Osteoporosis Society. No specific guidance is given here on the management of asthma/osteoporosis and this aspect of the guidance has not changed in the last 15 years. In addition, the latest NICE asthma guidelines do not mention osteoporosis in 350 pages. This lack of guidance is reflected in the literature.

Despite there being a wealth of data on the potential risk of OCS (and ICS) for inducing osteoporosis there are very few specific studies to asthma. There is only one randomised trial of bisphosphonates in asthma (16). In this study, 8% of the patients, experienced symptomatic fractures and 17.5% developed either a symptomatic fracture and/or a semi-quantitative vertebral fracture by the end of 5 years. Although the bisphosphonate prescribed improved bone mineral density, it did not protect against fracture. A Cochrane collaboration report from 2016 by Allen et al. examined 27 trials in 3075 adults receiving corticosteroids. Of these trials, less than half-contained patients with asthma and most of these studies contained patients with other conditions too. The analysis states that *"Overall, our review supports the use of bisphosphonates to reduce the risk of spinal fractures and in the prevention and treatment of steroid-induced bone loss"* but this advice is not disease specific.

However, use of bisphosphonates (BPs) is associated with side effects which include increased the risk of atypical fractures (17), health care providers need more evidence to guide their patients. According to Schilcher et al. the age-adjusted relative risk of atypical fracture with any BP use is 47.3 (95%CI: 25.6, 87.3) in "ever" bisphosphonate users compared with "never" users (18). Moreover, the risk of atypical fractures is now thought to be higher than previously realised and bone protection "holidays" after three to five years of bisphosphonate therapy are advised.

Atypical femoral fractures (AFFs) are the commonest atypical fracture due to long-term bisphosphonate use. To be defined an AFF the following criteria should be met; they are located at along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. They are associated with minimal or no trauma (fall from a standing height or less like a fragility fracture). In addition, the fracture is at a right angle with the bone's log axis (transverse) and in some cases it can be diagonal - >30° - to bone's long axis (oblique). Localized periosteal or endosteal thickening of the lateral cortex can also be present at the fracture site. Finally, a complete AFF extends through both cortices, whereas an incomplete AFF involve only the lateral cortex (19).

The risks and benefits of bisphosphonates and steroids are particularly pertinent in asthma as patients are younger and more likely to be female and receive long-term steroid treatment.

Study Type

This study will be a descriptive as well as both hypothesis testing and generating.

Study Design

Q 1: Incidence of osteoporosis, fragility fractures and atypical fractures in people with asthma.

We will conduct a matched cohort study comparing people with asthma and people without asthma to examine the incidence rates of osteoporosis and fragility fractures. We will follow all asthma patients from the index date until the incidence of osteoporosis and fragility fracture, died, left the practice, or follow-up ended in the medical records, whichever occurred first. Using a series of Cox regression models, we will determine whether asthma patients are more likely to have an incident diagnosis of osteoporosis and fragility fracture adjusting for potential confounders (age, gender, smoking status, corticosteroids and bisphosphonates exposure, alcohol consumption, fracture history).

Q2: The risk of osteoporosis and fragility fractures in patients with asthma exposed to oral or inhaled corticosteroids (OCS/ICS).

Using the cohort of people with a recorded diagnosis of asthma from 01/04/2004 to 31/12/2017. A case-control study will be constructed in this cohort using the linked CPRD and HES. Cases will be defined by first recorded osteoporosis and fragility fracture diagnosis using Read/ICD-10 codes and up to 4 controls per case will be matched based on, GP, gender, and age at index date (the date of first fragility fracture diagnosis) from the remaining population of people with asthma. We will exclude

asthma patients with any history of cancer in the preceding 10 years as well as patients with diseases that can affect bone integrity such as osteomalacia, osteopetrosis, hypoparathyroidism, myxoedema, hypothyroidism, and metabolic bone disease. We will explore several ways to categorise ICS/OCS exposure including cumulative exposure in the previous year, determining an individual rate of exposure from first asthma code to index date and cumulative steroid exposure from both ICS/OCS exposure. We will estimate the association between corticosteroids use and fragility fracture by using conditional logistic regression and adjust our models for potential confounders (e.g. age, gender, BMI, smoking status, bisphosphonate exposure, alcohol consumption, fracture history, post-menopausal status, calcium and vitamin D supplements comorbidity as defined by the Charlson Comorbidity Index score).

Q3: The incidence of subtrochanteric and femoral shaft fractures and their risk due to bisphosphonates in patients with asthma.

Using the cohort of people with a recorded diagnosis of asthma from 01/04/2004 to 31/12/2017. A case-control study will be performed in this cohort linking CPRD and HES. cases will be defined by first recorded atypical fracture diagnosis using previously defined Read/ICD-10 codes and up to 4 controls per case will be matched based on, GP, gender, and age at index date (the date of first atypical fracture diagnosis) from the remaining population of people with asthma. We will exclude asthma patients with any history of cancer in the preceding 10 years, conditions that may be associated with altered bone integrity such as osteomalacia, osteopetrosis, hypoparathyroidism, myxoedema, hypothyroidism, and metabolic bone disease. Similar to question 2, we will examine the use of all bisphosphonate prescriptions (grouping by type where appropriate, previous and current use) in a number of different ways, including a count of number of prescriptions in the previous year prior to the index date, 1-3 years, and 3-5 year. The rate of the bisphosphonate prescription will also be examined over the course of the record. We will estimate the association between bisphosphonate use and femoral shaft and subtrochanteric fractures by using

conditional logistic regression investing the models for potential confounders (e.g. age, gender, BMI, smoking status, corticosteroid exposure, alcohol consumption, calcium and vitamin D supplements, post-menopausal status, fracture history and comorbidity as defined by the Charlson Comorbidity Index score).

Feasibility counts

There are 591,981 patients identified using the study inclusion criteria (see section L). There are 329,641 people with asthma who are linked to HES, including 314,255 with at least 1 year of records.

Sample size considerations

Our first objective is to determine the incidence of osteoporosis, fragility fracture and femoral shaft and subtrochanteric (atypical) fractures within people with asthma adjusting for the appropriate confounding factors. This aim is descriptive to describe how much osteoporosis and fracture there is and therefore no power calculation is needed.

Our second objective is to establish the risk of fragility fractures in patients with asthma due to inhaled or oral corticosteroids. 4% - 5% asthma people who are on regular OCS use (20) and 80% of asthma patients in the UK are receiving ICS doses (21). A fragility fracture occurs in 30% to 50% of patients taking long-term systemic corticosteroids (12) and in 17% in patients receiving inhaled corticosteroids (16). Consequently, if we use the 314,255-asthma people who have at least 1-year data and 4%-5% are on regular OCS use and considering the average of 40% of them have a fracture (estimates 30-50%) we anticipate that 5,028 asthma people (OCS users) users will have a fragility fracture. Following the same logic, we anticipate 42,739 asthma people (ICS users) will have a fragility fracture. So, based on our sample size calculation for ICS exposure of 80%, 3,894 cases will be needed to detect a clinically important odds ratio of 1.2. For OCS exposure of 4%, 3,799 will be needed to detect a

clinically important odds ratio of 1.4. All calculations are done for a significance level of 1%, 90% power and correlation of exposure between cases and controls of 0.1

Finally, we will examine the risk of femoral shaft and subtrochanteric fractures due to bisphosphonate use in people with asthma. 11% of asthma people who treated with inhaled corticosteroids receive bisphosphonates (27,654) and 33% of asthma people with intermittent systemic steroid use receive bisphosphonates (4,148) (22). In total, 31,802 people with asthma are receiving bisphosphonates. So, based on our sample size calculation we will be able to detect a clinically important odds ratio of 1.1. The calculation is done for a significance level of 1%, 90% power and correlation of exposure between cases and controls of 0.1.

Planned use of linked data (if applicable):

Linkage to Admitted Patient Care records are required to address all of our research questions. The linkage is necessary on the grounds that the use of primary or secondary care data in isolation may underestimate disease incidence for the conditions, particularly those that can be treated in either care setting. Additionally, incomplete recording of events in UK stand-alone GP data limits its use in studies (23). We will include in our analysis a measure of socioeconomic deprivation as a potential confounder, consequently a linkage to Practice Level (UK) Index of Multiple Deprivation (Standard) is required (24).

Definition of the Study population

Inclusion criteria:

Adults aged ≥ 18 with:

-Read codes for asthma, fractures and osteoporosis as documented in Appendix.

-ICD-10 codes for the above as documented in Appendix.

Practice is "up to standard" at study start 01/04/2004. From this date onwards, the Quality and Outcomes Framework (QOF) came in effect. Thus, we intend to consider only up-to-standard follow up.

Exclusion criteria:
Younger than 18 years.

The study population will be a mixture of case-control or cohort study depending on the research questions.

Selection of comparison group(s) or controls
See above.

Exposures, Outcomes and Covariates
Exposures:
Records of Read codes for asthma, fractures and osteoporosis as listed in Appendix, and documented in the patient clinical or referral record will be used. Additionally, exposure to bisphosphonate as listed in the BNF section 6.6.2 and steroids as listed in the BNF section 6.3 and 3.2. Moreover, records of ICD-10 code for asthma, fractures, osteoporosis as listed in Appendix.

Data sources:
For this study will include primary care clinical records, prescription drug files and HES linked data to Admitted Patient Care records.

Covariates:
Age in years. All patients are 18 years or older, the categories will be based on the sample distribution.
Gender as male or female

Body Mass Index (BMI)

Smoking status

HRT therapy

Calcium and vitamin D supplements

Alcohol consumption

exposure to bisphosphonates

exposure to corticosteroids

Index of Multiple deprivation

fracture history before baseline

other co-morbid condition (e.g. Charlson comorbidity index)

Data/ Statistical Analysis

All data management and statistical analyses will be performed using STATA.

Q1: Incidence of osteoporosis, fragility fractures in people with asthma.

The incidence for each of the following: fragility fractures and osteoporosis will be estimated by dividing the number of people with the above disease of interest during the study period by the total person-years follow up. Afterwards, we will use Cox regression models to calculate the hazard ratio (HR) examining whether or not asthmatics are more likely to be diagnosed with fragility fractures and osteoporosis adjusting for potential confounding.

Q2: The risk of fragility fractures in asthmatics exposed to oral or inhaled corticosteroids (OCS/ICS)

We will conduct a multivariate conditional logistic regression analysis to calculate odds ratio (ORs) with 95% confidence intervals (CIs) for the association between inhaled and/or oral corticosteroid exposure and fragility fractures. We will then adjust the models for confounders.

Q3: Risk of subtrochanteric and femoral shaft fractures in patients with asthma exposed to bisphosphonates

We will conduct a multivariate conditional logistic regression analysis to calculate odds ratio (ORs) with 95% confidence intervals (CIs) for the association between bisphosphonate exposure and atypical fractures. We will then adjust the models for confounders.

In general, we will refer all p-values to provide the transparency of findings and will interpret them with great caution. Where necessary, we will make some statistical corrections (p-value adjustments) setting up a significance level of 0.01 to allow for multiple testing.

Plan for addressing confounding

Study will be adjusted for confounding factors such as calcium and vitamin D supplements, BMI, age, gender, smoking status, alcohol consumption, HRT therapy corticosteroids exposure, exposure to bisphosphonates, a fracture history before baseline and Charlson comorbidity index using multivariate conditional logistic regression and Cox regression modelling.

Plans for addressing missing data

From our experience, it is variables such as BMI, smoking status, alcohol consumption which are more likely to have the greatest amount of missing data. We expect the amount of missing data to be less when we are dealing with just the asthmatic population as group of people who are engaging with health care. We also expect the missing data to be missing at random therefore multiple imputation is an appropriate technique (25). The number of imputations is dependent on the amount of the missing data, and although we expect some it, it should only be a small proportion of the overall population so we expect up to 10 imputations should be applied (26). We will decide about what imputation approach (MVN or MICE) we will use based on the

'nature' of our data (27). We will include BMI, smoking status, and alcohol consumption in the model and will use other complete variables such as gender, age as explanatory variables in the imputation models.

Patient or user group involvement (if applicable)

The study has been discussed with patients at the Nottingham severe asthma service, led by Prof Shaw. The idea for the work came directly from one of his patient experience. She suffered bilateral atypical femoral fractures following bisphosphonate and oral steroid use. The patient is now involved in medical student teaching.

Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

This work forms part of a BMA charity grant. This is a national competition open to all BMA members and funds high quality asthma research. Consequently, the initial application has been peer reviewed by several academic asthma experts. It also forms part of a 3-year PhD at the University of Nottingham. All results will be presented at British, European, or international conferences. Moreover, it is anticipated that the research will lead to three (3) publications in subject-specific peer-reviewed journals.

Conflict of interest statement: No potential conflict of interest relevant to this study was reported.

Limitations of the study design, data sources, and analytic methods

Information gathered in this study is deduced from the code sets used in CPRD, HES Admitted Patient Care. Therefore, it is recognised that the study assumes that the healthcare professionals have used the most accurate code set at each patient visit, accepting that there may be variations in coding of the disease between healthcare professionals. Asthma recordings have been validated (28) as well as earlier studies have demonstrated that there is a high level of data validity with respect to reporting

of fractures from CPRD databases and >90 % of reported fractures were confirmed (29), however, errors in disease coding and time of diagnosis may also present problems in data quality. Variation in coding across different practices and over time may introduce systematic biases. Additionally, since not all GP practices contribute to CPRD, and patients might refuse to participate in the CPRD programme, this can result in selection bias. We will refer any limitation when we report the results of our study.

Amendments - 11/09/2019

Planned use of linked data (if applicable):

Linkage to Admitted Patient Care records are required in order to address all of our research questions.

The linkage is necessary on the grounds that the use of primary or secondary care data in isolation may underestimate disease incidence for the conditions, particularly those that can be treated in either care setting. Additionally, incomplete recording of events in UK stand-alone GP data limits its use in studies.

We will include in our analysis a measure of socioeconomic deprivation as a potential confounder, consequently a linkage to Patient Level (UK) Index of Multiple Deprivation (Standard) is required.

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APPENDIX 2: CODE LISTS

This appendix contains the code lists that were used in the conduct of the research included in this thesis.

Code list 1: Chemical substances (OpenPrescribing)

Codes	Chemical substance
0105020G0	Beclometasone Dipropionate
0105020A0	Budesonide
0603020C0	Betamethasone Sodium Phosphate
0603020F0	Cortisone Acetate
0603020I0	Deflazacort
0603020G0	Dexamethasone
0603020J0	Hydrocortisone
0603020S0	Methylprednisolone
0603020T0	Prednisolone
0603020X0	Prednisone
0606020A0	Alendronic Acid
0606020V0	Zoledronic Acid
0606020R0	Risedronate sodium

Code list 2: Asthma (CPRD)

Readcode	Description
H33..00	asthma
663..11	asthma monitoring
H333.00	acute exacerbation of asthma
H33z100	asthma attack
H33z011	severe asthma attack
H33..11	bronchial asthma
H330.11	allergic asthma
663V100	mild asthma
663V300	severe asthma
663V000	occasional asthma
H331.11	late onset asthma
H33z.00	asthma unspecified
H33zz11	exercise induced asthma
H33z000	status asthmaticus nos
H331.00	intrinsic asthma
H330011	hay fever with asthma
H312000	chronic asthmatic bronchitis
173A.00	exercise induced asthma
H330111	extrinsic asthma with asthma attack
8H2P.00	emergency admission, asthma

H330.00	extrinsic (atopic) asthma
663P.00	asthma limiting activities
663W.00	asthma prophylactic medication used
663U.00	asthma management plan given
663N.00	asthma disturbing sleep
H330.14	pollen asthma
H33z111	asthma attack nos
9OJA.11	asthma monitored
663y.00	number of asthma exacerbations in past year
66Y5.00	change in asthma management plan
66Y9.00	step up change in asthma management plan
66YJ.00	asthma annual review
8B3j.00	asthma medication review
663j.00	asthma - currently active
178..00	asthma trigger
1O2..00	asthma confirmed
H33z200	late-onset asthma
663V.00	asthma severity
663V200	moderate asthma
663h.00	asthma - currently dormant
663O.00	asthma not disturbing sleep
663Q.00	asthma not limiting activities
663N200	asthma disturbs sleep frequently
66YK.00	asthma follow-up
H330000	extrinsic asthma without status asthmaticus
H330.13	hay fever with asthma
H33zz00	asthma nos
8795.00	asthma control step 2
8794.00	asthma control step 1
66YA.00	step down change in asthma management plan
8796.00	asthma control step 3
H331111	intrinsic asthma with asthma attack
66YQ.00	asthma monitoring by nurse
663p.00	asthma treatment compliance unsatisfactory
663n.00	asthma treatment compliance satisfactory
8798.00	asthma control step 5
8797.00	asthma control step 4
H33zz12	allergic asthma nec
173c.00	occupational asthma
663d.00	emergency asthma admission since last appointment
8791.00	further asthma - drug prevent.
663u.00	asthma causes daytime symptoms 1 to 2 times per week
663e.00	asthma restricts exercise

8CR0.00	asthma clinical management plan
H332.00	mixed asthma
663s.00	asthma never causes daytime symptoms
663v.00	asthma causes daytime symptoms most days
663f.00	asthma never restricts exercise
663e100	asthma severely restricts exercise
663e000	asthma sometimes restricts exercise
H330100	extrinsic asthma with status asthmaticus
H331000	intrinsic asthma without status asthmaticus
66YR.00	asthma monitoring by doctor
663N000	asthma causing night waking
66YP.00	asthma night-time symptoms
663t.00	asthma causes daytime symptoms 1 to 2 times per month
663O000	asthma never disturbs sleep
663w.00	asthma limits walking up hills or stairs
663x.00	asthma limits walking on the flat
663N100	asthma disturbs sleep weekly
H35y700	wood asthma
663r.00	asthma causes night symptoms 1 to 2 times per month
H334.00	brittle asthma
1780.00	aspirin induced asthma
663q.00	asthma daytime symptoms
H331z00	intrinsic asthma nos
H330z00	extrinsic asthma nos
9OJ1.00	attends asthma monitoring
H47y000	detergent asthma
H331100	intrinsic asthma with status asthmaticus
173d.00	work aggravated asthma
8CMA000	patient has a written asthma personal action plan
679J000	health education - asthma self-management
38DT.00	asthma control questionnaire
9NNX.00	under care of asthma specialist nurse
679J100	health education - structured asthma discussion
38DV.00	mini asthma quality of life questionnaire
1787.00	asthma trigger - seasonal
1781.00	asthma trigger - pollen
66Yr.00	asthma causes symptoms most nights
66Yq.00	asthma causes nighttime symptoms 1 to 2 times per week
1789.00	asthma trigger - respiratory infection
663P000	asthma limits activities 1 to 2 times per month
178B.00	asthma trigger - exercise
663P100	asthma limits activities 1 to 2 times per week

1783.00	asthma trigger - warm air
1786.00	asthma trigger - animals
66Ys.00	asthma never causes night symptoms
1788.00	asthma trigger - cold air
178A.00	asthma trigger - airborne dust
1785.00	asthma trigger - damp
1784.00	asthma trigger - emotion
1782.00	asthma trigger - tobacco smoke
663P200	asthma limits activities most days
661N100	asthma self-management plan review
661M100	asthma self-management plan agreed
H335.00	chronic asthma with fixed airflow obstruction
H3B..00	asthma-chronic obstructive pulmonary disease overlap syndrome

Code list 3: Osteoporosis (CPRD & HES)

Readcode	Description
N330.00	osteoporosis
N330B00	vertebral osteoporosis
N331L00	collapse of vertebra due to osteoporosis nos
N331J00	collapse of lumbar vertebra due to osteoporosis
N330200	postmenopausal osteoporosis
N331900	osteoporosis + pathological fracture thoracic vertebrae
58E4.00	forearm dxa scan result osteoporotic
N330000	osteoporosis, unspecified
N330100	senile osteoporosis
N330C00	osteoporosis localized to spine
N331800	osteoporosis + pathological fracture lumbar vertebrae
NyuB800	[x]unspecified osteoporosis with pathological fracture
N331K00	collapse of thoracic vertebra due to osteoporosis
N330500	drug-induced osteoporosis
N330D00	osteoporosis due to corticosteroids
66a9.00	osteoporosis - falls prevention
66a6.00	osteoporosis - dietary advice
N331600	idiopathic osteoporosis with pathological fracture
N330A00	osteoporosis in endocrine disorders
N331300	osteoporosis of disuse with pathological fracture
66a4.00	osteoporosis treatment changed
N330z00	osteoporosis nos
N374600	osteoporotic kyphosis
66a3.00	osteoporosis treatment stopped
9Od..00	osteoporosis monitoring administration
66a2.00	osteoporosis treatment started

N331B00	postmenopausal osteoporosis with pathological fracture
66a7.00	osteoporosis - dietary assessment
58EM.00	lumbar dxa scan result osteoporotic
N331200	postoophorectomy osteoporosis with pathological fracture
66aE.00	refer to osteoporosis specialist
N330300	idiopathic osteoporosis
66a8.00	osteoporosis - exercise advice
NyuB100	[x]other osteoporosis
58EG.00	hip dxa scan result osteoporotic
N331.14	osteoporotic vertebral collapse
N331H00	collapse of cervical vertebra due to osteoporosis
58EA.00	heel dxa scan result osteoporotic
N331500	drug-induced osteoporosis with pathological fracture
N331A00	osteoporosis + pathological fracture cervical vertebrae
66a5.00	osteoporosis - no treatment
585O.00	quantitative ultrasound scan of heel - result osteoporotic
N330800	localized osteoporosis - lequesne
NyuB000	[x]other osteoporosis with pathological fracture
N330900	osteoporosis in multiple myelomatosis
N330400	dissuse osteoporosis
N331400	osteoporosis with fracture
66aA.00	osteoporosis - treatment response
N330600	Post ophorectomy osteoporosis
8I6c.00	osteoporosis treatment not indicated
N330700	postsurgical malabsorption osteoporosis
58EV.00	femoral neck dexa scan result osteoporotic
66aB.00	osteoporosis - no treatment response
8B6b.00	osteoporosis medication prophylaxis
NyuB200	[x]osteoporosis in other disorders classified elsewhere
ICD-10 code	**Description**
M80	Osteoporosis with current pathological fracture
M81	Osteoporosis without current pathological fracture

Code list 4: Fragility fractures (CPRD & HES)

readcode	description	location
S10B200	FRACTURE OF COCCYX	vertebra
N331.12	Collapse of vertebra NOS	vertebra
S10x.00	CLOSED FRACTURE OF SPINE, UNSPECIFIED,	vertebra
S10B100	FRACTURE OF SACRUM	vertebra
S104.00	CLOSED FRACTURE LUMBAR VERTEBRA	vertebra

S132.00	Closed fracture pubis	vertebra
S132100	Closed fracture pelvis, multiple pubic rami - stable	vertebra
S132000	Closed fracture pelvis, single pubic ramus	vertebra
S104100	CLOSED FRACTURE LUMBAR VERTEBRA, WEDGE	vertebra
S10B600	MULTIPLE FRACTURES OF LUMBAR SPINE AND PELVIS	vertebra
N331F00	Collapse of thoracic vertebra	vertebra
S10B000	FRACTURE OF LUMBAR VERTEBRA	vertebra
S150.00	Multiple fractures of thoracic spine	vertebra
S100.00	CLOSED FRACTURE OF CERVICAL SPINE	vertebra
N331G00	Collapse of lumbar vertebra	vertebra
S134z00	Other or multiple closed fracture of pelvis NOS	vertebra
S102y00	OTHER SPECIFIED CLOSED FRACTURE THORACIC VERTEBRA	vertebra
S10B.00	FRACTURE OF LUMBAR SPINE AND PELVIS	vertebra
S108.00	CLOSED FRACTURE PELVIS, COCCYX	vertebra
S100000	CLOSED FRACTURE OF UNSPECIFIED CERVICAL VERTEBRA	vertebra
S106.00	CLOSED FRACTURE SACRUM	vertebra
N1y1.00	Fatigue fracture of vertebra	vertebra
N331E00	Collapse of cervical vertebra	vertebra
S136000	Closed complete rupture pubic symphysis	vertebra
S138.00	Traumatic rupture of symphysis pubis	vertebra
S102.00	CLOSED FRACTURE THORACIC VERTEBRA	vertebra
S134600	Closed fracture pelvis, iliac wing	vertebra
S134400	Closed fracture pelvis, anterior superior iliac spine	vertebra
S13y.00	Closed fracture of pelvis NOS	vertebra
S102100	CLOSED FRACTURE THORACIC VERTEBRA, WEDGE	vertebra
S132z00	Closed fracture pubis NOS	vertebra
S104400	CLOSED FRACTURE LUMBAR VERTEBRA, TRANSVERSE PROCESS	vertebra
S136.00	Closed complete rupture of pelvic ring	vertebra
S134.00	Other or multiple closed fracture of pelvis	vertebra
S134800	Closed fracture dislocation of sacro-iliac joint	vertebra
S4J2100	Closed fracture-subluxation of pelvis	vertebra
S133000	Open fracture pelvis, single pubic ramus	vertebra
S134100	Closed fracture pelvis, ischium	vertebra
S4J0100	Closed fracture-dislocation of pelvis	vertebra
S135z00	Other/multiple open fracture of pelvis NOS	vertebra
S104300	CLOSED FRACTURE LUMBAR VERTEBRA, SPINOUS PROCESS	vertebra
S150000	Closed multiple fractures of thoracic spine	vertebra
N331D00	Collapsed vertebra NOS	vertebra
S132y00	Other specified closed fracture pubis	vertebra
S102000	CLOSED FRACTURE THORACIC VERTEBRA, BURST	vertebra
S134500	Closed fracture pelvis, anterior inferior iliac spine	vertebra
S134000	Closed fracture of ilium, unspecified	vertebra

S102z00	CLOSED FRACTURE THORACIC VERTEBRA NOT OTHERWISE SPECIFIED	vertebra
S134300	Closed fracture pelvis, ischial tuberosity	vertebra
S105.00	OPEN FRACTURE LUMBAR VERTEBRA	vertebra
S104000	CLOSED FRACTURE LUMBAR VERTEBRA, BURST	vertebra
S135400	Open fracture pelvis, anterior superior iliac spine	vertebra
S4J1100	Open fracture-dislocation of pelvis	vertebra
S132200	Closed fracture pelvis, multiple pubic rami - unstable	vertebra
S102400	CLOSED FRACTURE THORACIC VERTEBRA, TRANSVERSE PROCESS	vertebra
S133.00	Open fracture of pubis	vertebra
S133100	Open fracture pelvis, multiple pubic rami - stable	vertebra
S134700	Closed vertical fracture of ilium	vertebra
S100H00	CLOSED FRACTURE CERVICAL VERTEBRA, WEDGE	vertebra
S109.00	OPEN FRACTURE PELVIS, COCCYX	vertebra
S100x00	MULTIPLE CLOSED FRACTURES OF CERVICAL VERTEBRAE	vertebra
S101.00	OPEN FRACTURE OF CERVICAL SPINE	vertebra
S137100	Open complete rupture of sacro-iliac joint	vertebra
S104200	Closed fracture lumbar vertebra, spondylolysis	vertebra
S103100	OPEN FRACTURE THORACIC VERTEBRA, WEDGE	vertebra
S103.00	OPEN FRACTURE THORACIC VERTEBRA	vertebra
S13z.00	Open fracture of pelvis NOS	vertebra
S134200	Closed multiple disruptions of pelvis	vertebra
S102300	CLOSED FRACTURE THORACIC VERTEBRA, SPINOUS PROCESS	vertebra
S135.00	Other or multiple open fracture of pelvis	vertebra
S4J3100	Open fracture-subluxation of pelvis	vertebra
S105100	OPEN FRACTURE LUMBAR VERTEBRA, WEDGE	vertebra
S150100	Open multiple fracture of thoracic spine	vertebra
S107.00	OPEN FRACTURE SACRUM	vertebra
S135600	Open fracture pelvis, iliac wing	vertebra
S100G00	CLOSED FRACTURE CERVICAL VERTEBRA, BURST	vertebra
S135300	Open fracture pelvis, ischial tuberosity	vertebra
S137000	Open complete rupture pubic symphysis	vertebra
S133z00	Open fracture of pubis NOS	vertebra
S136100	Closed complete rupture sacro-iliac joint	vertebra
S106000	CLOSED COMPRESSION FRACTURE SACRUM	vertebra
S135200	Open multiple disruptions of pelvis	vertebra
S106100	CLOSED VERTICAL FRACTURE OF SACRUM	vertebra
S101x00	MULTIPLE OPEN FRACTURES OF CERVICAL VERTEBRAE	vertebra
S105000	OPEN FRACTURE LUMBAR VERTEBRA, BURST	vertebra
S133y00	Other specified open fracture of pubis	vertebra
Syu1500	[X]Fracture of other specified cervical vertebra	vertebra
S135800	Open fracture dislocation of sacro-iliac joint	vertebra

S104600	CLOSED FRACTURE LUMBAR VERTEBRA, TRICOLUMNAR	vertebra
S104500	CLOSED FRACTURE LUMBAR VERTEBRA, POSTERIOR ARCH	vertebra
S102200	CLOSED FRACTURE THORACIC VERTEBRA, SPONDYLOLYSIS	vertebra
S135000	Open fracture of ilium, unspecified	vertebra
S107100	OPEN VERTICAL FRACTURE OF SACRUM	vertebra
S135y00	Other open fracture of pelvis	vertebra
S102500	CLOSED FRACTURE THORACIC VERTEBRA, POSTERIOR ARCH	vertebra
S103500	OPEN FRACTURE THORACIC VERTEBRA, POSTERIOR ARCH	vertebra
S133200	Open fracture pelvis, multiple pubic rami - unstable	vertebra
S101000	OPEN FRACTURE OF UNSPECIFIED CERVICAL VERTEBRA	vertebra
S137.00	Open complete rupture of pelvic ring	vertebra
S105400	OPEN FRACTURE LUMBAR VERTEBRA, TRANSVERSE PROCESS	vertebra
S107000	OPEN COMPRESSION FRACTURE SACRUM	vertebra
S135100	Open fracture pelvis, ischium	vertebra
N331C11	Collapse of cervical vertebra	vertebra
S135500	Open fracture pelvis, anterior inferior iliac spine	vertebra
S15..00	Fracture of thoracic vertebra	vertebra
S112100	Cls spinal fracture wth complete thoracic cord lesion,T1-6	vertebra
S11x.00	Closed fracture of spine with spinal cord lesion unspecified	vertebra
N331.14	Osteoporotic vertebral collapse	vertebra
S112.00	Closed fracture of thoracic spine with spinal cord lesion	vertebra
N331.11	Collapse of spine NOS	vertebra
N331111	Collapse of lumbar vertebra	vertebra
14G8.00	H/O: vertebral fracture	vertebra
S112A00	Cls spinal fracture with posterior thorac cord lesion, T7-12	vertebra
S10z.00	Fracture of spine without mention of spinal cord lesion NOS	vertebra
N331K00	Collapse of thoracic vertebra due to osteoporosis	vertebra
N331L00	Collapse of vertebra due to osteoporosis NOS	vertebra
S112600	Cls spinal fracture with unspec thoracic cord lesion, T7-12	vertebra
N331J00	Collapse of lumbar vertebra due to osteoporosis	vertebra
S114000	Closed spinal fracture with unspecified lumbar cord lesion	vertebra
N331011	Collapse of thoracic vertebra	vertebra
S10..00	Fracture of spine without mention of spinal cord injury	vertebra
S112700	Cls spinal fracture with complete thorac cord lesion, T7-12	vertebra
S114100	Closed spinal fracture with complete lumbar cord lesion	vertebra

S10..12	Fracture of vertebra without spinal cord lesion	vertebra
S11z.00	Fracture of spine with spinal cord lesion NOS	vertebra
S112000	Cls spinal fracture with unspec thoracic cord lesion,T1-6	vertebra
S114.00	Closed fracture of lumbar spine with spinal cord lesion	vertebra
N331H00	Collapse of cervical vertebra due to osteoporosis	vertebra
S11..00	Fracture of spine with spinal cord lesion	vertebra
S11..12	Fracture of vertebra with spinal cord lesion	vertebra
S112z00	Closed fracture of thoracic spine with cord lesion NOS	vertebra
Nyu6700	[X]Collapsed vertebra in diseases classified elsewhere	vertebra
SR11.00	Fractures involving thorax with lower back and pelvis	vertebra
Q203000	fracture of humerus due to birth trauma	humerus
S2...11	Arm fracture	humerus
S22..00	fracture of humerus	humerus
S220.00	closed fracture of the proximal humerus	humerus
S220000	closed fracture of proximal humerus, unspecified part	humerus
S220100	closed fracture proximal humerus, neck	humerus
S220200	closed fracture of proximal humerus, anatomical neck	humerus
S220300	closed fracture proximal humerus, greater tuberosity	humerus
S220400	closed fracture proximal humerus, head	humerus
S220500	closed fracture of humerus, upper epiphysis	humerus
S220600	closed fracture proximal humerus, three part	humerus
S220700	closed fracture proximal humerus, four part	humerus
S220z00	closed fracture of proximal humerus not otherwise specified	humerus
S222.00	closed fracture of humerus, shaft or unspecified part	humerus
S222000	closed fracture of humerus nos	humerus
S222100	closed fracture of humerus, shaft	humerus
S222z00	closed fracture of humerus, shaft or unspecified part nos	humerus
S224.00	closed fracture of the distal humerus	humerus
S224100	closed fracture distal humerus, supracondylar	humerus
S224200	closed fracture distal humerus, lateral condyle	humerus
S224300	closed fracture distal humerus, medial condyle	humerus
S224400	closed fracture of distal humerus, condyle(s) unspecified	humerus
S224500	closed fracture of distal humerus, trochlea	humerus
S224600	closed fracture distal humerus, lateral epicondyle	humerus
S224700	closed fracture distal humerus, medial epicondyle	humerus
S224800	closed fracture distal humerus, capitellum	humerus
S224900	closed fracture distal humerus, bicondylar (t-y fracture)	humerus
S224x00	closed fracture of distal humerus, multiple	humerus
S224z00	closed fracture of distal humerus, not otherwise specified	humerus
S226.00	fracture of upper end of humerus	humerus
S227.00	fracture of shaft of humerus	humerus
S228.00	fracture of lower end of humerus	humerus
S22z.00	fracture of humerus nos	humerus
S292.00	multiple fractures of clavicle, scapula and humerus	humerus

S292000	closed multiple fractures of clavicle, scapula and humerus	humerus
Syu4200	[x]multiple fractures of clavicle, scapula and humerus	humerus
S31z.00	FRACTURE OF FEMUR, NOS	Hip
S30..11	Hip fracture	Hip
S30..00	Fracture of neck of femur	Hip
S302.00	Closed fracture of proximal femur, pertrochanteric	Hip
S312300	CLOSED FRACTURE DISTAL FEMUR, SUPRACONDYLAR	Hip
S312100	Closed fracture of femoral condyle, unspecified	Hip
7K1L400	Closed reduction of fracture of hip	Hip
S310.00	CLOSED FRACTURE OF FEMUR, SHAFT OR UNSPECIFIED PART	Hip
S31..00	OTHER FRACTURE OF FEMUR	Hip
S305.00	SUBTROCHANTERIC FRACTURE	Hip
S315.00	FRACTURE OF LOWER END OF FEMUR	Hip
S314.00	FRACTURE OF SHAFT OF FEMUR	Hip
S302400	Closed fracture of femur, intertrochanteric	Hip
7K1J000	Cls red+int fxn proximal femoral #+screw/nail device alone	Hip
7K1D01E	DHS - Dynamic hip screw primary fixation of neck of femur	Hip
S30y.11	Hip fracture NOS	Hip
7K1D01F	Dynamic hip screw primary fixation of neck of femur	Hip
S310011	Thigh fracture NOS	Hip
S300500	Cls # prox femur, subcapital, Garden grade unspec.	Hip
S30y.00	Closed fracture of neck of femur NOS	Hip
7K1L500	CLOSED REDUCTION OF FRACTURE OF FEMUR	Hip
S302000	Cls # proximal femur, trochanteric section, unspecified	Hip
S302011	Closed fracture of femur, greater trochanter	Hip
S310012	Upper leg fracture NOS	Hip
S3x2.00	MULTIPLE FRACTURES OF FEMUR	Hip
S312200	CLOSED FRACTURE OF FEMUR, LOWER EPIPHYSIS	Hip
S312.11	CLOSED FRACTURE OF FEMUR, DISTAL END	Hip
S30w.00	Closed fracture of unspecified proximal femur	Hip
S4E..00	FRACTURE-DISLOCATION OR SUBLUXATION HIP	Hip
S310100	CLOSED FRACTURE SHAFT OF FEMUR	Hip
SC3D400	SEQUELAE OF FRACTURE OF FEMUR	Hip
S312.00	CLOSED FRACTURE DISTAL FEMUR	Hip
S304.00	Pertrochanteric fracture	Hip
S302200	CLOSED FRACTURE PROXIMAL FEMUR, SUBTROCHANTERIC	Hip
S300700	Closed fracture proximal femur, subcapital, Garden grade II	Hip
S300900	Closed fracture proximal femur, subcapital, Garden grade IV	Hip
S300600	Closed fracture proximal femur, subcapital, Garden grade I	Hip

7K1J500	Primary int fxn(no red) prox fem #+screw/nail device alone	Hip
S300400	CLOSED FRACTURE HEAD OF FEMUR	Hip
S300800	Closed fracture proximal femur, subcapital, Garden grade III	Hip
S310000	CLOSED FRACTURE OF FEMUR, UNSPECIFIED PART	Hip
S312500	CLOSED FRACTURE DISTAL FEMUR, LATERAL CONDYLE	Hip
S300.00	Closed fracture proximal femur, transcervical	Hip
7K1J700	Primary int fxn(no red) prox fem #+screw/nail+plate device	Hip
7K1Jd00	Closed reduction of intracapsular # NOF internal fixat DHS	Hip
S300000	Cls # prox femur, intracapsular section, unspecified	Hip
S4E0.00	CLOSED FRACTURE-DISLOCATION, HIP JOINT	Hip
7K1J012	Cl red intracaps fract neck femur fix - Smith-Petersen nail	Hip
7K1J600	Primary int fxn(no red) prox fem #+scrw/nail+intramed device	Hip
S302z00	Cls # of proximal femur, pertrochanteric section, NOS	Hip
S302100	Closed fracture proximal femur, intertrochanteric, two part	Hip
S312400	CLOSED FRACTURE DISTAL FEMUR, MEDIAL CONDYLE	Hip
S300A00	Closed fracture of femur, upper epiphysis	Hip
7K1JD00	Primary cls red+int fxn prox fem #+screw/nail+plate device	Hip
S302012	Closed fracture of femur, lesser trochanter	Hip
S300y00	Closed fracture proximal femur, other transcervical	Hip
S302300	Cls # proximal femur, intertrochanteric, comminuted	Hip
S300311	Closed fracture, base of neck of femur	Hip
S300300	Closed fracture proximal femur, basicervical	Hip
S310z00	Closed fracture of shaft or unspecified part, NOS	Hip
S312000	CLOSED FRACTURE OF DISTAL FEMUR, UNSPECIFIED	Hip
7K1J011	Cl red intracaps frac neck femur fix-Garden cannulated screw	Hip
S312600	CLOSED FRACTURE DISTAL FEMUR, BICONDYLAR (T-Y FRACTURE)	Hip
7K1JC00	Prim cls rd+int fxn prox fem #+screw/nail+intramdulry device	Hip
S312x00	CLOSED FRACTURE DISTAL FEMUR, COMMINUTED/INTRA-ARTICULAR	Hip
7K1JB00	Primary cls red+int fxn prox fem #+screw/nail device alone	Hip
7K1J013	Cls red+int fxn prox femoral #+Richard's cannulat hip screw	Hip
S312z00	CLOSED FRACTURE OF DISTAL FEMUR NOT OTHERWISE SPECIFIED	Hip
S300z00	Closed fracture proximal femur, transcervical, NOS	Hip

S300200	Closed fracture proximal femur, midcervical section	Hip
S300y11	Closed fracture of femur, subcapital	Hip
S300100	Closed fracture proximal femur, transepiphyseal	Hip
Syu7200	[X]FRACTURES OF OTHER PARTS OF FEMUR	Hip
K7805F	REDUCTION CLOSED FRACTURE FEMUR	Hip
S4E2.00	CLOSED FRACTURE-SUBLUXATION, HIP JOINT	Hip
7K1K500	Primary cls reduction+external fixation proximal femoral #	Hip
S130.00	Closed fracture acetabulum	Hip
S23x111	FRACTURE OF RADIUS NOS	forearm/wrist
S23B.00	FRACTURE OF LOWER END OF RADIUS	forearm/wrist
S234.11	WRIST FRACTURE - CLOSED	forearm/wrist
S234100	CLOSED COLLES' FRACTURE	forearm/wrist
S23z.00	FRACTURE OF RADIUS AND ULNA, NOS	forearm/wrist
S23x211	FRACTURE OF ULNA NOS	forearm/wrist
S234200	CLOSED FRACTURE OF THE DISTAL RADIUS, UNSPECIFIED	forearm/wrist
S237.00	FRACTURE OF UPPER END OF RADIUS	forearm/wrist
S230300	CLOSED MONTEGGIA'S FRACTURE	forearm/wrist
S234700	CLOSED SMITH'S FRACTURE	forearm/wrist
S23x300	CLOSED FRACTURE OF THE RADIUS AND ULNA	forearm/wrist
S23C.00	FRACTURE OF LOWER END OF BOTH ULNA AND RADIUS	forearm/wrist
S23..00	FRACTURE OF RADIUS AND ULNA	forearm/wrist
S234B00	CLOSED FRACTURE RADIAL STYLOID	forearm/wrist
S230600	CLOSED FRACTURE RADIUS, HEAD	forearm/wrist
S230700	CLOSED FRACTURE RADIUS, NECK	forearm/wrist
S239.00	FRACTURE OF SHAFT OF RADIUS	forearm/wrist
S238.00	FRACTURE OF SHAFT OF ULNA	forearm/wrist
S234300	CLOSED FRACTURE OF ULNA, STYLOID PROCESS	forearm/wrist
S230100	CLOSED FRACTURE OLECRANON, EXTRA-ARTICULAR	forearm/wrist
S234F00	CLOSED BARTON'S FRACTURE	forearm/wrist
S23A.00	FRACTURE OF SHAFTS OF BOTH ULNA AND RADIUS	forearm/wrist
S23..11	FOREARM FRACTURE	forearm/wrist
S234900	CLOSED VOLAR BARTON'S FRACTURE	forearm/wrist
S230B00	CLOSED FRACTURE OLECRANON, INTRA-ARTICULAR	forearm/wrist
S23x.00	CLOSED FRACTURE OF RADIUS AND ULNA, UNSPECIFIED PART	forearm/wrist
S230200	CLOSED FRACTURE OF ULNA, CORONOID	forearm/wrist
S23x100	CLOSED FRACTURE OF RADIUS (ALONE), UNSPECIFIED	forearm/wrist
S234.00	CLOSED FRACTURE OF RADIUS AND ULNA, LOWER END	forearm/wrist
S234000	CLOSED FRACTURE OF FOREARM, LOWER END, UNSPECIFIED	forearm/wrist

S234D00	CLOSED FRACTURE DISTAL RADIUS, EXTRA-ARTICULAR, OTHER TYPE	forearm/wrist
S234211	DUPUYTREN'S FRACTURE, RADIUS - CLOSED	forearm/wrist
S23x200	CLOSED FRACTURE OF ULNA (ALONE), UNSPECIFIED	forearm/wrist
S232.00	CLOSED FRACTURE OF RADIUS AND ULNA, SHAFT	forearm/wrist
S234z00	CLOSED FRACTURE OF FOREARM, LOWER END, NOS	forearm/wrist
S234E00	CLOSED FRACTURE DISTAL RADIUS, INTRA-ARTICULAR, OTHER TYPE	forearm/wrist
S234600	CLOSED FRACTURE RADIUS AND ULNA, DISTAL	forearm/wrist
S236.00	FRACTURE OF UPPER END OF ULNA	forearm/wrist
S232z00	CLOSED FRACTURE OF RADIUS AND ULNA, SHAFT, NOS	forearm/wrist
S230900	CLOSED FRACTURE OF THE PROXIMAL RADIUS	forearm/wrist
S230000	CLOSED FRACTURE OF PROXIMAL FOREARM, UNSPECIFIED PART	forearm/wrist
S230711	CLOSED # RADIUS NECK	forearm/wrist
S230800	CLOSED FRACTURE PROXIMAL RADIUS, COMMINUTED	forearm/wrist
S230400	CLOSED FRACTURE OF PROXIMAL ULNA, COMMINUTED	forearm/wrist
S230500	CLOSED FRACTURE OF THE PROXIMAL ULNA	forearm/wrist
S232300	CLOSED FRACTURE RADIUS AND ULNA, MIDDLE	forearm/wrist
S23xz00	CLOSED FRACTURE OF RADIUS AND ULNA, NOS	forearm/wrist
S234800	CLOSED GALEAZZI FRACTURE	forearm/wrist
S234500	CLOSED FRACTURE DISTAL ULNA, UNSPECIFIED	forearm/wrist
S234400	CLOSED FRACTURE OF ULNA, LOWER EPIPHYSIS	forearm/wrist
S232100	CLOSED FRACTURE OF THE RADIAL SHAFT	forearm/wrist
S230z00	CLOSED FRACTURE OF PROXIMAL FOREARM NOT OTHERWISE SPECIFIED	forearm/wrist
S230.00	CLOSED FRACTURE OF PROXIMAL RADIUS AND ULNA	forearm/wrist
S230A00	CLOSED FRACTURE RADIUS AND ULNA, PROXIMAL	forearm/wrist
S232200	CLOSED FRACTURE OF THE ULNAR SHAFT	forearm/wrist
S234C00	CLOSED FRACTURE DISTAL RADIUS, INTRA-ARTICULAR, DIE-PUNCH	forearm/wrist
S234A00	CLOSD DORSAL BARTON'S FRACTURE	forearm/wrist
S23x000	CLOSED FRACTURE OF FOREARM, UNSPECIFIED	forearm/wrist
S232000	CLOSED FRACTURE OF RADIUS, SHAFT, UNSPECIFIED	forearm/wrist
S234111	SMITH'S FRACTURE - CLOSED	forearm/wrist
S234911	CLOSED VOLAR BARTON'S FRACTURE-DISLOCATION	forearm/wrist
S234A11	CLOSED DORSAL BARTON'S FRACTURE-DISLOCATION	forearm/wrist
S234912	CLOSED VOLAR BARTON FRACTURE-SUBLUXATION	forearm/wrist

S234A12	CLOSED DORSAL BARTON FRACTURE-SUBLUXATION	forearm/wrist
S4C2100	Closed fracture-subluxation radiocarpal joint	forearm/wrist
Syu5400	[X]Fracture of forearm, unspecified	forearm/wrist
S242.00	Fracture at wrist and hand level	forearm/wrist
S4C2000	Closed fracture-subluxation, distal radio-ulnar jt	forearm/wrist
Syu5300	[X]Fracture of other parts of forearm	forearm/wrist
Syu6500	[X]Fracture of other & unspecified parts of wrist and hand	forearm/wrist
S4C2.00	Closed fracture-subluxation of the wrist	forearm/wrist
N331N00	fragility fracture	fragility
N331M00	fragility fracture due to unspecified osteoporosis	fragility
N331M11	minimal trauma fracture due to unspecified osteoporosis	fragility
N331N11	Minimal trauma fracture	fragility
ICD-10	**Description**	**Location**
S62.00	Fracture of navicular [scaphoid] bone of hand, closed	forearm/wrist
S62.80	Fracture of other and unspecified parts of wrist and hand, closed	forearm/wrist
S72.00	Fracture of neck of femur, closed	Hip
S72.10	Pertrochanteric fracture, closed	Hip
S72.20	Subtrochanteric fracture, closed	Hip
S72.30	Fracture of shaft of femur, closed	Hip
S72.40	Fracture of lower end of femur, closed	Hip
S72.70	Multiple fractures of femur, closed	Hip
S72.80	Fractures of other parts of femur, closed	Hip
S72.90	Fracture of femur, part unspecified, closed	Hip
S42.00	Fracture of clavicle, closed	humerus
S42.10	Fracture of scapula, closed	humerus
S42.20	Fracture of upper end of humerus, closed	humerus
S42.30	Fracture of shaft of humerus, closed	humerus
S42.40	Fracture of lower end of humerus, closed	humerus
S42.70	Multiple fractures of clavicle, scapula and humerus, closed	humerus
S42.80	Fracture of other parts of shoulder and upper arm, closed	humerus
S42.90	Fracture of shoulder girdle, part unspecified, closed	humerus
S12.00	Fracture of first cervical vertebra, closed	vertebra
S12.10	Fracture of second cervical vertebra, closed	vertebra
S12.20	Fracture of other specified cervical vertebra, closed	vertebra
S12.70	Multiple fractures of cervical spine, closed	vertebra
S32.00	Fracture of lumbar vertebra, closed	vertebra
S32.10	Fracture of sacrum, closed	vertebra
S32.20	Fracture of coccyx, closed	vertebra
S32.30	Fracture of Ilium, closed	vertebra
S32.40	Fracture of acetabulum, closed	vertebra
S32.50	Fracture of pubis, closed	vertebra
S32.70	Multiple fractures of lumbar spine and pelvis, closed	vertebra

S32.80	Fracture of other and unspecified parts of lumbar spine and pelvis, closed	vertebra
S22.00	Fracture of thoracic vertebra, closed	vertebra
S22.10	Multiple fractures of thoracic spine, closed	vertebra
M48.4	Fatigue fracture of vertebra	vertebra
M48.40	Fatigue fracture of vertebra, multiple sites in spine	vertebra
M48.41	Fatigue fracture of vertebra, occipito-atlanto-axial region	vertebra
M48.42	Fatigue fracture of vertebra, cervical region	vertebra
M48.43	Fatigue fracture of vertebra, cervicothoracic region	vertebra
M48.44	Fatigue fracture of vertebra, thoracic region	vertebra
M48.45	Fatigue fracture of vertebra, thoracolumbar region	vertebra
M48.46	Fatigue fracture of vertebra, lumbar region	vertebra
M48.47	Fatigue fracture of vertebra, lumbosacral region	vertebra
M48.48	Fatigue fracture of vertebra, sacral and sacrococcygeal region	vertebra
M48.49	Fatigue fracture of vertebra, site unspecified	vertebra
M48.5	Collapsed vertebra, not elsewhere classified	vertebra
M48.50	Collapsed vertebra, not elsewhere classified, multiple sites in spine	vertebra
M48.51	Collapsed vertebra, not elsewhere classified, occipito-atlanto-axial region	vertebra
M48.52	Collapsed vertebra, not elsewhere classified, cervical region	vertebra
M48.53	Collapsed vertebra, not elsewhere classified, cervicothoracic region	vertebra
M48.54	Collapsed vertebra, not elsewhere classified, thoracic region	vertebra
M48.55	Collapsed vertebra, not elsewhere classified, thoracolumbar region	vertebra
M48.56	Collapsed vertebra, not elsewhere classified, lumbar region	vertebra
M48.57	Collapsed vertebra, not elsewhere classified, lumbosacral region	vertebra
M48.58	Collapsed vertebra, not elsewhere classified, sacral and sacrococcygeal region	vertebra
M48.59	Collapsed vertebra, not elsewhere classified, site unspecified	vertebra
S52.0	Fracture of upper end of ulna, closed	forearm/wrist
S52.1	Fracture of upper end of radius, closed	forearm/wrist
S52.2	Fracture of shaft of ulna, closed	forearm/wrist
S52.3	Fracture of shaft of radius, closed	forearm/wrist
S52.4	Fracture of shafts of both ulna and radius, closed	forearm/wrist
S52.5	Fracture of lower end of radius, closed	forearm/wrist
S52.6	Fracture of lower end of both ulna and radius, closed	forearm/wrist
S52.7	Multiple fractures of forearm, closed	forearm/wrist
S52.8	Fracture of other parts of forearm, closed	forearm/wrist
S52.9	Fracture of forearm, part unspecified	forearm/wrist
S62.0	Fracture of navicular [scaphoid] bone of hand, closed	forearm/wrist

S62.8	Fracture of other and unspecified parts of wrist and hand, closed	forearm/wrist
S72.0	Fracture of neck of femur, closed	Hip
S72.1	Pertrochanteric fracture, closed	Hip
S72.2	Subtrochanteric fracture, closed	Hip
S72.3	Fracture of shaft of femur, closed	Hip
S72.4	Fracture of lower end of femur, closed	Hip
S72.7	Multiple fractures of femur, closed	Hip
S72.8	Fractures of other parts of femur, closed	Hip
S72.9	Fracture of femur, part unspecified, closed	Hip
S42.0	Fracture of clavicle, closed	humerus
S42.1	Fracture of scapula, closed	humerus
S42.2	Fracture of upper end of humerus, closed	humerus
S42.3	Fracture of shaft of humerus, closed	humerus
S42.4	Fracture of lower end of humerus, closed	humerus
S42.7	Multiple fractures of clavicle, scapula and humerus, closed	humerus
S42.8	Fracture of other parts of shoulder and upper arm, closed	humerus
S42.9	Fracture of shoulder girdle, part unspecified, closed	humerus
S12.0	Fracture of first cervical vertebra, closed	vertebra
S12.1	Fracture of second cervical vertebra, closed	vertebra
S12.2	Fracture of other specified cervical vertebra, closed	vertebra
S12.7	Multiple fractures of cervical spine, closed	vertebra
S32.0	Fracture of lumbar vertebra, closed	vertebra
S32.1	Fracture of sacrum, closed	vertebra
S32.2	Fracture of coccyx, closed	vertebra
S32.3	Fracture of Ilium, closed	vertebra
S32.4	Fracture of acetabulum, closed	vertebra
S32.5	Fracture of pubis, closed	vertebra
S32.7	Multiple fractures of lumbar spine and pelvis, closed	vertebra
S32.8	Fracture of other and unspecified parts of lumbar spine and pelvis, closed	vertebra
S22.0	Fracture of thoracic vertebra, closed	vertebra
S22.1	Multiple fractures of thoracic spine, closed	vertebra

Code list 5: Subtrochanteric and femoral shaft fractures (CPRD & HES).

Readcode	**Description**
S302200	Closed fracture proximal femur, subtrochanteric
S305.00	Subtrochanteric fracture
S310.00	Closed fracture of femur, shaft or unspecified part
S310100	Closed fracture shaft of femur
S314.00	Fracture of shaft of femur
ICD-10 code	**Description**
S72.2	Subtrochanteric fracture
S72.3	femoral shaft fracture

Code list 6: Bisphosphonates (CPRD).

Prodcode	Productname
50278	Alendronic acid 70mg tablets (Wockhardt UK Ltd)
56730	Alendronic acid 70mg tablets (Almus Pharmaceuticals Ltd)
66618	Bondronat 6mg/6ml concentrate for solution for infusion vials (Atnahs Pharma UK Ltd)
72541	Alendronic acid 70mg/5ml oral solution
6634	Risedronate sodium 5mg tablets
7112	Bonviva 150mg tablets (Atnahs Pharma UK Ltd)
64331	Alendronic acid 10mg tablets (DE Pharmaceuticals)
7146	Ibandronic acid 150mg tablets
56030	Ibandronic acid 150mg tablets (A A H Pharmaceuticals Ltd)
45787	Alendronic acid 70mg/100ml oral solution unit dose sugar free
25387	Bonviva 3mg/3ml solution for injection pre-filled syringes (Atnahs Pharma UK Ltd)
72208	Alendronic acid 70mg/100ml oral solution unit dose sugar free (A A H Pharmaceuticals Ltd)
47380	Alendronic acid 70mg tablets (Arrow Generics Ltd)
7546	Actonel 30mg tablets (Warner Chilcott UK Ltd)
7530	Alendronic acid 5mg tablets
6058	Risedronate sodium 35mg tablets
26913	Bondronat 50mg tablets (Atnahs Pharma UK Ltd)
71874	Ibandronic acid 2mg/2ml concentrate for solution for infusion vials (Accord Healthcare Ltd)
66203	Binosto 70mg effervescent tablets (Internis Pharmaceuticals Ltd)
59079	Alendronic acid 10mg tablets (Almus Pharmaceuticals Ltd)
782	Fosamax 5mg tablets (Merck Sharp & Dohme Ltd)
71209	Risedronate sodium 35mg tablets (Mawdsley-Brooks & Company Ltd)
58618	Risedronate sodium 35mg/5ml oral solution
69995	Alendronic acid 35mg/5ml oral solution
54453	Bonviva 150mg tablets (Lexon (UK) Ltd)
43958	Alendronic acid 70mg tablets (Actavis UK Ltd)
40449	Alendronic acid 70mg tablets (PLIVA Pharma Ltd)
51877	Alendronic acid 70mg tablets (Alliance Healthcare (Distribution) Ltd)
48013	Risedronate sodium 35mg tablets (A A H Pharmaceuticals Ltd)
688	Alendronic acid 70mg tablets
52284	Fosamax 10mg tablets (Sigma Pharmaceuticals Plc)
58744	Fosamax Once Weekly 70mg tablets (DE Pharmaceuticals)
2298	Alendronic acid 10mg tablets
56061	Alendronic acid 10mg tablets (Actavis UK Ltd)
47911	Iasibon 50mg tablets (Aspire Pharma Ltd)
51342	Bonviva 150mg tablets (DE Pharmaceuticals)
37218	Alendronic acid 70mg tablets (Teva UK Ltd)
10193	Ibandronic acid 50mg tablets

59449	Risedronate sodium 35mg tablets (Bluefish Pharmaceuticals AB)
59485	Alendronic acid 10mg tablets (Accord Healthcare Ltd)
63175	Alendronic acid 10mg tablets (Phoenix Healthcare Distribution Ltd)
37217	Alendronic acid 10mg tablets (Teva UK Ltd)
52834	Alendronic acid 70mg tablets (Accord Healthcare Ltd)
61686	Alendronic acid 70mg tablets (DE Pharmaceuticals)
50880	Fosamax 10mg tablets (Necessity Supplies Ltd)
71963	Alendronic acid 10mg tablets (Sigma Pharmaceuticals Plc)
64431	Risedronate sodium 30mg tablets (Aspire Pharma Ltd)
766	Didronel 200mg tablets (Warner Chilcott UK Ltd)
63371	Etidronate disodium 200mg tablets (Mylan)
63802	Actonel Once a Week 35mg tablets (Lexon (UK) Ltd)
62017	Ibandronic acid 2mg/2ml solution for infusion vials
71000	Ibandronic acid 150mg tablets (Alliance Healthcare (Distribution) Ltd)
54566	Alendronic acid 10mg tablets (A A H Pharmaceuticals Ltd)
55998	Alendronic acid 70mg/75ml oral solution unit dose
7527	Actonel 5mg tablets (Warner Chilcott UK Ltd)
56369	Ibandronic acid 150mg tablets (Zentiva)
56260	Alendronic acid 70mg tablets (Kent Pharmaceuticals Ltd)
55965	Alendronic acid 70mg tablets (Zentiva)
32426	Ibandronic acid 3mg/3ml solution for injection pre-filled syringes
44265	Bondronat 2mg/2ml Concentrate for solution for infusion (Roche Products Ltd)
544	Fosamax Once Weekly 70mg tablets (Merck Sharp & Dohme Ltd)
24998	Ibandronic acid 6mg/6ml solution for infusion vials
65905	Alendronic acid 10mg tablets (Mylan)
67078	Risedronate sodium 35mg tablets (Teva UK Ltd)
71851	Alendronic acid 70mg tablets (Sigma Pharmaceuticals Plc)
60144	Alendronic acid 70mg/100ml oral solution unit dose sugar free (Waymade Healthcare Plc)
69630	Risedronate sodium 35mg tablets (Almus Pharmaceuticals Ltd)
6084	Actonel once a week 35mg Tablet (Procter & Gamble (Health & Beauty Care) Ltd)
23223	Ibandronic acid 2mg/2ml concentrated Solution for infusion
57875	Fosamax Once Weekly 70mg tablets (Lexon (UK) Ltd)
52624	Alendronic acid 70mg tablets (Phoenix Healthcare Distribution Ltd)
66028	Actonel 35mg tablets (Teva UK Ltd)
61313	Risedronate sodium 30mg tablets (A A H Pharmaceuticals Ltd)
69929	Risedronate sodium 35mg tablets (Alliance Healthcare (Distribution) Ltd)
65008	Alendronic acid 70mg effervescent tablets sugar free
59916	Risedronate sodium 35mg tablets (Sandoz Ltd)
7089	Risedronate sodium 30mg tablets
59587	Ibandronic acid 150mg tablets (Ranbaxy (UK) Ltd)
4680	Etidronate disodium 200mg tablets

35937	Alendronic acid 70mg tablets (A A H Pharmaceuticals Ltd)
56663	Risedronate sodium 35mg tablets (Waymade Healthcare Plc)
663	Fosamax 10mg tablets (Merck Sharp & Dohme Ltd)
59247	Fosamax Once Weekly 70mg tablets (Necessity Supplies Ltd)
57980	Ibandronic acid 50mg tablets (Actavis UK Ltd)
65971	Risedronate sodium 35mg/5ml oral suspension
67159	Ibandronic acid 50mg tablets (Teva UK Ltd)
46245	Alendronic acid 70mg tablets (Mylan)
44511	Actonel Once a Week 35mg tablets (Warner Chilcott UK Ltd)
59555	Alendronic acid 10mg tablets (Alliance Healthcare (Distribution) Ltd)
52373	Risedronate sodium 35mg tablets (Phoenix Healthcare Distribution Ltd)
69958	Risedronate sodium 35mg tablets (Mylan)
56431	Risedronate sodium 35mg tablets (Actavis UK Ltd)
60288	Actonel Once a Week 35mg tablets (Mawdsley-Brooks & Company Ltd)
55295	Alendronic acid 70mg/100ml oral solution unit dose sugar free (Alliance Healthcare (Distribution) Ltd)
52564	Alendronic acid 70mg/100ml oral solution unit dose sugar free (Rosemont Pharmaceuticals Ltd)
63008	Alendronic acid 70mg tablets (Somex Pharma)

Code list 7: Corticosteroid medication (CPRD).

Procode	Productname	Group
38	beclometasone 100micrograms/dose inhaler	ICS
44	prednisolone 5mg gastro-resistant tablets	OCS
95	prednisolone 5mg tablets	OCS
99	becotide 100 inhaler (glaxosmithkline uk ltd)	ICS
454	pulmicort 200microgram inhaler (astrazeneca uk ltd)	ICS
557	prednisolone 2.5mg gastro-resistant tablets	OCS
578	prednisolone 1mg tablets	OCS
638	seretide 250 accuhaler (glaxosmithkline uk ltd)	LABA_ICS
665	seretide 100 accuhaler (glaxosmithkline uk ltd)	LABA_ICS
883	becodisks 200microgram disc (allen & hanburys ltd)	ICS
895	beclazone 100 easi-breathe inhaler (teva uk ltd)	ICS
896	becotide easi-breathe 100microgram/actuation pressurised inhalation (allen & hanburys ltd)	ICS
	ventolin evohaler 100 100microgram/inhalation pressurised inhalation	
908	pulmicort 400 turbohaler (astrazeneca uk ltd)	ICS
909	budesonide 200micrograms/dose inhaler	ICS
	serevent diskhaler 50microgram inhalation powder (glaxo wellcome uk	
	flixotide accuhaler 250 250microgram/inhalation inhalation powder (allen	
911	& hanburys ltd)	ICS
947	budesonide 50micrograms/actuation refill canister	ICS
955	prednisolone 5mg soluble tablets	OCS
956	pulmicort 200 turbohaler (astrazeneca uk ltd)	ICS
	salamol easi-breathe 100microgram/actuation pressurised inhalation	
959	budesonide 50micrograms/dose inhaler	ICS

960	pulmicort 100 turbohaler (astrazeneca uk ltd)	ICS
1063	prednesol 5mg tablet (sovereign medical ltd)	OCS
1100	beclazone 100 inhaler (teva uk ltd)	ICS
1236	becloforte 250micrograms/dose inhaler (glaxosmithkline uk ltd)	ICS
1242	beclometasone 250micrograms/dose inhaler	ICS
1243	beclazone 250 easi-breathe inhaler (teva uk ltd)	ICS
1258	becotide 200 inhaler (glaxosmithkline uk ltd)	ICS
1259	beclometasone 200micrograms/dose inhaler	ICS
1406	becotide 50 inhaler (glaxosmithkline uk ltd)	ICS
1412	flixotide 250microgram/actuation inhalation powder (allen & hanburys ltd)	ICS
1424	flixotide 250microgram disc (allen & hanburys ltd)	ICS
1426	flixotide 500microgram disc (allen & hanburys ltd)	ICS
1518	flixotide 50microgram/actuation inhalation powder (allen & hanburys ltd)	ICS
1537	becotide 200microgram rotacaps (glaxosmithkline uk ltd)	ICS
1551	beclazone 250 inhaler (teva uk ltd)	ICS
1552	becloforte easi-breathe 250microgram/actuation pressurised inhalation (allen & hanburys ltd)	ICS
1642	budesonide 400micrograms/dose dry powder inhaler	ICS
1676	flixotide 125microgram/actuation inhalation powder (allen & hanburys ltd)	ICS
1680	pulmicort ls 50micrograms/dose inhaler (astrazeneca uk ltd)	ICS
1725	beclazone 50 easi-breathe inhaler (teva uk ltd)	ICS
1727	becotide easi-breathe 50microgram/actuation pressurised inhalation (allen & hanburys ltd)	ICS
1734	beclometasone 100micrograms/dose breath actuated inhaler	ICS
1801	ventide inhaler (glaxosmithkline uk ltd)	SABA_ICS
1861	aerobec 100 autohaler (meda pharmaceuticals ltd)	ICS
1885	beclazone 200 inhaler (teva uk ltd)	ICS
1951	becodisks 400microgram disc (allen & hanburys ltd)	ICS
1956	pulmicort 1mg respules (astrazeneca uk ltd)	ICS
1959	pulmicort 0.5mg respules (astrazeneca uk ltd)	ICS
2044	prednisone 2.5 mg tab	OCS
2092	budesonide 200micrograms/dose dry powder inhaler	ICS
2124	pulmicort refil 200 mcg inh	ICS
2125	pulmicort 200microgram refill canister (astrazeneca uk ltd)	ICS
2148	beclometasone 400microgram disc	ICS
2159	aerobec 50 autohaler (meda pharmaceuticals ltd)	ICS
2160	beclometasone 50micrograms/dose breath actuated inhaler	ICS
2229	becodisks 100microgram disc (allen & hanburys ltd)	ICS
2282	fluticasone propionate 500micrograms/dose dry powder inhaler	ICS
2335	qvar 100 inhaler (teva uk ltd)	ICS
2368	prednisolone 2.5mg tablet	OCS
2390	prednisolone e/c 1 mg tab	OCS
2440	flixotide accuhaler 500 500microgram/inhalation inhalation powder (allen & hanburys ltd)	ICS
2600	beclometasone 250micrograms/dose breath actuated inhaler	ICS
2704	prednisolone 25mg tablets	OCS
2723	fluticasone 25micrograms/dose inhaler	ICS
2799	prednisolone 10 mg tab	OCS

2892	becloforte 400microgram disks (glaxosmithkline uk ltd)	ICS
2893	beclometasone 200micrograms disc	ICS
2949	prednisone 5mg tablets	OCS
2951	fluticasone 250microgram/actuation pressurised inhalation	ICS
2992	beclazone 50 inhaler (teva uk ltd)	ICS
	atrovent aerocaps 40microgram inhalation powder (boehringer ingelheim	
3018	beclometasone 50micrograms/dose inhaler	ICS
3059	prednisolone 50 mg tab	OCS
3065	bextasol inhalation powder (allen & hanburys ltd)	ICS
3075	becotide 400microgram rotacaps (glaxosmithkline uk ltd)	ICS
	becloforte integra 250microgram/actuation inhaler with compact spacer	
3119	(glaxo laboratories ltd)	ICS
3150	beclometasone 100micrograms/actuation extrafine particle cfc free inhaler	ICS
3188	pulmicort complete 50 mcg inh	ICS
3220	qvar 50 autohaler (teva uk ltd)	ICS
3289	flixotide 25micrograms/dose inhaler (glaxosmithkline uk ltd)	ICS
3345	sintisone tablet (pharmacia ltd)	OCS
3363	becloforte 400microgram disks with diskhaler (glaxosmithkline uk ltd)	ICS
	becotide rotahaler type 4 insufflator inhalation powder (allen and	
3437	hanburys ltd)	ICS
3442	pulmicort complete 200 mcg inh	ICS
	beclometasone 50micrograms with salbutamol 100micrograms/inhalation	
3556	inhaler	SABA_ICS
3557	prednisone 1mg tablets	OCS
3570	budesonide 200micrograms/actuation refill canister	ICS
3743	filair 50 inhaler (meda pharmaceuticals ltd)	ICS
3753	flixotide diskhaler-community pack 250 mcg	ICS
3927	filair 100 inhaler (meda pharmaceuticals ltd)	ICS
3947	becotide 100microgram rotacaps (glaxosmithkline uk ltd)	ICS
3988	flixotide diskhaler-community pack 100 mcg	ICS
3989	flixotide 100microgram disc (allen & hanburys ltd)	ICS
3993	filair forte 250micrograms/dose inhaler (meda pharmaceuticals ltd)	ICS
4131	fluticasone 100microgram disc	ICS
4132	fluticasone 125microgram/actuation pressurised inhalation	ICS
4365	beclometasone 100micrograms disc	ICS
4413	qvar 100 autohaler (teva uk ltd)	ICS
	ventolin accuhaler 200 200microgram/actuation inhalation powder (glaxo	
4499	pharmaceuticals ltd)	ICS
4545	pulmicort ls 50microgram refill canister (astrazeneca uk ltd)	ICS
4601	asmabec 100 clickhaler (focus pharmaceuticals ltd)	ICS
4688	fluticasone 50microgram/actuation pressurised inhalation	ICS
4759	beclometasone 100microgram inhalation powder capsules	ICS
4803	beclazone 250microgram/actuation inhalation powder (actavis uk ltd)	ICS
	flixotide accuhaler 100 100microgram/inhalation inhalation powder (allen	
4926	& hanburys ltd)	ICS
5143	seretide 50 evohaler (glaxosmithkline uk ltd)	LABA_ICS
5161	seretide 125 evohaler (glaxosmithkline uk ltd)	LABA_ICS
5172	seretide 250 evohaler (glaxosmithkline uk ltd)	LABA_ICS
5223	fluticasone 50micrograms/dose inhaler cfc free	ICS
5309	flixotide 50micrograms/dose evohaler (glaxosmithkline uk ltd)	ICS
5490	deltacortril 5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	OCS

5521	beclometasone 200micrograms/dose dry powder inhaler	ICS
5522	beclometasone 100micrograms/dose dry powder inhaler	ICS
5551	flixotide 0.5mg/2ml nebules (glaxosmithkline uk ltd)	ICS
5558	salmeterol 50micrograms with fluticasone 500micrograms cfc free inhaler	LABA_ICS
5580	flixotide accuhaler 50 50microgram/inhalation inhalation powder (allen & hanburys ltd)	ICS
5683	flixotide 250micrograms/dose evohaler (glaxosmithkline uk ltd)	ICS
5718	flixotide 125micrograms/dose evohaler (glaxosmithkline uk ltd)	ICS
5804	beclometasone 250micrograms/dose dry powder inhaler	ICS
5822	fluticasone 250micrograms/dose inhaler cfc free	ICS
5864	salmeterol 25micrograms with fluticasone 250micrograms cfc free inhaler	LABA_ICS
5885	fluticasone propionate 100micrograms/dose dry powder inhaler	ICS
5913	deltacortril 2.5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	OCS
5942	salmeterol 50micrograms with fluticasone 250micrograms cfc free inhaler	LABA_ICS
5975	fluticasone 125micrograms/dose inhaler cfc free	ICS
5992	beclometasone 50micrograms/dose dry powder inhaler	ICS
6325	symbicort 200/6 turbohaler (astrazeneca uk ltd)	LABA_ICS
6569	salmeterol 25micrograms with fluticasone 125micrograms cfc free inhaler	LABA_ICS
6616	salmeterol 25micrograms with fluticasone 50micrograms cfc free inhaler	LABA_ICS
6746	budesonide 400micrograms/dose / formoterol 12micrograms/dose dry powder inhaler	LABA_ICS
6780	symbicort 400/12 turbohaler (astrazeneca uk ltd)	LABA_ICS
6796	budesonide 200micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	LABA_ICS
6938	salmeterol 50micrograms with fluticasone 100micrograms dry powder inhaler	LABA_ICS
7013	symbicort 100/6 turbohaler (astrazeneca uk ltd)	LABA_ICS
7584	prednisolone 4 mg tab	OCS
7602	fluticasone 50microgram disc	ICS
7638	fluticasone 250microgram disc	ICS
7653	beclometasone 400microgram inhalation powder capsules	ICS
7710	prednisolone 15 mg tab	OCS
7724	betamethasone valerate 100micrograms/actuation inhaler	ICS
7788	budesonide 100micrograms/dose dry powder inhaler	ICS
7891	fluticasone 500microgram disc	ICS
7934	prednisone 30 mg tab	OCS
7948	fluticasone propionate 250micrograms/dose dry powder inhaler	ICS
8111	becloforte vm 250microgram/actuation vm pack (allen & hanburys ltd)	ICS
8251	pulmicort refil 50 mg inh	ICS
8433	budesonide 100micrograms/actuation inhaler	ICS
8450	flixotide diskhaler-community pack 50 mcg	ICS
8635	flixotide 50microgram disc (allen & hanburys ltd)	ICS
9164	fluticasone propionate 50micrograms/dose dry powder inhaler	ICS
9233	beclometasone 200microgram inhalation powder capsules	ICS
9356	becotide rotahaler insufflator inhalation powder (allen and hanburys ltd)	ICS
9477	asmabec 100microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
9571	beclometasone 250micrograms/actuation vortex inhaler	ICS
9577	asmabec 50 clickhaler (focus pharmaceuticals ltd)	ICS
9599	beclazone 50microgram/actuation inhalation powder (actavis uk ltd)	ICS
9727	prednisolone 50mg tablets	OCS
9921	beclometasone 100micrograms/dose breath actuated inhaler cfc free	ICS

10090	beclometasone 50micrograms/actuation extrafine particle cfc free inhaler	ICS
10218	budesonide 100micrograms/dose / formoterol 6micrograms/dose dry powder inhaler	LABA_ICS
10254	mometasone 400micrograms/dose dry powder inhaler	ICS
10321	budesonide 400microgram inhalation powder capsules	ICS
11149	betnelan 500microgram tablets (focus pharmaceuticals ltd)	ICS
11198	beclometasons 50 micrograms/actuation vortex inhaler	ICS
11307	salbutamol 100micrograms/dose / beclometasone 50micrograms/dose inhaler	SABA_ICS
11410	fluticasone propionate 500micrograms/dose / salmeterol 50micrograms/dose dry powder inhaler	LABA_ICS
11497	beclometasone 400micrograms/dose dry powder inhaler	ICS
11588	fluticasone 125micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	LABA_ICS
11618	fluticasone 250micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	LABA_ICS
11732	beclometasone 50micrograms/dose breath actuated inhaler cfc free	ICS
12994	fluticasone 50micrograms/dose / salmeterol 25micrograms/dose inhaler cfc free	LABA_ICS
13037	pulvinal beclometasone dipropionate 200micrograms/dose dry powder inhaler (chiesi ltd)	ICS
13040	50micrograms/dose dry powder inhaler	LABA_ICS
13273	easyhaler salbutamol sulfate 100micrograms/dose dry powder inhaler 50micrograms/dose dry powder inhaler	LABA_ICS
13290	clenil modulite 100micrograms/dose inhaler (chiesi ltd)	ICS
13522	prednisolone 2 mg tab	OCS
13615	prednisone 10 mg tab	OCS
13815	beclazone 100microgram/actuation inhalation powder (actavis uk ltd)	ICS
14294	qvar 50micrograms/dose easi-breathe inhaler (teva uk ltd)	ICS
14321	beclometasone 200micrograms/dose inhaler cfc free	ICS
14524	bdp 250microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
14561	salbutamol 400microgram / beclometasone 200microgram inhalation powder capsules	SABA_ICS
14567	asmabec 250 clickhaler (focus pharmaceuticals ltd)	ICS
14590	asmabec 250microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
14700	budesonide 400micrograms/actuation inhaler	ICS
14736	pulvinal beclometasone dipropionate 400micrograms/dose dry powder inhaler (chiesi ltd)	ICS
14757	pulvinal beclometasone dipropionate 100micrograms/dose dry powder inhaler (chiesi ltd)	ICS
15326	beclometasone 100micrograms/dose inhaler cfc free	ICS
15706	beclometasone 100 micrograms/actuation vortex inhaler	ICS
16018	mometasone 200micrograms/dose dry powder inhaler	ICS
16054	budesonide 200micrograms/actuation breath actuated powder inhaler	ICS
16148	clenil modulite 250micrograms/dose inhaler (chiesi ltd)	ICS
16151	clenil modulite 200micrograms/dose inhaler (chiesi ltd)	ICS
16158	clenil modulite 50micrograms/dose inhaler (chiesi ltd)	ICS
16305	flixotide 2mg/2ml nebules (glaxosmithkline uk ltd)	ICS
16584	beclometasone 50micrograms/dose inhaler cfc free	ICS
16625	ventide rotacaps (glaxosmithkline uk ltd)	SABA_ICS
16724	prednisone 50 mg tab	OCS

	easyhaler beclometasone 200micrograms/dose dry powder inhaler (orion	
17654	pharma (uk) ltd)	ICS
	easyhaler budesonide 100micrograms/dose dry powder inhaler (orion	
17670	pharma (uk) ltd)	ICS
18394	bdp 50microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
	salbutamol 200microgram / beclometasone 100microgram inhalation	
18456	powder capsules	SABA_ICS
18484	ventide paediatric rotacaps (glaxosmithkline uk ltd)	SABA_ICS
18537	budesonide 200microgram inhalation powder capsules	ICS
18848	qvar 100micrograms/dose easi-breathe inhaler (teva uk ltd)	ICS
19031	bdp 100microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
	beclometasone 100micrograms with salbutamol 200micrograms	
19121	inhalation capsules	SABA_ICS
19141	prednisolone 5mg soluble tablets (amco)	OCS
	beclometasone 200micrograms with salbutamol 400micrograms	
19376	inhalation capsules	SABA_ICS
19389	asmabec 50microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
19401	beclometasone 250micrograms/actuation inhaler and compact spacer	ICS
19736	becotide susp for nebulisation	ICS
20095	precortisyl forte 25mg tablet (aventis pharma)	OCS
20670	prednisolone e/c	OCS
20707	becotide 100	ICS
20763	becloforte	ICS
20812	pulmicort refill	ICS
	spacehaler bdp 250microgram/actuation spacehaler (celltech pharma	
20825	europe ltd)	ICS
21005	beclometasone 250micrograms/dose inhaler cfc free	ICS
21417	prednisolone 5mg tablets (a a h pharmaceuticals ltd)	OCS
21482	beclometasone 100micrograms/dose inhaler (generics (uk) ltd)	ICS
21833	decortisyl 5mg tablet (roussel laboratories ltd)	OCS
23512	precortisyl 5mg tablet (hoechst marion roussel)	OCS
23675	pulmicort l.s. refil	ICS
	novolizer budesonide 200microgram/actuation pressurised inhalation	
23741	(meda pharmaceuticals ltd)	ICS
24219	becotide rotacaps	ICS
24660	betamethasone valerate	ICS
24716	prednisolone e/c	OCS
	spacehaler bdp 100microgram/actuation spacehaler (celltech pharma	
24898	europe ltd)	ICS
25204	beclometasone 100micrograms/dose inhaler (a a h pharmaceuticals ltd)	ICS
25272	precortisyl 1mg tablet (hoechst marion roussel)	OCS
26063	beclometasone 100micrograms/dose inhaler (teva uk ltd)	ICS
26665	pulmicort complete	ICS
	easyhaler budesonide 200micrograms/dose dry powder inhaler (orion	
27188	pharma (uk) ltd)	ICS
	ipratropium bromide with fenoterol hydrobromide 40micrograms +	
27525	becotide 50	ICS
27583	pulmicort	ICS
	beclometasone 100microgram/actuation pressurised inhalation (approved	
27679	prescription services ltd)	ICS
27889	prednisolone	OCS

27915	fluticasone prop disk refill	ICS
27959	prednisolone	OCS
27962	deltastab 1mg tablet (waymade healthcare plc)	OCS
28073	beclometasone 250microgram/actuation pressurised inhalation (approved prescription services ltd)	ICS
28375	prednisolone 2.5mg gastro-resistant tablets (a a h pharmaceuticals ltd)	OCS
28376	prednisolone 2.5mg gastro-resistant tablet (biorex laboratories ltd)	OCS
28640	beclometasone 100microgram/actuation inhalation powder (actavis uk ltd)	ICS
28761	spacehaler bdp 50microgram/actuation spacehaler (celltech pharma europe ltd)	ICS
28859	deltastab 5mg tablet (waymade healthcare plc)	OCS
29325	beclometasone 250micrograms/dose inhaler (generics (uk) ltd)	ICS
29333	prednisolone 5mg tablets (actavis uk ltd)	OCS
30210	beclometasone 250micrograms/dose inhaler (teva uk ltd)	ICS
30238	beclometasone 50microgram/actuation pressurised inhalation (approved prescription services ltd)	ICS
30390	deltastab 2 mg tab	OCS
30649	easyhaler budesonide 400micrograms/dose dry powder inhaler (orion pharma (uk) ltd)	ICS
30971	decortisyl 25 mg tab	OCS
31327	prednisolone steaglate 6.65mg tablet	OCS
31532	prednisolone 5mg gastro-resistant tablets (a a h pharmaceuticals ltd)	OCS
31774	beclometasone 50micrograms/dose inhaler (generics (uk) ltd)	ICS
32803	prednisolone 5mg gastro-resistant tablets (actavis uk ltd)	OCS
32835	prednisolone 5mg tablets (wockhardt uk ltd)	OCS
32874	beclometasone 50microgram/actuation inhalation powder (actavis uk ltd)	ICS
33258	beclometasone 250micrograms/dose inhaler (a a h pharmaceuticals ltd)	ICS
33691	prednisolone 5mg gastro-resistant tablet (biorex laboratories ltd)	OCS
33849	beclometasone 100microgram/actuation inhalation powder (neo laboratories ltd)	ICS
33988	prednisolone 5mg tablet (co-pharma ltd)	OCS
33990	prednisolone 5mg tablet (ivax pharmaceuticals uk ltd)	OCS
34109	prednisolone 5 mg gastro-resistant tablet	OCS
34315	beclometasone 250microgram/actuation inhalation powder (actavis uk ltd)	ICS
34393	prednisolone 5mg gastro-resistant tablets (teva uk ltd)	OCS
34404	prednisolone 1mg tablets (actavis uk ltd)	OCS
34428	beclometasone 50microgram/actuation inhalation powder (neo laboratories ltd)	ICS
34452	prednisolone 1mg tablets (a a h pharmaceuticals ltd)	OCS
34461	prednisolone 2.5mg gastro-resistant tablets (actavis uk ltd)	OCS
34631	prednisolone 1mg tablet (co-pharma ltd)	OCS
34660	prednisolone 1mg tablets (kent pharmaceuticals ltd)	OCS
34739	beclometasone 50micrograms/dose inhaler (teva uk ltd)	ICS
34748	prednisolone 1mg tablets (teva uk ltd)	OCS
34781	prednisolone 5mg tablets (kent pharmaceuticals ltd)	OCS
34794	beclometasone 200micrograms/dose inhaler (a a h pharmaceuticals ltd)	ICS
34859	beclometasone 250microgram/actuation inhalation powder (neo laboratories ltd)	ICS
34914	prednisolone 1mg tablet (celltech pharma europe ltd)	OCS

34919	beclometasone 50micrograms/dose inhaler (a a h pharmaceuticals ltd)	ICS
34978	prednisolone 1mg tablets (wockhardt uk ltd)	OCS
	spiriva 18microgram inhalation powder capsules with handihaler	
35071	becodisks 200microgram (glaxosmithkline uk ltd)	ICS
35106	becodisks 100microgram with diskhaler (glaxosmithkline uk ltd)	ICS
35107	beclometasone 400microgram inhalation powder blisters with device	ICS
35113	beclometasone 200microgram inhalation powder blisters	ICS
35118	becodisks 400microgram with diskhaler (glaxosmithkline uk ltd)	ICS
35225	flixotide 100microgram disks with diskhaler (glaxosmithkline uk ltd)	ICS
35288	beclometasone 400microgram inhalation powder blisters	ICS
35293	beclometasone 200microgram inhalation powder blisters with device	ICS
35299	becodisks 400microgram (glaxosmithkline uk ltd)	ICS
35374	flixotide 500microgram disks (glaxosmithkline uk ltd)	ICS
35392	flixotide 500microgram disks with diskhaler (glaxosmithkline uk ltd)	ICS
35408	becodisks 100microgram (glaxosmithkline uk ltd)	ICS
35430	becodisks 200microgram with diskhaler (glaxosmithkline uk ltd)	ICS
35461	flixotide 250microgram disks with diskhaler (glaxosmithkline uk ltd)	ICS
	budesonide 200micrograms/dose dry powder inhalation cartridge with	
35510	device	ICS
35580	beclometasone 100microgram inhalation powder blisters with device	ICS
35602	budesonide 200micrograms/dose dry powder inhalation cartridge	ICS
35611	flixotide 250microgram disks (glaxosmithkline uk ltd)	ICS
	budelin novolizer 200micrograms/dose inhalation powder (meda	
35631	pharmaceuticals ltd)	ICS
	fluticasone propionate 100microgram inhalation powder blisters with	
35638	device	ICS
35652	beclometasone 100microgram inhalation powder blisters	ICS
	fluticasone propionate 500microgram inhalation powder blisters with	
35700	device	ICS
	budelin novolizer 200micrograms/dose inhalation powder refill (meda	
35724	pharmaceuticals ltd)	ICS
35772	fluticasone propionate 100microgram inhalation powder blisters	ICS
35905	fluticasone propionate 250microgram inhalation powder blisters	ICS
35986	flixotide 50microgram disks (glaxosmithkline uk ltd)	ICS
	fluticasone propionate 50microgram inhalation powder blisters with	
36021	device	ICS
36090	flixotide 100microgram disks (glaxosmithkline uk ltd)	ICS
36290	flixotide 50microgram disks with diskhaler (glaxosmithkline uk ltd)	ICS
	fluticasone propionate 250microgram inhalation powder blisters with	
36401	device	ICS
36462	fluticasone propionate 500microgram inhalation powder blisters	ICS
37432	fostair 100micrograms/dose / 6micrograms/dose inhaler (chiesi ltd)	LABA_ICS
37447	fluticasone propionate 50microgram inhalation powder blisters	ICS
	beclometasone 100micrograms/dose / formoterol 6micrograms/dose	
37470	inhaler cfc free	LABA_ICS
38407	prednisolone 20mg tablet	OCS
	salbutamol cyclocaps 400microgram inhalation powder (dupont	
39099	pulmicort 100micrograms/dose inhaler cfc free (astrazeneca uk ltd)	ICS
39102	budesonide 100micrograms/dose inhaler cfc free	ICS
39200	aerobec forte 250 autohaler (meda pharmaceuticals ltd)	ICS
39879	budesonide 200micrograms/dose inhaler cfc free	ICS

40057	pulmicort 200micrograms/dose inhaler cfc free (astrazeneca uk ltd)	ICS
41269	beclometasone 400 cyclocaps (teva uk ltd)	ICS
41412	beclometasone 400micrograms/actuation inhaler	ICS
41515	prednisolone 5mg tablets (teva uk ltd)	OCS
41745	prednisolone 25mg tablets (zentiva)	OCS
42928	flixotide 100micrograms/dose accuhaler (glaxosmithkline uk ltd)	ICS
42985	flixotide 50micrograms/dose accuhaler (glaxosmithkline uk ltd)	ICS
42994	flixotide 250micrograms/dose accuhaler (glaxosmithkline uk ltd)	ICS
43074	flixotide 500micrograms/dose accuhaler (glaxosmithkline uk ltd)	ICS
43544	prednisone 5mg tablet (knoll ltd)	OCS
44380	prednisone 1mg modified-release tablets	OCS
44723	prednisone 5mg modified-release tablets	OCS
44802	lodotra 5mg modified-release tablets (napp pharmaceuticals ltd)	OCS
44803	lodotra 2mg modified-release tablets (napp pharmaceuticals ltd)	OCS
45302	prednisolone 5mg tablet (biorex laboratories ltd)	OCS
46157	beclometasone 200 cyclocaps (teva uk ltd)	ICS
46711	prednisone 2mg modified-release tablets	OCS
47142	prednisolone 5mg soluble tablet (amdipharm plc)	OCS
47943	inhalation (ivax pharmaceuticals ireland)	ICS
48340	clenil modulite 100micrograms/dose inhaler (mawdsley-brooks & company ltd)	ICS
48666	flutiform 250micrograms/dose / 10micrograms/dose inhaler (napp pharmaceuticals ltd)	LABA_ICS
48709	qvar 100micrograms/dose easi-breathe inhaler (sigma pharmaceuticals plc)	ICS
48739	seretide 250 evohaler (de pharmaceuticals)	LABA_ICS
49000	seretide 250 evohaler (waymade healthcare plc)	LABA_ICS
49114	symbicort 100/6 turbohaler (sigma pharmaceuticals plc)	LABA_ICS
49367	clenil modulite 50micrograms/dose inhaler (mawdsley-brooks & company ltd)	ICS
49711	pulmicort 200micrograms/dose inhaler (astrazeneca uk ltd)	ICS
49772	fluticasone 250micrograms/dose evohaler (sigma pharmaceuticals plc)	ICS
49868	fluticasone 250micrograms/dose / formoterol 10micrograms/dose inhaler cfc free	LABA_ICS
50036	flutiform 125micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd)	LABA_ICS
50037	pulmicort 0.5mg respules (waymade healthcare plc)	ICS
50129	qvar 100micrograms/dose easi-breathe inhaler (de pharmaceuticals)	ICS
50287	qvar 100 inhaler (de pharmaceuticals)	ICS
50560	seretide 250 accuhaler (sigma pharmaceuticals plc)	LABA_ICS
50689	flutiform 50micrograms/dose / 5micrograms/dose inhaler (napp pharmaceuticals ltd)	LABA_ICS
50701	becotide rotahaler (glaxosmithkline uk ltd)	ICS
50739	symbicort 400/12 turbohaler (mawdsley-brooks & company ltd)	LABA_ICS
50886	seretide 250 evohaler (stephar (u.k.) ltd)	LABA_ICS
50945	symbicort 100/6 turbohaler (mawdsley-brooks & company ltd)	LABA_ICS
51027	seretide 125 evohaler (de pharmaceuticals)	LABA_ICS
51151	seretide 125 evohaler (lexon (uk) ltd)	LABA_ICS
51209	fluticasone 125micrograms/dose / formoterol 5micrograms/dose inhaler cfc free	LABA_ICS
51234	qvar 100 inhaler (waymade healthcare plc)	ICS

	fluticasone 50micrograms/dose / formoterol 5micrograms/dose inhaler cfc	
51270	free	LABA_ICS
51394	seretide 500 accuhaler (waymade healthcare plc)	LABA_ICS
51415	qvar 50 inhaler (mawdsley-brooks & company ltd)	ICS
51480	qvar 100 autohaler (de pharmaceuticals)	ICS
51570	symbicort 200/6 turbohaler (de pharmaceuticals)	LABA_ICS
51593	seretide 500 accuhaler (de pharmaceuticals)	LABA_ICS
51681	qvar 100 inhaler (sigma pharmaceuticals plc)	ICS
51753	prednisolone 1mg tablets (co-pharma ltd)	OCS
51759	symbicort 200/6 turbohaler (mawdsley-brooks & company ltd)	LABA_ICS
51815	flixotide 250micrograms/dose evohaler (waymade healthcare plc)	ICS
51861	seretide 500 accuhaler (mawdsley-brooks & company ltd)	LABA_ICS
51909	seretide 250 evohaler (necessity supplies ltd)	LABA_ICS
52732	pulmicort 0.5mg respules (necessity supplies ltd)	ICS
52806	qvar 100 autohaler (lexon (uk) ltd)	ICS
53057	flixotide 50micrograms/dose evohaler (lexon (uk) ltd)	ICS
53230	seretide 250 accuhaler (de pharmaceuticals)	LABA_ICS
53237	symbicort 400/12 turbohaler (de pharmaceuticals)	LABA_ICS
53283	seretide 100 accuhaler (waymade healthcare plc)	LABA_ICS
53313	prednisolone 20mg/5ml oral suspension	OCS
53336	prednisolone 25mg tablets (a a h pharmaceuticals ltd)	OCS
53480	qvar 100 autohaler (stephar (u.k.) ltd)	ICS
53491	symbicort 200/6 turbohaler (sigma pharmaceuticals plc)	LABA_ICS
54118	prednisolone 25mg/5ml oral suspension	OCS
54207	qvar 50 inhaler (de pharmaceuticals)	ICS
54399	qvar 100 autohaler (sigma pharmaceuticals plc)	ICS
54432	lodotra 1mg modified-release tablets (napp pharmaceuticals ltd)	OCS
54434	prednisolone 2.5mg/5ml oral suspension	OCS
55024	prednisolone 5mg/5ml oral solution	OCS
55480	prednisolone 2.5mg gastro-resistant tablets (alliance pharmaceuticals ltd)	OCS
55677	seretide 500 accuhaler (lexon (uk) ltd)	LABA_ICS
56462	becodisks 400microgram (waymade healthcare plc)	ICS
56471	becodisks 200microgram (mawdsley-brooks & company ltd)	ICS
56474	flixotide 125micrograms/dose evohaler (de pharmaceuticals)	ICS
56475	flixotide 50micrograms/dose accuhaler (sigma pharmaceuticals plc)	ICS
56477	flixotide 100micrograms/dose accuhaler (waymade healthcare plc)	ICS
56484	flixotide 250micrograms/dose accuhaler (waymade healthcare plc)	ICS
56493	qvar 50micrograms/dose easi-breathe inhaler (sigma pharmaceuticals plc)	ICS
56498	pulmicort 200 turbohaler (waymade healthcare plc)	ICS
56499	flixotide 500micrograms/dose accuhaler (waymade healthcare plc)	ICS
56891	prednisolone 1mg tablets (waymade healthcare plc)	OCS
57525	flixotide 250micrograms/dose accuhaler (stephar (u.k.) ltd)	ICS
57555	flixotide 125micrograms/dose evohaler (dowelhurst ltd)	ICS
57579	flixotide 50micrograms/dose accuhaler (de pharmaceuticals)	ICS
57589	becloforte 250micrograms/dose inhaler (dowelhurst ltd)	ICS
58000	prednisolone 5mg tablets (almus pharmaceuticals ltd)	OCS
58061	prednisone 50mg tablets	OCS
58234	prednisolone 10mg/5ml oral solution	OCS
58369	prednisolone 5mg tablets (boston healthcare ltd)	OCS
58384	prednisolone 1mg tablets (almus pharmaceuticals ltd)	OCS
	prednisolone 5mg gastro-resistant tablets (phoenix healthcare	

58987	distribution ltd)	OCS
	dilacort 5mg gastro-resistant tablets (auden mckenzie (pharma division)	
59229	ltd)	OCS
	dilacort 2.5mg gastro-resistant tablets (auden mckenzie (pharma division)	
59283	ltd)	OCS
	relvar ellipta 92micrograms/dose / 22micrograms/dose dry powder	
59327	inhaler (glaxosmithkline uk ltd)	LABA_ICS
59338	prednisolone 1mg/5ml oral solution	OCS
	fluticasone furoate 92micrograms/dose / vilanterol 22micrograms/dose	
59439	dry powder inhaler	LABA_ICS
	relvar ellipta 184micrograms/dose / 22micrograms/dose dry powder	
59573	inhaler (glaxosmithkline uk ltd)	LABA_ICS
	fluticasone furoate 184micrograms/dose / vilanterol 22micrograms/dose	
59899	dry powder inhaler	LABA_ICS
59912	prednisolone 5mg gastro-resistant tablets (waymade healthcare plc)	OCS
60421	prednisolone 5mg tablets (co-pharma ltd)	OCS
60937	pulmicort 200 turbohaler (dowelhurst ltd)	ICS
61132	prednisolone 1mg tablets (boston healthcare ltd)	OCS
61162	prednisolone 5mg tablets (waymade healthcare plc)	OCS
	anoro ellipta 55micrograms/dose / 22micrograms/dose dry powder	
61280	seretide 250 accuhaler (waymade healthcare plc)	LABA_ICS
	umeclidinium bromide 65micrograms/dose / vilanterol	
	fostair nexthaler 100micrograms/dose / 6micrograms/dose dry powder	
61644	inhaler (chiesi ltd)	LABA_ICS
61664	clenil modulite 250micrograms/dose inhaler (waymade healthcare plc)	ICS
	duoresp spiromax 320micrograms/dose / 9micrograms/dose dry powder	
61666	inhaler (teva uk ltd)	LABA_ICS
61689	prednisolone 5mg soluble tablets (a a h pharmaceuticals ltd)	OCS
	duoresp spiromax 160micrograms/dose / 4.5micrograms/dose dry	
61782	powder inhaler (teva uk ltd)	LABA_ICS
	beclometasone 100micrograms/dose / formoterol 6micrograms/dose dry	
62030	powder inhaler	LABA_ICS
62126	seretide 100 accuhaler (de pharmaceuticals)	LABA_ICS